Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective *C*-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures

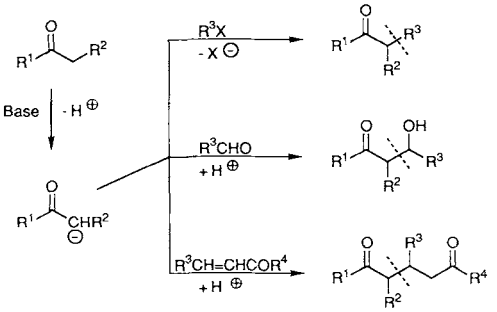
By Dieter Seebach*

The chemistry of lithium enolates is used to demonstrate that complex structures held together by noncovalent bonds ("supramolecules") may dramatically influence the result of seemingly simple standard reactions of organic synthesis. Detailed structural data have been obtained by crystallographic investigations of numerous Li enolates and analogous derivatives. The most remarkable features of these structures are aggregation to give dimers, tetramers, and higher oligomers, complexation of the metal centers by solvent molecules and chelating ligands, and hydrogen-bond formation of weak acids such as secondary amines with the anionoid part of the enolates. The presence in nonpolar solvents of the same supramolecules has been established by NMR-spectroscopic, by osmometric, and by calorimetric measurements. The structures and the order of magnitude of the interactions have also been reproduced by ab-initio calculations. Most importantly, supramolecules may be product-forming species in synthetic reactions of Li enolates. A knowledge of the complex structures of Li enolates also improves our understanding of their reactivity. Thus, simple procedures have been developed to avoid complications caused by secondary amines, formed concomitantly with Li enolates by the common methods. Mixtures of achiral Li enolates and chiral Li amides can give rise to enantioselective reactions. Solubilization by LiX is observed, especially of multiply lithiated compounds. This effect is exploited for alkylations of N-methylglycine (sarcosine) CH_2 groups in open-chain oligopeptides. Thus, the cyclic undecapeptide cyclosporine, a potent immunosuppressant, is converted into a THF-soluble hexalithio derivative (without epimerization of stereogenic centers) and alkylated by a variety of electrophiles in the presence of either excess lithiumdiisopropyl amide or of up to 30 equivalents of lithium chloride. Depending on the nature of the LiX additive, a new stereogenic center of (*R*) or (*S*) configuration is created in the peptide chain by this process. A structure-activity correlation in the series of cyclosporine derivatives thus available is discussed.

Nowadays, the molecular program of
chemistry has arrived at its successful termination.
H. Primas, ETH Zürich (1982)

1. Introduction—from α-Carbonyl Carbanions to Metal Enolates

Carbon-carbon bond formation in α-carbonyl positions is one of the most important processes for elaboration of carbon skeletons ("backbone of organic synthesis"). From the very beginning,[1] the variety of reactions of this type carried out under alkaline conditions was described as involving enolates which were drawn with the negative charge on carbon, pragmatically so, because that is where they react (Scheme 1). This notation continued to be used, especially in teaching, even when these reactions were no longer carried out in aqueous or other protic media, where solvent-separated "free" ions occur, and even though one realized that the negative charge is located on the more electronegative oxygen atom. The decisive role of the metal was appreciated when silyl enol ethers ("silyl enolates") were discovered for synthetic purposes[2]—they can be activated[3,4] by transmetalation or by treatment with fluoride ion, and they combine with electrophiles in reactions mediated by Lewis acids—and when the correlation between the configuration of the Li, B, Mg, and Sn[11] enolate double bond and the steric course of aldol additions[5-7] and other reactions[8] was disclosed.[9,10] Most of these reactions are



Scheme 1. Three classical reactions of carbonyl compounds: α-alkylation, aldol addition, and Michael addition.

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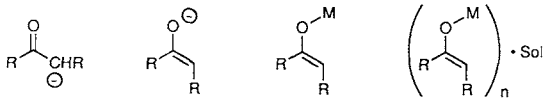
performed in nonpolar solvents (hydrocarbons, chlorohydrocarbons, open-chain or cyclic ethers, amines),[11] preferably at low temperatures, i.e., under conditions disfavoring the formation of ions, the separation of charges.[12-14]

While the important role of the metal in aldol additions quickly became part of synthetic planning, another property of the polar alkali and alkaline-earth enolates remained the "esoteric science" of only a few specialists: *the aggregation to higher-order structures.* It was known that potassium *tert*-butoxide is tetrameric in the solid state and in the gas phase[15] and that alkali enolates, even of β-diketones, form dimeric aggregates in the crystalline state.[16-18] It was concluded from ebullioscopic measurements[19] and from NMR spectra[20,21] that Li and Na enolates and phenolates are dimeric or tetrameric[22] in nonpolar solvents.[11] It is especially in the footnotes of early synthetic papers where one finds speculative suggestions that such enolate aggregates may be influential in product formation. In contrast, it has been well known for almost 30 years that aggregates of organolithium compounds with carbon–lithium bonds *may be* the product-forming species.[23,24] References are found in a classical monograph on the structure and reactivity of alkali and alkaline-earth metal derivatives[25] and in more recent books[26-36] and review articles (general,[37-41] NMR spectroscopy,[42-46] crystal structure analysis[47-53]).

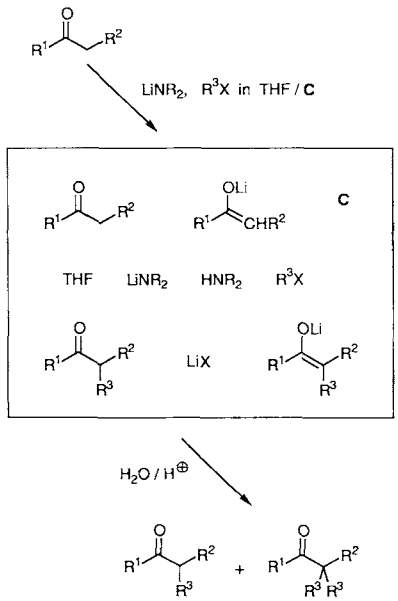
In this article we describe results of the past decade which not only increased our knowledge of Li enolates[53] but also enlarged the scope of these most important reagents and their nitrogen analogues, which are widely applied in research laboratories as well as in industrial development and production of drugs, pesticides, and fine chemicals. The choice of examples to be discussed is necessarily influenced by the personal experiences of the author and his collaborators: by making structural investigations on synthetically relevant reagents we try to reduce frustration originating from the fact that part of our group keeps discovering highly selective transformations which we do not understand at all.[54-57] Thus, the route of the sorcerer's apprentice is described, as indicated by the sequence of formulae in Scheme 2.



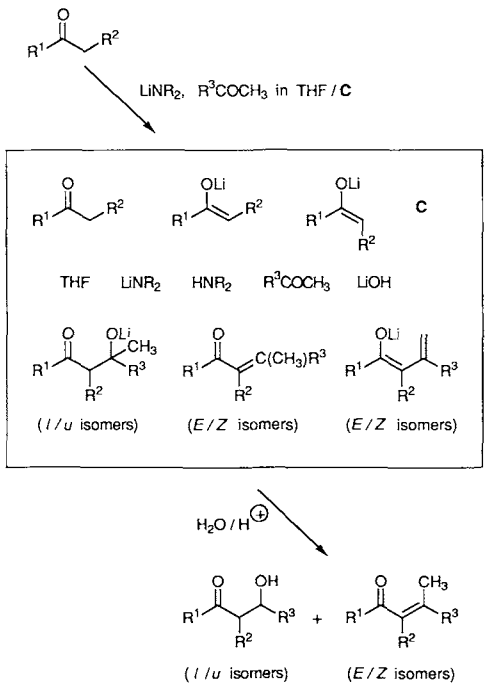
Scheme 2. From the deprotonated carbonyl derivative, via the metal enolate (M = metal), to aggregates, solvated and complexed by additives ("supramolecules" [58]). Sol = solvent molecules (ligands) in the coordination sphere of the metal.

2. The Complex World of Li Enolates—in Crystals and in Solution

Today's standard method of doing enolate reactions involves deprotonation of carbonyl compounds by lithium amide bases, for instance, lithium diisopropylamide (LDA),[59] tetramethylpiperidide (LTMP),[60] or hexamethyldisilazanide (LHMDS)[61] in THF, possibly in the presence of a cosolvent[8,62-65] or of a complexing agent.[26,52,66] The enolate solution thus obtained is combined with an electrophile. For CC bond formation this is usually an alkyl halide (Scheme 3) or a carbonyl compound (aldehyde/ketone,[67] Scheme 4). During these procedures, mixtures of the species shown inside the boxes of Schemes 3 and 4 are present. Since the first crystal structure analyses of ketone Li enolate aggregates[68] in 1981, numerous aggregates and complexes between these species have been isolated as single crystals suitable for X-ray analysis and/or have been



Scheme 3. Components which may coexist in a reaction mixture under the normal alkylation conditions of carbonyl compounds. **C** should be taken to represent an additive [cosolvent, complexing agent, e.g., hexamethylphosphoric triamide (HMPT) [62], "*N,N'*-dimethylpropyleneurea" (1,3-dimethyltetrahydropyrimidin-2(1*H*)-one, DMPU) [63], *N,N,N',N'*-tetramethylethylenediamine (TMEDA) [26], *N,N,N'*-trimethylethylenediamine (TriMEDA) [66], pentamethyldiethylenetriamine (PMDET) [26], dimethoxyethane (DME)].



Scheme 4. Components that may occur in an aldol reaction performed with an enolate generated by R_2NLi. **C** is an additive (see caption to Scheme 3).

detected in solution. Thermochemical data were collected and force-field calculations, as well as quantum-mechanical "investigations", were performed. This will form the subject of the following sections, before we turn to the question of whether these complex structures are involved in product-forming steps.[69]

2.1. Li enolates and "Ingredients" in the Crystalline State

... la virtùe della geometria esser il più potente strumento d'ogni altro per acuir l'ingegnio e disporlo al perfettamente discorrere e specolare.[*]
Galileo Galilei

All crystalline Li enolates for which an X-ray structure analysis has been successfully performed so far are dimeric, tetrameric, or hexameric aggregates, the degree of aggregation depending less upon the particular enolate structure than upon solvent and added complexing or chelating agents (Figs. 1–12). Dimers tend to be favored in the presence of ethylenediamines and tetramers with ethers such as THF; a hexamer was crystallized from a non-donor hydrocarbon solvent. Lithium enolates of pinacolone (3,3-dimethyl-2-butanone, Figs. 1–3) and its derivatives (Figs. 7, 8, 10) prevail among the structures solved, for obvious reasons (high stability, only one enolate possible).

Lithium enolates of esters are unstable even in the crystalline state, due to their decomposition to ketenes and alkoxides.[72, 73] Special techniques are required for the generation and isolation of suitable single crystals at low temperatures[51, 67c, 87] (Figs. 4 and 13). Amide enolates are much more stable (Figs. 5 and 6, compare the leaving groups $LiNR_2$ and LiOR). Again, dimeric and tetrameric aggregates are present in the crystals of these Li enolates containing additional heteroatoms. Other components of the mixtures present during generation and during reactions of Li enolates with electrophiles have been crystallized and successfully subjected to X-ray crystal structure analysis in recent years. Oligomeric aggregates of Li amides (Fig. 9, dimer), of an aldolate (Fig. 7, tetramer), and of a dienolate (Fig. 8, dimer) were found, the Li atoms of which are solvated by the oxygens of ethers (Figs. 2, 6, 9) or carbonyl compounds (Fig. 7, 8, 11), by the oxygens of HMPT (Fig. 12), or by the nitrogens of secondary or tertiary amines (Figs. 3–5). The formation of aggregates, $[(LiX)_n]$, is not limited to identical components; mixed aggregates $[(LiX)_n(LiY)_m]$ may also be formed from different components, for instance, the complex skeleton assembled from LDA and a siloxy-substituted Li enolate (Fig. 10).

Since lithium is *usually* tetracoordinated, it is possible—with due care—to deduce the degree of aggregation of Li enolates, alkoxides, phenolates,[90] and their nitrogen analogues from the stoichiometric composition of isolated samples. In order to achieve tetracoordination, one, two, or three "external" ligand atoms are present per lithium in a tetramer, dimer, or monomer, respectively. The ratios given in Table 1 confirm that aggregation of LiX in the crystalline state is a general phenomenon, also by this criterion. Furthermore, inspection of Table 1 reveals that lithiated nitriles (Li ketene imines) and iminoesters (Li enamides) are also aggregated, which was confirmed by crystal structure analysis:[98] see Table 2 and Figures 14 and 15, showing a lithio "bis-lactim ether" (reagent for enantioselective amino acid synthesis[99, 100]) and the HMPT-solvated lithio malononitrile, respectively.

The structures of sodium, magnesium, aluminum, and zinc enolates (Figs. 16–19) exemplify the fact that aggregation is by no means a peculiarity of Li derivatives, but is a general phenomenon in polar metal enolates.[115]

Many a crystallographer and inorganic chemist does not quite share the excitement of us organic chemists about the structures described here; these colleagues live with the fact that aggregates and clusters are "ubiquitous all over the periodic table".[115] For synthetic organic chemists[116]

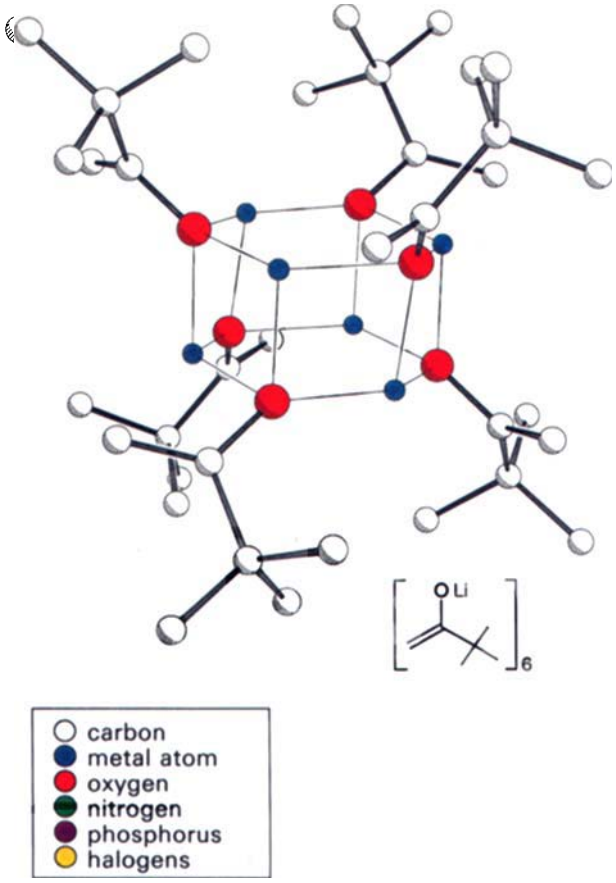


Fig. 1. Hexameric lithium enolate derived from pinacolone (enolate generated with LDA in heptane) [70, 71]. The crystal does not contain any solvent. The Li atoms are only threefold coordinated. Three square units of dimers are assembled in a hexagonal prism. A threefold axis runs perpendicularly to the hexagonal basis plane. The coordinates are stored in the *Cambridge Structural Database (CSD)* under the code CUYVOH. Here, and in all other illustrated structures (Figs. 1–12, 14–20, 23, 25, as well as the structures in [115]), the atoms are color-coded according to the key shown above. Other, non-carbon atoms are signified by their chemical symbol. The first coordination sphere of the metals is represented throughout by thin connection lines—for clarity, the neutral ligands or solvent molecules are not drawn to the same scale—while the anionic ligands are emphasized by bolder connection lines and larger spheres for the atoms.

[*] ... whoever has a grasp of geometry is capable of understanding this world.

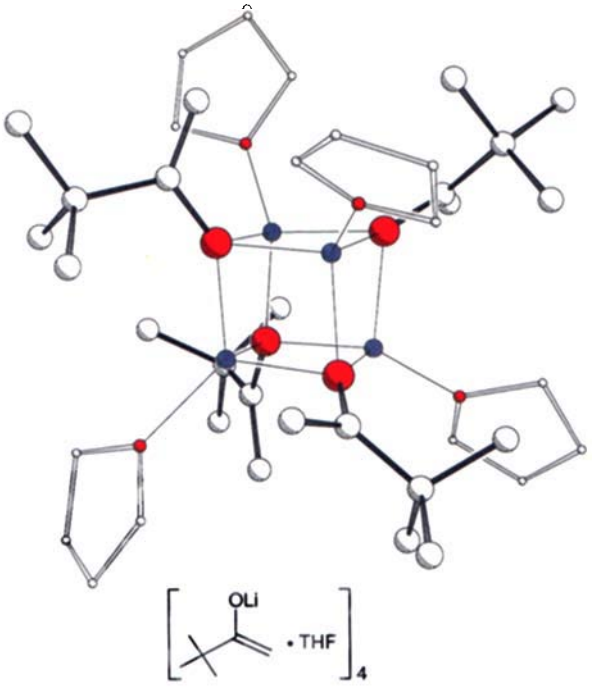


Fig. 2. Tetrameric Li enolate of pinacolone, crystallized from tetrahydrofuran. An almost perfect cube of four Li and four O atoms is surrounded by a "shell" of organic units—the enolate carbon skeleton and the THF molecules. The Li atoms are each surrounded by three enolate oxygens and one THF oxygen, so that a distorted tetrahedral coordination sphere results [68] (*CSD*: BEDYOY). The structure of the analogously arranged cyclopentanone-derived Li enolate is described in the same publication [68]; the corresponding coordinates are deposited under the *CSD* code BEDYUE.

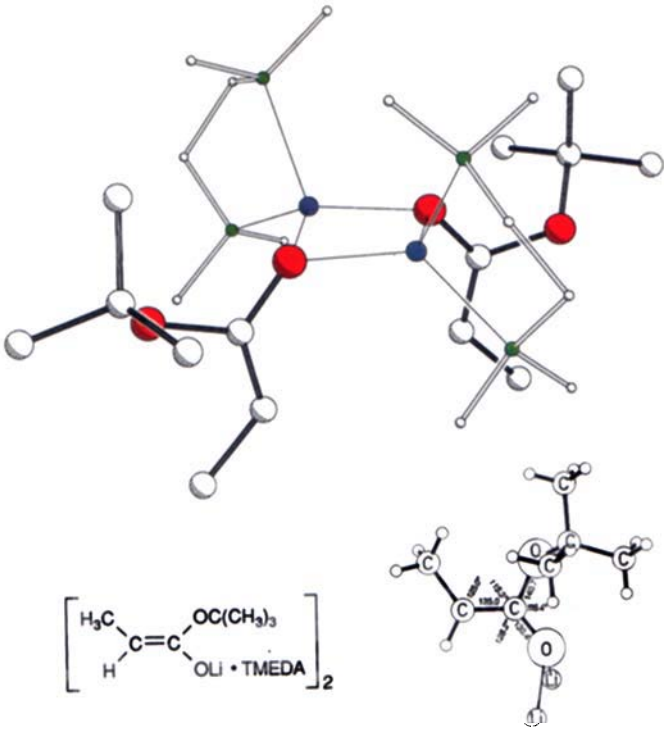


Fig. 4. Dimeric lithium (*Z*)-enolate of *tert*-butyl propionate, crystallized in the presence of TMEDA. The two enolate units are *cis* to each other on the LiOLiO four-membered ring through the center of which runs a C_2 axis of the dimeric aggregate. Even in the crystal, the ester enolate is unstable above −30°C. Its decomposition to a ketene [72, 73] and lithium *tert*-butoxide is perhaps indicated by the different C–O bond lengths (141 vs. 130 pm) and C=C–O bond angles (ca. 115 vs. 128°) at the trigonal O-substituted center of the double bond [73]. The *tert*-butyl group stands nearly perpendicular to the enolate plane (*CSD*: DEDXEP).

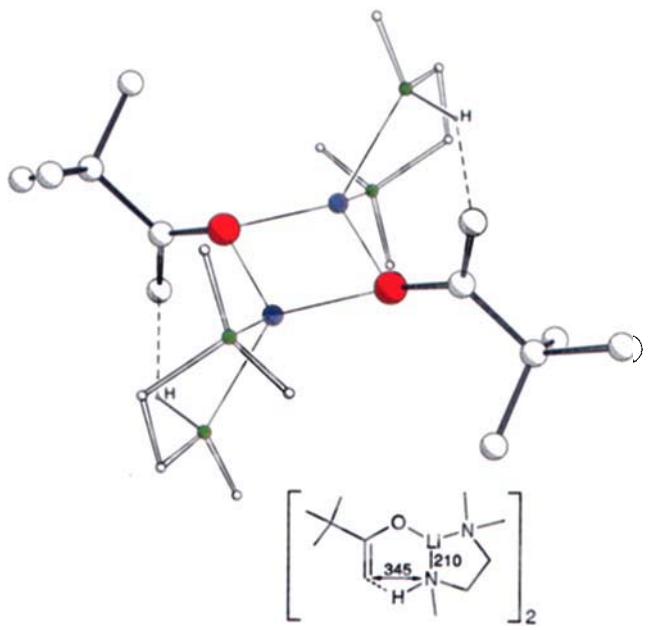


Fig. 3. Dimeric Li enolate of pinacolone crystallized in the presence of TriMEDA [66]. The nitrogens of the bidentate chelate ligand and two enolate oxygen atoms form a pseudo-tetrahedral arrangement around the Li atom. The distance between the NH hydrogen of the secondary amino group and the terminal C atom of the enolate double bond amounts to ca. 260 pm. The plane in which the atoms H···C=C lie forms an angle of ca. 60°C with that of the double bond. In the center of the LiOLiO quadrangle, there is a center of symmetry (*CSD*: DETRAV) [66], i.e., the enolate units are *trans* to each other (like the TriMEDA complex in Fig. 5 and the dienolate in Fig. 8, but unlike the dimers "solvated" with TMEDA or THF in Figs. 4 and 6).

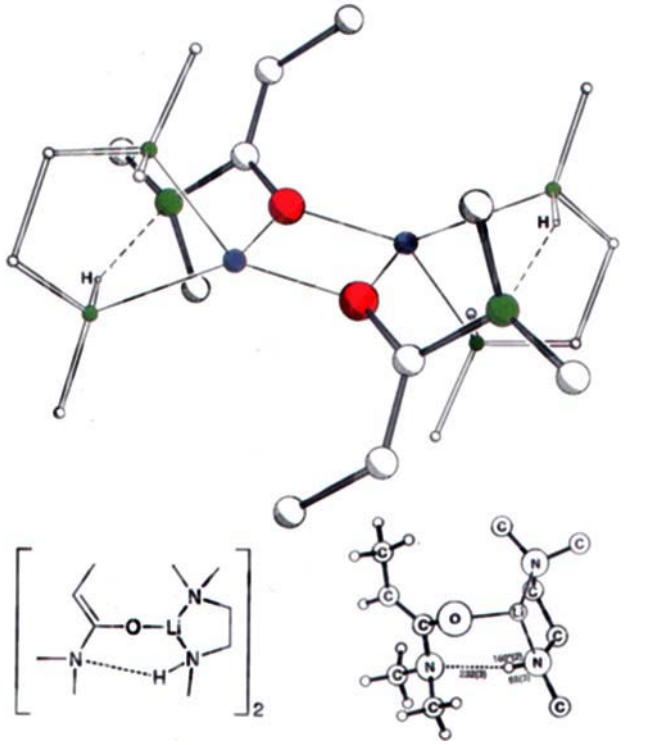


Fig. 5. *N,N*-Dimethylpropionamide lithium (*Z*)-enolate dimer, crystallized with TriMEDA. The center of the LiOLiO quadrangle is a center of inversion in the aggregate. The dimethylamino group of the enolate is like that in enamines [74], but much more strongly pyramidalized; the H atom of the secondary amino group lies in the direction of the virtual electron pair on this enamine nitrogen (lengths of hydrogen bonds, see [75, 76]) (*CSD*: DETPUN) [66].

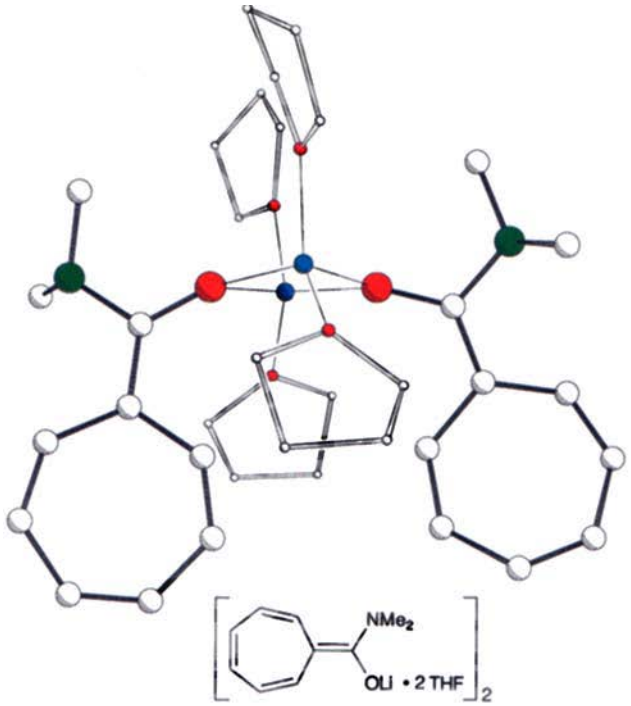


Fig. 6. Dimeric lithium enolate of *N,N*-dimethylcycloheptatrienecarboxamide, crystallized from THF [77]. As in the dimeric Li enolates of esters (Fig. 4), the enolate units are *cis* to each other at the LiOLiO quadrangle (with a C_2 axis through the ring center). THF molecules occupy quasi-axial and quasi-equatorial positions at the Li atoms of the folded four-membered ring (puckering angle between OLiO planes 68.6°, between the LiOLi planes 47.3°). The extended π systems do not participate in the complexation of the Li atoms. The Me_2N groups are turned out of the π plane, and the nitrogen is pyramidal ($\Delta = 36.5$ pm) as in the propionamide enolate of Fig. 5.

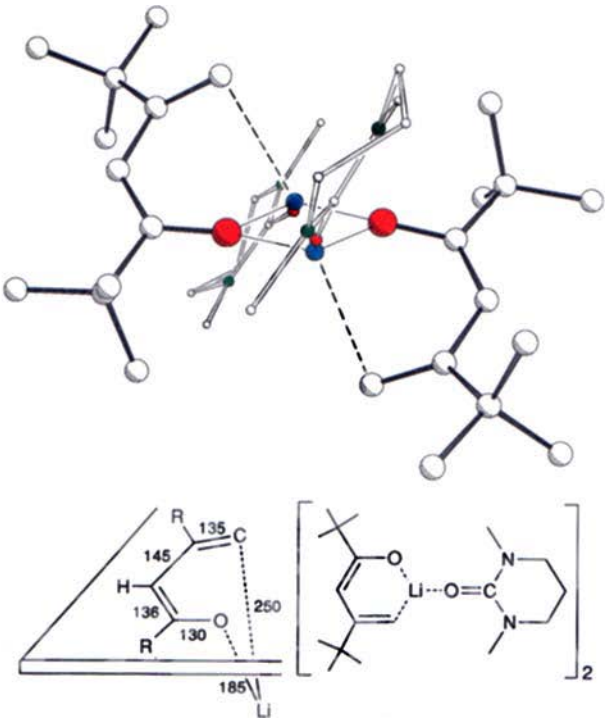


Fig. 8. Dimeric lithium (*Z*)-dienolate of 2,2,5,6,6-pentamethylhept-4-en-3-one (the product of aldol condensation between two pinacolone molecules), crystallized in the presence of DMPU [79]. The carbonyl oxygens of the cyclic urea and the terminal C atom of the dienolate (LiC bond distance 250 pm; cf. that in trityllithium, 223 pm [80]), as well as two oxygen atoms of the LiOLiO ring, surround the Li atom in the centrosymmetric dimeric aggregate (*CSD*: DIXWIQ).

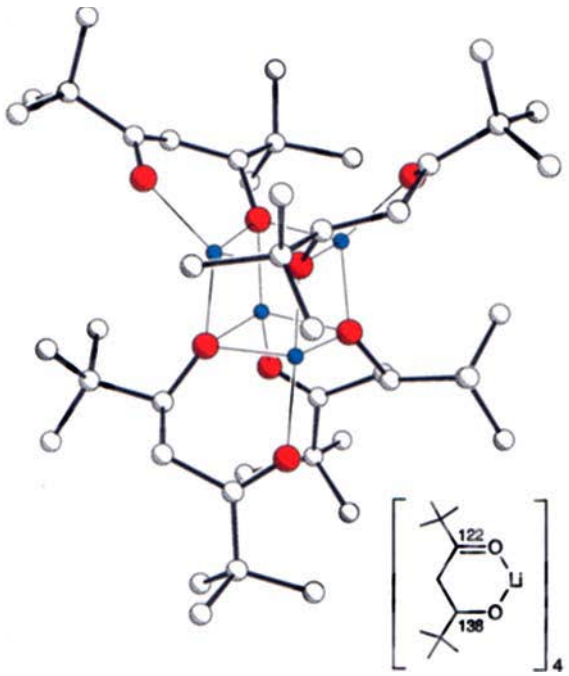


Fig. 7. Tetrameric aggregate of the Li aldolate from pinacolone and pivalaldehyde [78]. The negatively charged alkoxide oxygens and four Li atoms form a distorted cube (LiO distances 191–195 pm). The carbonyl oxygens of the aldolates are bonded to the Li atoms from outside (LiO distance 197 pm), as in other cases with the oxygen atoms of the solvent or nitrogen atoms of the ethylenediamine unit. In this arrangement, four "external" six-membered rings are formed, fused to alternating edges of the cube. The tetramer crystallized from pentane (*CSD*: DEWBIQ).

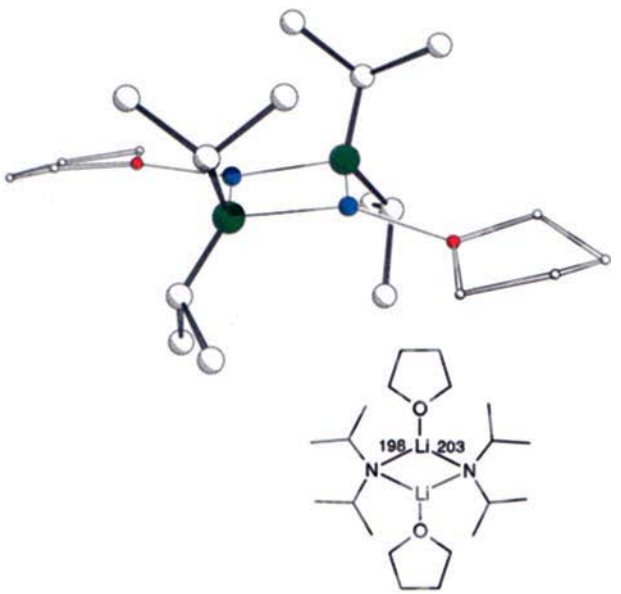
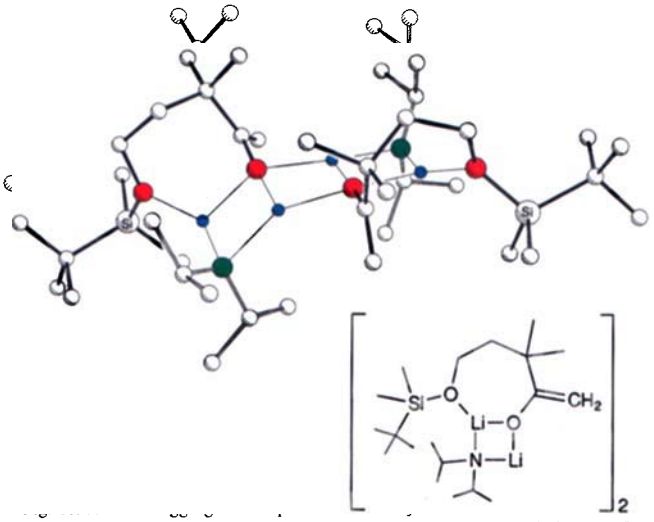


Fig. 9. Dimeric lithium diisopropylamide, obtained from THF [$(LDA)_2 \cdot (THF)_2$] [81]. The methyl groups of the isopropyl units point inwards, i.e., towards the LiNLiN four-membered ring. The Li atoms are each threefold coordinated as in other lithium amides (steric hindrance?). Additional $LiNR_2$ structures (monomer, four-membered ring dimer, six-membered ring trimer, and eight-membered ring tetramer) are shown in a review article on Li structures [47]; among these are also found lithium tetramethylpiperidide and hexamethyldisilazanide. (For more recent structure determinations of lithium anilide derivatives, see [82–84].)



(from a methyl ketone, 5-(*tert*-butyldimethylsiloxy-3,3-dimethylpentan-2-one) and LDA. Three LiXLiY four-membered rings are fused to form a step-like structure. The siloxy oxygen serves as an "external" ligand to Li [85].

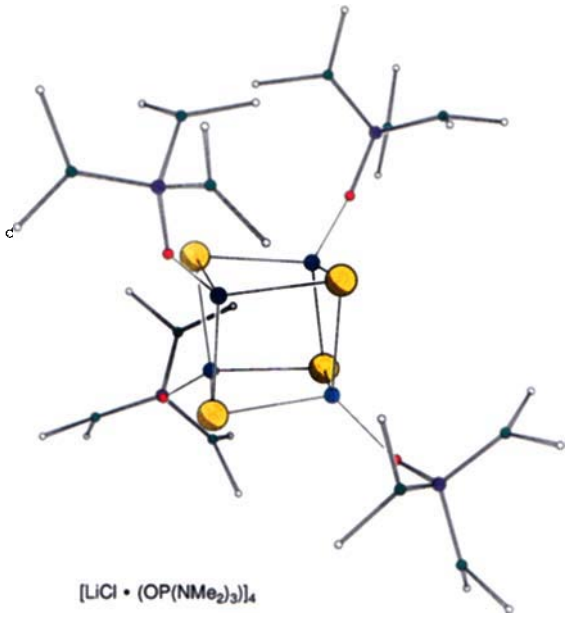
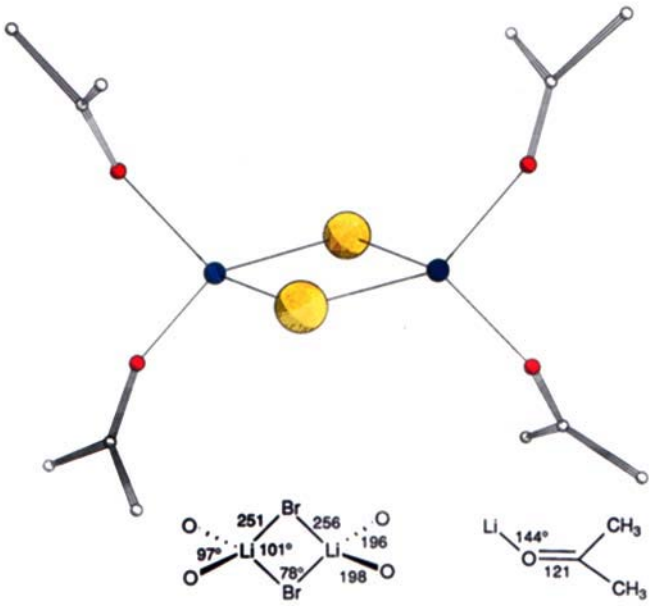


Fig. 12. Lithium chloride tetramer with four HMPT molecules, which are bonded to lithium via oxygen (from an "utterly fortuitous in situ preparation in high yield" involving $LiNCBu_2$, HMPT, $AlCl_3$ (1 : 1 : 0.3) in hexane/ether) [86] (*CSD*: CAWSIC). (For additional crystal structures with HMPT as "solvating ligand", see the review in [47], cf. also Fig. 15.)



lithium atoms form a rhombus with acute angles at the bromine atoms. As in the case of protonated carbonyl compounds, the bond angle at oxygen is less than 180° in this complex between a ketone and LiBr (*CSD*: DECXEO 01). (See also the other adducts involving alkali-metal derivatives and carbonyl compounds in Figs. 7, 8, and 16 and in Tables 1, 2, 4, and 7 as well as the discussions in [79] and in Sections 2.3, 3, and 4.)

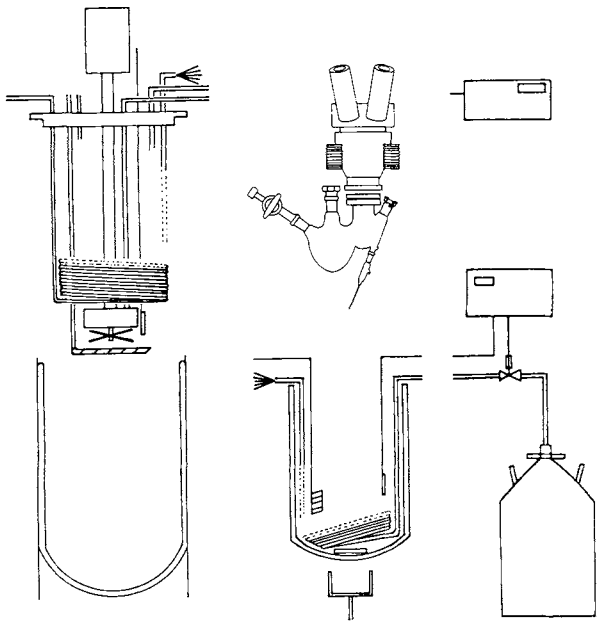
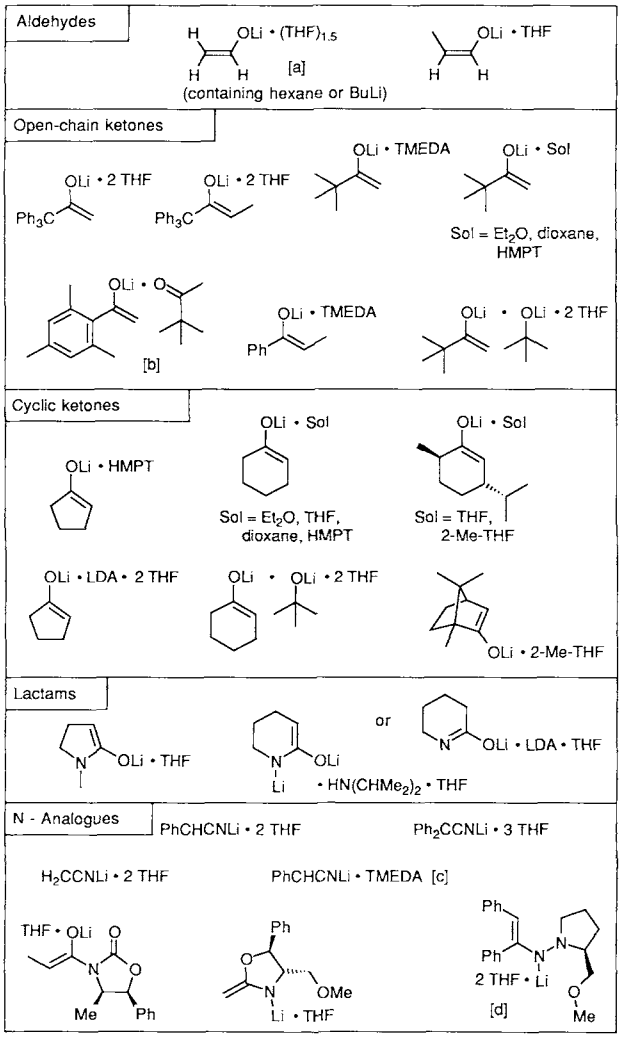


Fig. 13. Apparatus for the preparation of single crystals at low temperatures under inert atmosphere following the procedure in [67c, 73]. In this way, crystals of the ester enolates [73] (Fig. 4) and of a very unstable lithiated allyl thioether [87] were obtained; cf. also the X-ray structure analyses of aliphatic carbocation derivatives [88, 89] and the review article cited above [51].

these structures are of enormous importance for the following reasons: (1) With an accuracy provided only by X-ray crystal structure analysis, we finally have structural parameters of the reactive intermediates used in the most important CC bond-forming synthetic methods. (2) Applications of the structure-reactivity correlation principle[117–124] lead to conclusions about mechanistic details of the reactions of these species, and these conclusions become more and more reliable with an increasing number of structures. (3) The less stable these species are, the more their structures hint at their reactivity; reaction trajectories can be read from distortions of the molecules as they occur in the crystalline state.[73,87–89] (4) Finally, knowing the rich complexity of the reagents involved, we can use these structures to reconsider and discuss in a more systematic way the jumble of excellent preparative results, useful recipes, and procedures.

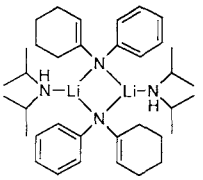
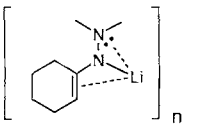
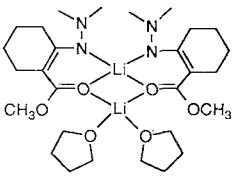
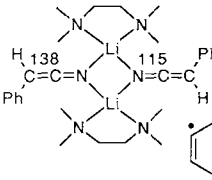
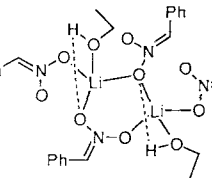
Before doing so, the results of structural investigations of Li enolates in solution will be briefly discussed.

Table 1. Composition of crystalline samples of Li enolates and nitrogen analogues. The samples were obtained in the course of attempted preparations of single crystals for X-ray structure analysis. The solvent content was determined, after drying the crystals under high vacuum, by addition of excess CD_3COOD in an NMR tube and integration of appropriate signals in the resulting spectra [91–94]; for further examples see [66].



[a] Beautiful looking crystals separated from THF to which BuLi/hexane had been added [95]. Unfortunately, the crystals are not suitable for X-ray crystal structure analysis. [b] Compare with the Na enolate solvated by pinacolone (Fig. 16). [c] In the meantime, the dimeric Li phenylacetonitrile-TMEDA complex solvated by one molecule of benzene per aggregate unit was isolated and successfully subjected to X-ray crystal structure analysis [96]. [d] For the crystal structure of the Li enehydrazide of the hydrazone obtained from 2-naphthyl methyl ketone and *N*-aminoprolinol methyl ether, see [97] (monomeric, with two THF oxygens and the oxygen of the prolinol ether unit surrounding the Li atom).

Table 2. Schematic representation of some crystal structures of N-analogues of Li enolates. The PLUTO plots of two further structures of this type are shown in Figures 14 and 15 (see also a review article [47] covering the literature up to the beginning of 1984).

	Li enamide of the product formed from cyclohexanone and aniline [102]
	Polymeric Li enehydrazide of the product formed from 1,1-dimethylhydrazine and cyclohexanone [102]
	Dimeric Li enehydrazide of the product formed from 1,1-dimethylhydrazine and 1-oxocyclohexanecarboxylate. The compound contains two "very different" Li atoms [101a] (cf. Fig. 14)
	Dimeric Li ketenimide formed from phenylacetonitrile and TMEDA. A molecule of "crystal benzene"[96, 98] is present (for "simple" Li imides see [103–105])
	Section of the polymeric structure of the Li nitronate of phenylnitromethane $[PhCH{=}NO_2Li \cdot EtOH]_n$ [106]

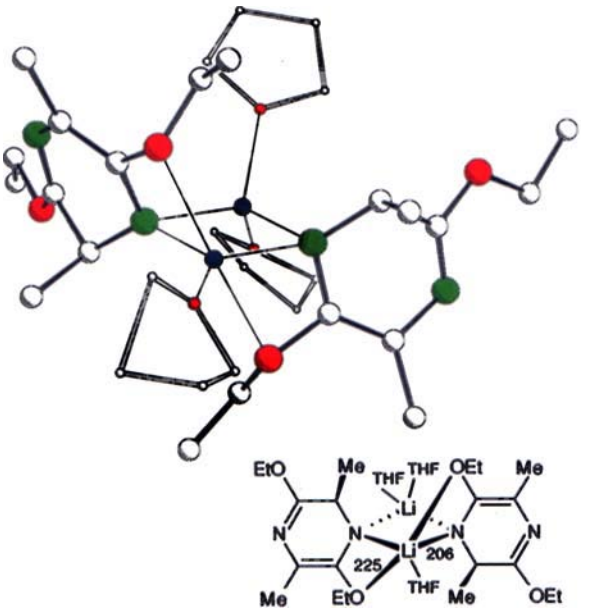


Fig. 14. Dimeric aggregate of the lithium bis-lactim ether derived from alanine [107] (*CSD*: CIFBOI). The two lithium atoms have very different environments; if the Li–Li neighborhood is not included, one Li atom is fivefold coordinated, the other fourfold. In this way, the diastereotopic faces of the dihydropyrazine ring are differentiated more strongly than by the methyl group at the stereogenic center (cf. the structure of the lithiated oxocyclohexanecarboxylic acid derivative in Table 2).

2.2. Li Enolate Structures in Solution—Not Simple Either!

2.2.1. Osmometric Measurements—Colligative Properties

From effects which ideally depend upon the number of particles per volume, the average molecular weight can be calculated, in the present case the degree of aggregation of Li enolates in solution. Ebullioscopy, vapor pressure osmometry, differential vapor pressure barometry, and cryoscopy applied to enolate solutions thus led to aggregation numbers between 1.0 and 4.0 (in certain cases several hundred), depending upon the type of enolate, the solvent,

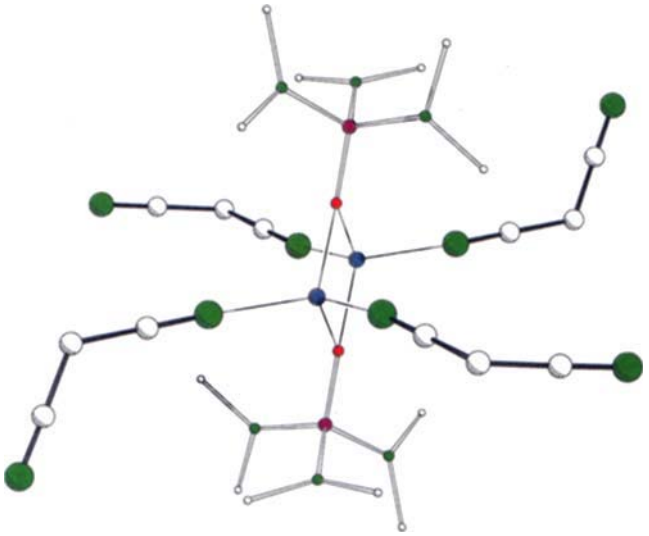


Fig. 15. Section of the polymeric structure of lithiated malononitrile $[LiCH(CN)_2 \cdot HMPT]_n$, which crystallized from a mixture of HMPT, hexane, and THF [108]. It is striking that the LiXLiX four-membered ring is not built up from the heteroatoms of the counterion (here the nitrogen) with the Li atoms, as usual, but from the oxygens of the HMPT. The nitrogen atoms of the dicyanomethanide lie "outside" of the aggregate. In the LiCl structure of Fig. 12, the HMPT oxygens are "outside". (Compare the structures in Fig. 12 and in Fig. 15 with a possible interpretation [69] of the HMPT effect on enolate reactions given in 1981, when there was no structural information about HMPT complexes. See also Scheme 9.)

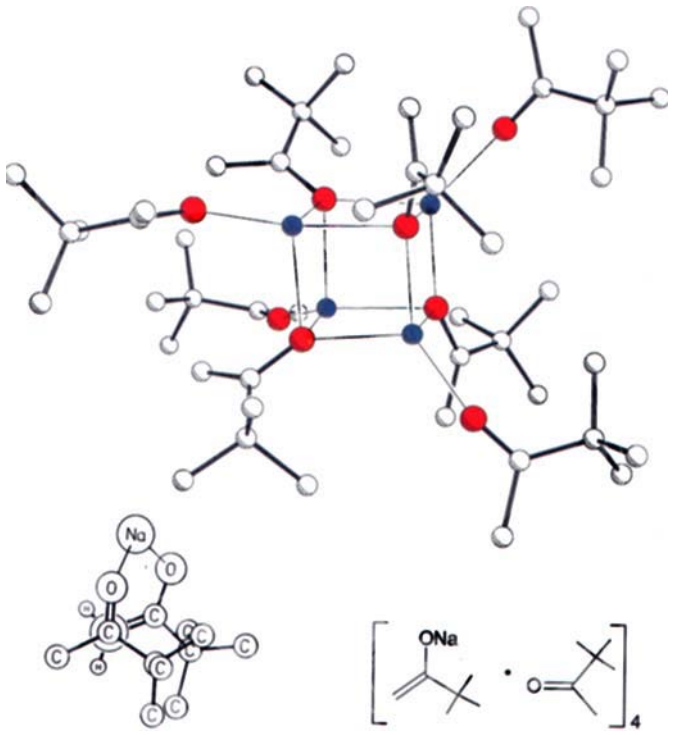


Fig. 16. Tetrameric sodium enolate of pinacolone, with pinacolone as "solvate molecule" (*CSD*: DIPSAW) [71]. A section shows that the planes of the π systems of the enolate and the ketone (bound together by the sodium) are more or less parallel, as they would have to be in a reaction between the electrophilic carbonyl carbon and the nucleophilic enolate one (separation distance 380 pm). The structure of the hexameric pinacolone K enolate solvated with THF, $[t\mathrm{BuC(OK)CH_2} \cdot \mathrm{THF}]_6$, is described in the same publication (*CSD*: DIPSEA). A complete collection of the structures of Na, K, Rb, and Cs organometallic compounds was published in 1987 [48].

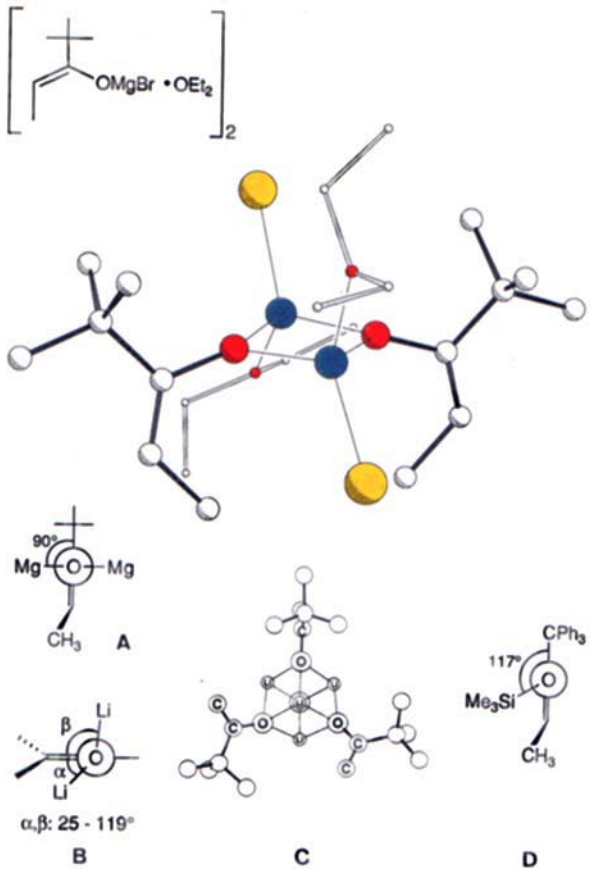


Fig. 17. Dimeric bromomagnesium (*Z*)-enolate of *tert*-butyl ethyl ketone (2,2-dimethylpentan-3-one), crystallized from diethyl ether (*CSD*: DILPUJ) [109]. The plane of the MgOMgO four-membered ring and that containing the enolate double bond are more or less perpendicular to each other (A). In the Li enolate dimers, the Li atoms lie outside the plane of the double bonds (Figs. 3-6) with very different LiOC=C torsion angles (B). In the tetramer (Fig. 2), however, a lithium atom does lie in the plane of the enolate (C). In a crystalline silyl enol ether (*CSD*: DIWXOW), the Si-O bond forms an angle of 117° with the plane of the enolate double bond [110a] (D).

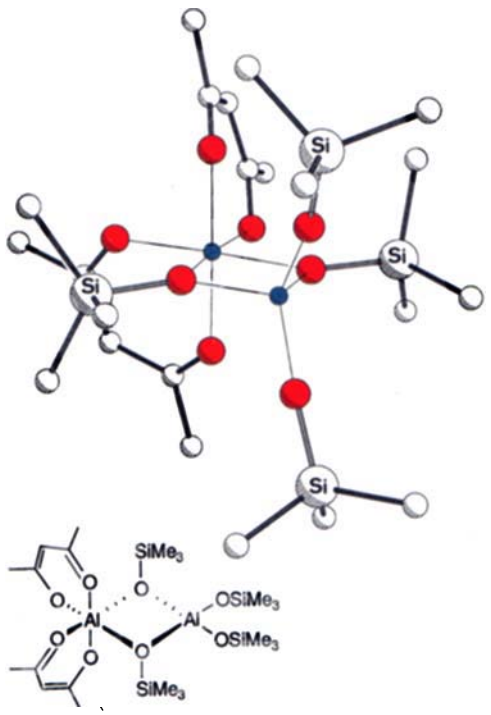


Fig. 18. Crystal structure of $[Al(OSiMe_3)_2(acac)]_2$, with two very different aluminum atoms (*CSD*: CIRMOF) [111]. In the opinion of the authors, the unexpectedly complex structure of these kinds of Al derivatives has to be borne in mind when considering their application as catalysts and as precursors of ceramic materials!

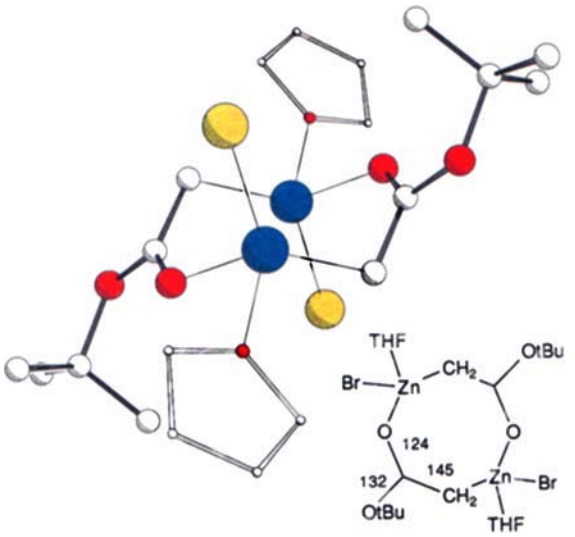


Fig. 19. Crystal structure of a Reformatsky reagent, $[BrZnCH_2COO(tBu)\cdot THF]_2$, crystallized from THF (*CSD*: BUDKAM) [112]. Two each of Zn, CH_2, C(O-*t*Bu), and O form an eight-membered ring. Each Zn bears a Br and a THF as substituents. In contrast to the alkali and Mg enolates, where the metal atoms are always bound to oxygens, the Zn atom here is simultaneously attached to the CH_2 group of one unit and the CO group of the other (see also the C-C and C-O bond lengths of the eight-membered ring). A discussion on the structures of cyclopropane and aziridine carboxylic ester enolates in which α-metallocarbonyl derivatives may also be present instead of the usual metal enolates can be found in [113, 114]. It is noteworthy that the Zn is σ-coordinated to oxygen, but π-coordinated to carbon (torsion angle Zn-O-C-O 164°, Zn-C-C-O −83°, respectively).

and the temperature.[22, 25, 27, 30, 94, 125, 126] Since many Li enolate reactions are preferentially carried out at dry-ice temperature in THF, the melting-point depressions measured[94] in this solvent (m.p. −107 °C) are especially "realistic". Of the numerous measurements only one will be referred to here: the Li enolate of cyclopentanone, which crystallizes as a tetramer from THF (see Fig. 2[68]), gives an aggregation number of 2.6–2.8 in THF solution at −107 °C, corresponding to a tetramer/dimer mixture of ca. 1:2. Vapor pressure measurements at higher temperature indicate that Li phenolates are largely tetrameric in ether solvents[127] (with polar organometallic compounds the entropy term may be such that larger aggregates—fewer solvent molecules bonded per Li—prevail at higher temperature and smaller ones at lower temperature[42c]).

2.2.2. *NMR Spectroscopy—More Detail*

By definition (*W. Wundt* and *W. Ostwald*) it is not possible to obtain information about the structure of aggregates in solution from colligative effects. Today's method of choice for studying solution structures is NMR spectroscopy. With the modern techniques (2D, 3D[128–131]) proximity between *nonbonded nuclei* (nuclear Overhauser effects) is detected, relaxation times are measured, quadrupole resonance spectra are obtained, dynamic processes are studied at very low temperatures, and the sensitivity is increased by isotopic labeling (^6Li, ^{13}C, ^{15}N, ^{17}O). All of this has provided a vast amount of detailed information about the species present in solution and the equilibria between them.[132] With *C*-metalated, "true" organolithium compounds the direct $^6Li,^{13}C$ coupling is the most valuable source of information about bonding between these two nuclei, about aggregation and the lifetime of aggregates (the multiplicity of the ^{13}C signals reveals the number of Li atoms bonded to the observed carbon[133]). Corresponding $^6Li,^{15}N$ coupling was used most recently for the determination of $LiNR_2$ aggregation in weakly polar solvents.[101b, 132b, 132c, 134, 135] There are no reports about Li,O coupling in enolates and phenolates; the investigation of Li enolates in solution by NMR spectroscopy is more difficult. So far, we owe the measurements in this area essentially to a single research group.[21, 22, 127, 136–140] From elaborate studies, especially of isobutyrophenone Li enolate and of Li phenolates, rather stable representatives of this type of species, many structural details have been deduced. Not only was the equilibrium between dimeric and tetrameric aggregates discovered, but also the presence of mixed aggregates between Li enolates or phenolates and LiBr, LiCl, and $LiClO_4$ in solution (all of this work has been carefully described; for an early review article on structure and reactivity of Li enolates see Ref. [22]). From hitherto unpublished ^1H and ^{13}C NMR measurements of the Li (*Z*)-enolate of propiophenone in THF, the following conclusions were drawn:[141] (1) There is an equilibrium between dimers and tetramers. (2) The dimer, but not the tetramer, forms a mixed aggregate with LDA. (3) Complexes between the Li enolate and diisopropylamine are formed; most likely these are more stable with the tetramer than with the dimer. (4) Addition of HMPT does not destroy the dimeric and tetrameric aggregates. (5) Mixed aggregates are formed upon addition of LiCl to the Li enolate solution. Also from NMR measurements, it is known that the parent compound, the Li enolate of acetaldehyde, is tetrameric in THF solution[142] (cf. Table 1 and Section 3), and that dimeric aggregates and mixed aggregates with LiBr exist in solutions of lithium amides.[101b, 102b, 132b, 132c, 143]

2.2.3. *ate Complexes—Also of Li Enolates?*

In the early fifties, *Wittig* interpreted the fact that organolithium compounds self-associate as arising from the formation of "autocomplexes"[144a] ("triple ions"). He ranked the dimeric phenyllithium in ether as $[Ph_2Li]Li$ in a series with the complexes $[Ph_3Be]Li$ and $[Ph_4B]Li$. Subsequently, such species were called *ate* complexes,[144b] by analogy with *onium* salts (cf. $[Me_4N]Cl$). When the first X-ray crystal structure analyses of Li,C and Li,O compounds appeared, it was realized that ate complexes form especially in those cases in which different metal cations or different anions are involved. In both the crystal[145, 146] (Fig. 20) and in solution[21] organolithium compounds with lithium halides were shown to be present as mixed aggregates rather than ate complexes, the formation of the latter being accompanied by charge separation.[150] Under these circumstances it is questionable whether ate complexes are present in solutions of Li enolates under the usual conditions, i.e., in nonpolar solvents and at low temperatures. Indeed, the only Li enolates for which ate complex-type structures have been detected are derived from β-dicarbonyl compounds (e.g., acetylacetone, acetoacetic esters; see the examples in Refs. [22, 47]). Some recent examples of Li ate complexes are collected in Table 3; cryptands and HMPT seem to favor their formation.

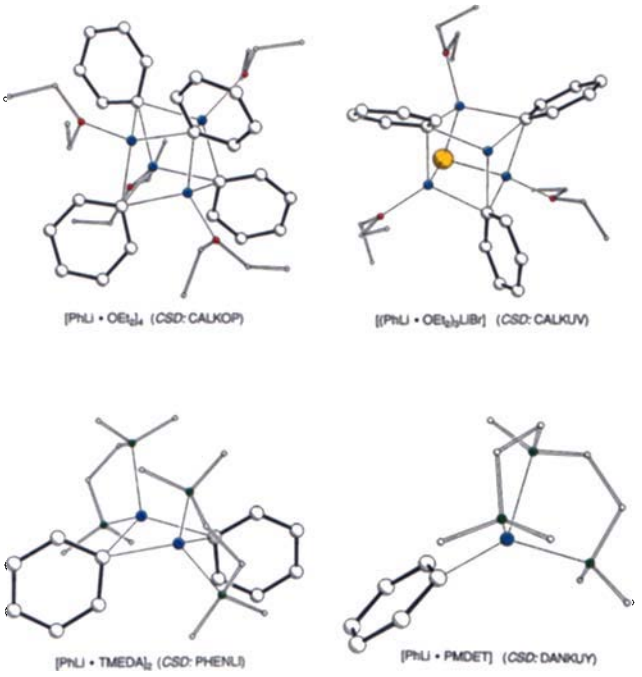
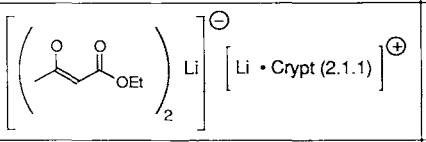
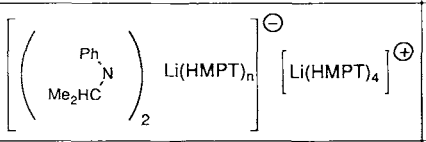
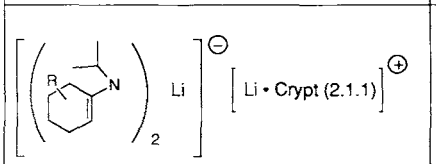
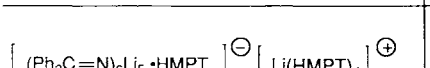
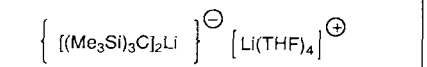
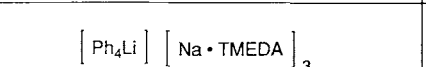
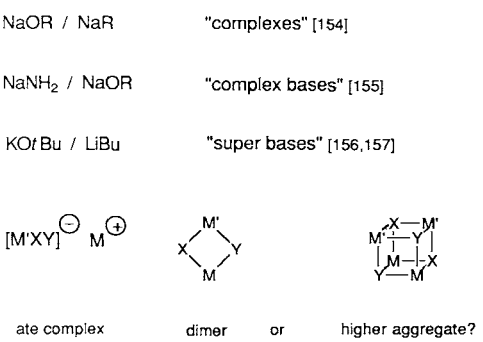


Fig. 20. Four different forms of phenyllithium in the crystalline state. From ether, a tetrameric aggregate crystallizes; in its center there are two "intertwined" tetrahedra, a larger one of four carbons and a smaller one of four lithiums [145]. In the presence of LiBr, a mixed tetrameric aggregate of three PhLi and one LiBr was crystallized from ether; three of the four Li atoms are complexed by ether oxygens, the fourth one, diagonally across the cube from the bromide, is not [145]. With TMEDA, a dimeric aggregate crystallizes [147], with PMDET a monomer was isolated [148] (for recent papers on PhLi structures in solution see Ref. [42a, 94, 149]). Until now, the "de-aggregation" of Li derivatives by addition of the tridentate PMDET has hardly been used by preparative organic chemists as a simple means of avoiding complications caused by aggregation.

Table 3. Some Li ate complexes detected in the solid state and in solution. In the examples chosen, oxygen-, nitrogen-, or carbon-centered anionic ligands are present.

Li ate complex ("triple ion")	Method	Ref.
	NMR	[151]
	NMR	[135]
	NMR	[102b]
	X-ray crystal structure	[103]
 (C-Li-C linear, C,Li: 216-220 pm)	X-ray crystal structure	[152]
	X-ray crystal structure	[153]

There are mixtures of bases (see Scheme 5) which exhibit properties drastically different from those of the components. It is not clear at this point[158] whether this is due to ate complexes or to dimeric, tetrameric, or even higher-order aggregates.



Scheme 5. Mixtures of bases may cause rate enhancements of deprotonations or eliminations in THF by several orders of magnitude as compared to the individual components.

2.3. Thermodynamic Data

Some thermodynamic data relevant to our discussion are listed in Tables 4–6. Again, many more measurements have been performed with Li,C than with Li,O derivatives.[22–53, 150] The most simple model for explaining the formation of aggregates may be to assume that it is caused by charge attraction. Lithium may be considered a small sphere of high positive charge density. In a Li enolate dimer each Li is "neutralized" by two counterions (and vice versa), and in a tetramer, by three (cf. the Madelung energy stabilization in an ionic crystal lattice). The large solvation energy of $Li^{\oplus}$ (interestingly, it is 7 kcal mol^{-1} more with NH_3 than with H_2O) is a consequence of the high charge density, and so is the exothermicity of LiX dimerization—the first step in formation of an ionic inorganic crystal lattice (Table 4).

The heats of deprotonation of carbonyl compounds by Li amides and of formation of an aldolate from Li enolate and aldehyde were measured only very recently (Table 5). The latter reaction is exothermic by 18 kcal mol^{-1} in THF and by 30 kcal mol^{-1} in cyclohexane (the calculated average bond energy change is $\Delta mBE = -19.4$ kcal mol^{-1}, i.e., the difference between a CC double and two CC single bonds).

The contributions of charge neutralization and complexation of the Li atoms by oxygens is clearly evident from these calorimetric measurements. Some of the reactions are so highly exothermic that their transition states should be more similar to the starting material than to the product (cf. the more selective deprotonations by LHMDS with the smaller heat of reaction!).

Some properties of Li enolates, such as the equilibrium ratios between regioisomers and between *E*/*Z* isomers (cf.

Table 4. Enthalpies of solvation, dimerization, and complexation of $Li^{\oplus}$ and LiX, respectively.

Gas-phase solvation enthalpies ΔH_{sol} (kcal mol^{-1}) of the lithium cation with water [159] and with ammonia [160]

$Li^{\oplus} + n\,H_2X \longrightarrow [Li{\bullet}(H_2O)_n]^{\oplus}$ or $[Li{\bullet}(NH_3)_n]^{\oplus}$

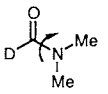
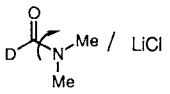
n	1	2	3	4	5	6
$\Delta H_{sol}^{H_2O}$	-34	-60	-81	-97	-111	-123
$\Delta H_{sol}^{NH_3}$	-39	-72	-93	-109	-121	-130

Gas-phase dimerization enthalpies ΔH_{dim} (kcal mol^{-1}) of lithium halides [161]

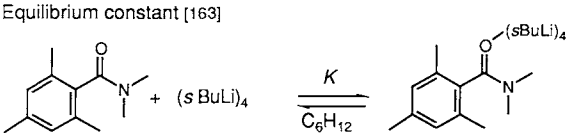
$2\,LiX \longrightarrow$ 

X	F	Cl	Br	I
ΔH_{dim}	-60	-49	-48	-43

Complexation of LiX with amides

		 / LiCl
Rotation barrier [162]		
E_a	21.6	25.0 kcal mol^{-1}
$\Delta G^{\neq}$	21.2	21.8 kcal mol^{-1}
$\Delta S^{\neq}$	-1.0	+5.8 cal K^{-1} mol^{-1}

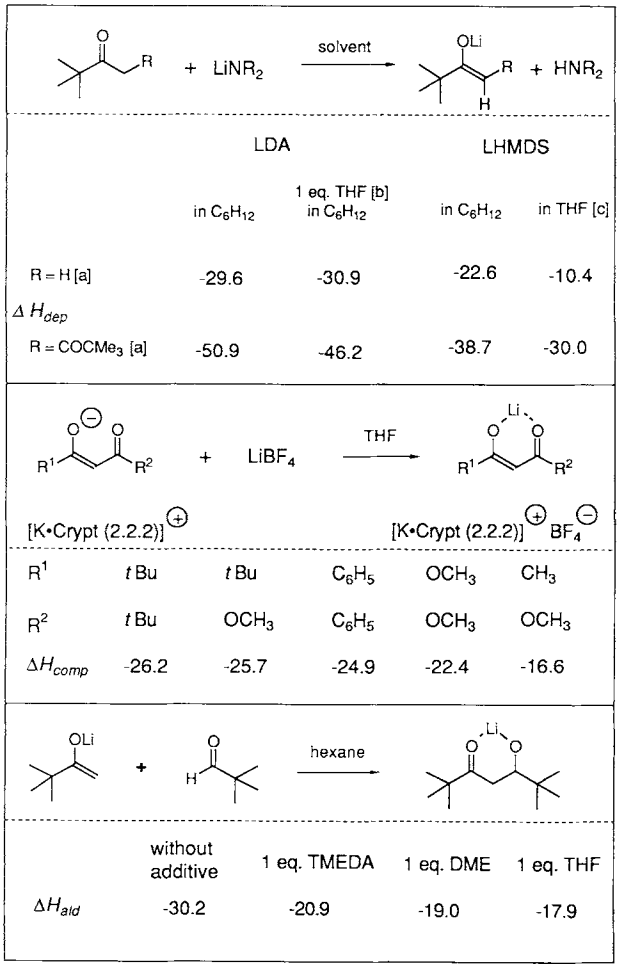
Equilibrium constant [163]



$K = 300 \pm 50$ (25°C)

the correlation between enolate and product configuration in aldol and other addition reactions[5-10,72a,173,174]), are collected in Table 6.

Table 5. Calorimetric determination of the different steps of the aldol reaction of Li enolates at 25°C by *Arnett* et al. [164]. All the ΔH values are given in kcal mol^{-1} (compare with the structures in Figs. 3, 5, 7, 8, 11, and 16). ΔH_{dep}, enthalpy of deprotonation; ΔH_{comp}, enthalpy of complexation; ΔH_{ald}, enthalpy of aldol addition.



	LDA		LHMDS	
	in C_6H_{12}	1 eq. THF [b] in C_6H_{12}	in C_6H_{12}	in THF [c]
R = H [a]	-29.6	-30.9	-22.6	-10.4
ΔH_{dep}				
R = $COCMe_3$ [a]	-50.9	-46.2	-38.7	-30.0

[K•Crypt (2.2.2)]$^{\oplus}$ [K•Crypt (2.2.2)]$^{\oplus}$ $BF_4^{\ominus}$

R^1	*t*Bu	*t*Bu	C_6H_5	OCH_3	CH_3
R^2	*t*Bu	OCH_3	C_6H_5	OCH_3	OCH_3
ΔH_{comp}	-26.2	-25.7	-24.9	-22.4	-16.6

	without additive	1 eq. TMEDA	1 eq. DME	1 eq. THF
ΔH_{ald}	-30.2	-20.9	-19.0	-17.9

[a] pK_a (DMSO scale [165]) of pinacolone, 27.7; of dipivaloylmethane, 15.4. [b] Other ketones and 1,3-dicarbonyl compounds give similar values under the same conditions: cyclohexanone, −34.9; dimethyl malonate, −52.5 kcal mol^{-1}. [c] Under these conditions, enthalpies for the deprotonation (ΔH_{dep} of phenylethanol [$PhCH(OH)CH_3$] and of ephedrine derivatives [$PhCH(OH)CH(CH_3)NR_2$] are between −18.7 and −20.6 kcal mol^{-1}, thus, there is no indication of (OLi···N) chelation (see, however, Refs. [166-169]).

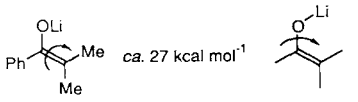
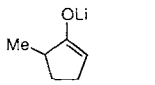
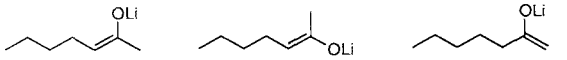
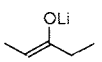
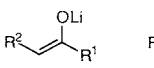
3. Computational Studies of Formation and Reactions of Li Enolates—Contributions from Force-Field Calculations and Quantum Mechanics

In view of the availability of more and more powerful (super) computers, and of ab-initio[175] and force-field programs with an increasing number of improved parameters,[176] it is not surprising to see that almost all of the renowned research groups in this area of theoretical chemistry have contributed calculations of ground-state and transition-state geometries of Li and other polar metal enolates and of their reactions. It is impossible to do justice to this work in these pages and it is hoped that the accompanying Tables 7 and 8 and Figure 21 may suffice for the presentation of some of the results.

The examples in Table 7 and Figure 21 show that very large supramolecular structures have become subject to computational studies. These confirm the decisive role of solvation in the structures of polar Li derivatives; reasonable results, i.e., compatibility with experimental parameters, are frequently not obtained unless Li is given a solvent shell or is "removed" from an intramolecular chelating heteroatom by fixing the geometry otherwise (see the Li dienolate and the dioxanone Li enolate in entries 4 and 5, respectively, of Table 7). Table 8 contains the results of modeling, MNDO, and ab-initio calculations of reaction coordinates involving enolates. The layman certainly has cause to marvel at the ability of theory to reach conclusions about the structures of extremely complex arrangements of atoms, including those of higher periods such as zinc.

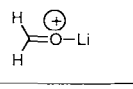
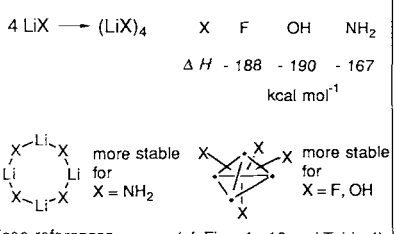
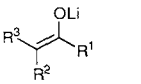
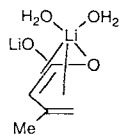
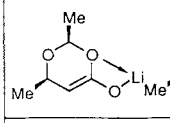
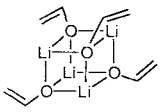
With the calculations, we have gone on to the gas phase in which minimum-energy structures may deviate from those in solution even more noticeably than in the crystalline state. It is evident that computations have become so

Table 6. Rotational barriers in Li enolates and relative stabilities of isomeric Li enolates as determined by equilibrium studies under various conditions.

Rotational barriers	Determined by NMR spectroscopy
	*ca.* 27 kcal mol^{-1}
	1.6 kcal mol^{-1} [136,142]
Equilibria	Ph_3CLi as base / excess ketone DME as solvent at room temperature [2, 170,171]
	94 : 6
	65 : 22 : 13
	$LiNR_2$ in THF at 0°C various secondary amines with / without addition of HMPT / TMEDA [64]
84 : 16 bis 94 : 6	
	Equilibrations with cat. PhHgCl at 25°C in THF [172]

Z					
E					
R^1	Me	Me	*t* Bu	H	H
R^2	Me	*t* Bu	Me	Me	*t* Bu
Z/E	82 : 18	20 : 80	99.8 : 0.2	65 : 35	3.5 : 96.5

Table 7. Calculations on complexation and aggregation of LiX derivatives and on the structures of Li enolates.

Calculated structure, remarks, and references to the experimental results	Method (basis set)	Ref.
 Linear structure most stable (cf. Figs. 7, 8, 11,16)	3 - 21G 6 - 31G*	[177a]
 (see references in Fig. 9) (cf. Figs. 1 - 12 and Table 4)	6 - 31G + sp + d // 3 -21G	[177b]
 Force-field parameters for Li enolates [a]	MM2	[172]
 Calculation and comparison with NMR data (cf. Fig. 8) [b]	STO - 3G	[178] [179]
 Pyramidalization and reactivity (cf. Figs. 4 and 17)	3 -21G	[182]
 Modeling and ab initio calculation (cf. also Figs. 2 and 21)	Modeling 3 - 21G	[183] [184]

[a] From isomerization equilibria and crystal structure data. [b] Compare also with 3-21+G, 4-31G and 6-31+G* calculations of lithiated acetaldoxime [180], of *E/Z*-isomeric enamide, enehydrazide, and oximate anions [181], and of lithiated thioallyl ethers [87].

powerful that solvent molecules can also be included. It is to be expected that discrepancies between calculated and observed values will eventually vanish. So far, theory has reproduced experimental results in this area. As far as I know, there is no instance of an organometallic reaction mechanism being put forward solely on the basis of calculation which was not first proposed, prior to calculation, on grounds of structural investigations in the solid or liquid phase,[199] or on the basis of preparative results, or of chemical intuition.

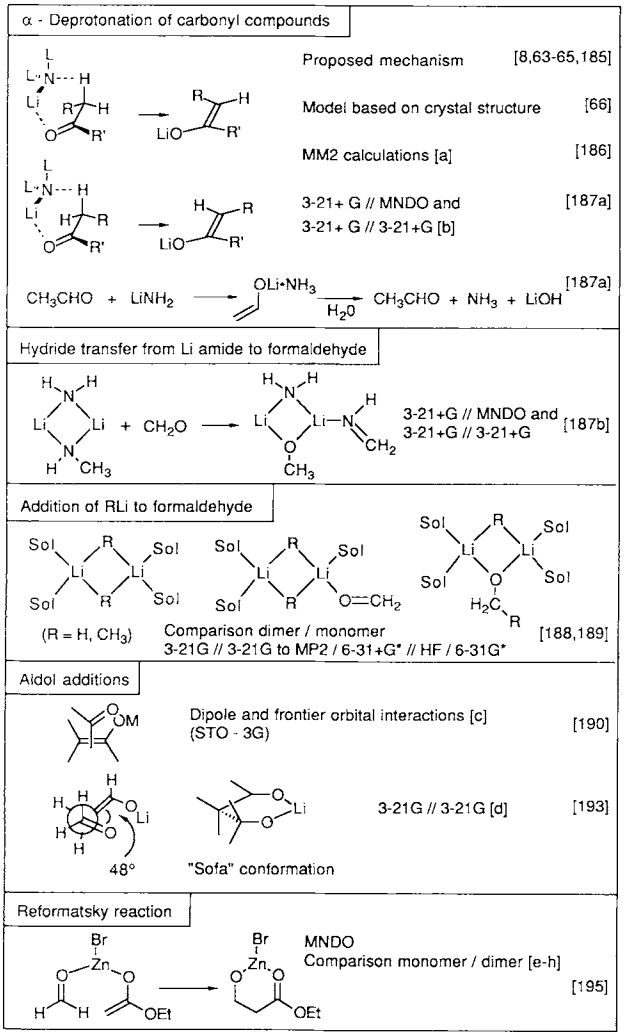
4. Reactions of Li Enolates—Supramolecules as Product-Forming Species

The behavior and properties of any organized system arise not only from its parts but also from the manner in which they are arranged.[200]

The fact that Li enolates are found to be more or less aggregated in solution and crystals does not, of course, tell us anything about the actual reactive species, at this point. As with Li,C derivatives,[24,25] it is not at all easy to furnish proof for the participation of aggregates in product-forming steps. Elaborate kinetic measurements of fast reactions of air-sensitive compounds at low temperature are necessary. NMR spectroscopy is the method of choice, and it was used early on, in a masterly manner,[21,137,138,201] to demonstrate that Li enolate aggregates *may* be directly involved in reactions, rather than being the pre-equilibrium precursors of monomeric reactants: the degree of aggregation and the presence of Li salts were clearly correlated with ratios of isomeric products formed (e.g., *C*- vs. *O*-alkylation of Li enolates[21,137,138]), the conclusion being that "ion-pair aggregates are the true reactants".[137] Dimeric aggregates turn out to be more reactive than tetrameric ones, according to these measurements.[138]

A new dimension of mechanistic details was made accessible by a new NMR technique, the method of rapid injection (RINMR):[202,203] reactants are quickly mixed in an NMR tube—also possible at very low temperatures—and the first spectrum can be taken after a few milliseconds.[204-206] This allows one to see different species, as well as transient ones, disappearing and appearing in the reaction mixture. Thereby, it was found[141] that the reac-

Table 8. Calculations on various nucleophilic additions to carbonyl groups, including the aldol addition of Li enolates and the Reformatsky reaction.



[a] Calculations without consideration of experimental results. [b] The protonation of the enolate-ammonia complex was also calculated (cf. the discussion in Section 3.1 (R_2NH effect)). [c] Compare the model of "unsuccessful cycloaddition" [191], earlier comments on the significance of HOMO-LUMO interaction [192], the chelate model [5, 12], and the general topological rules for coupling of trigonal centers following the Bürgi–Dunitz trajectory,[13,14] see also: D. Seebach, V. Prelog, *Angew. Chem. 94* (1982) 696-702; *Angew. Chem. Int. Ed. Engl. 21* (1982) 654-660. [d] For MNDO calculations of the aldol addition of *E*/*Z*-isomeric boron enolates to aldehydes, see Ref. [194]. [e] According to this calculation, reactions starting from the dimeric Reformatsky reagent, as present in the crystal (Fig. 19), have an activation energy at least 15 kcal mol^{-1} higher than those with the monomeric reagent. [f] According to the calculation, a reaction starting from the α-Zn-ester (*C*-metalated enolate), a formal [3,1]-sigmatropic rearrangement, has a higher activation barrier (by ca. 15 kcal mol^{-1}). [g] A general comparison of aldol addition and other reactions of metal derivatives in nonpolar solvents with pericyclic processes (Woodward-Hoffmann type) is certainly apparent [102c, 195]. The present example would have to be called a [3,3]-sigmatropic rearrangement [196], a metallo-oxa-Claisen, or a metallo-dioxa-Cope reaction [197]. However, considering the involvement of strongly polar (ionic?) bonds and, more importantly, the presence of an element of the higher periods (Zn), this comparison should be regarded as a formalism. [h] According to the formalism proposed by *Baldwin* [198], a metal-atom-involving aldol addition between the two trigonal carbon atoms of the carbonyl and the enolate double bond may be regarded as an "allowed bis-(6-*endo-trig*) process". On the other hand, the 1,3-shift mentioned in footnote [f] would be a "forbidden (4-*endo-trig*) process"!

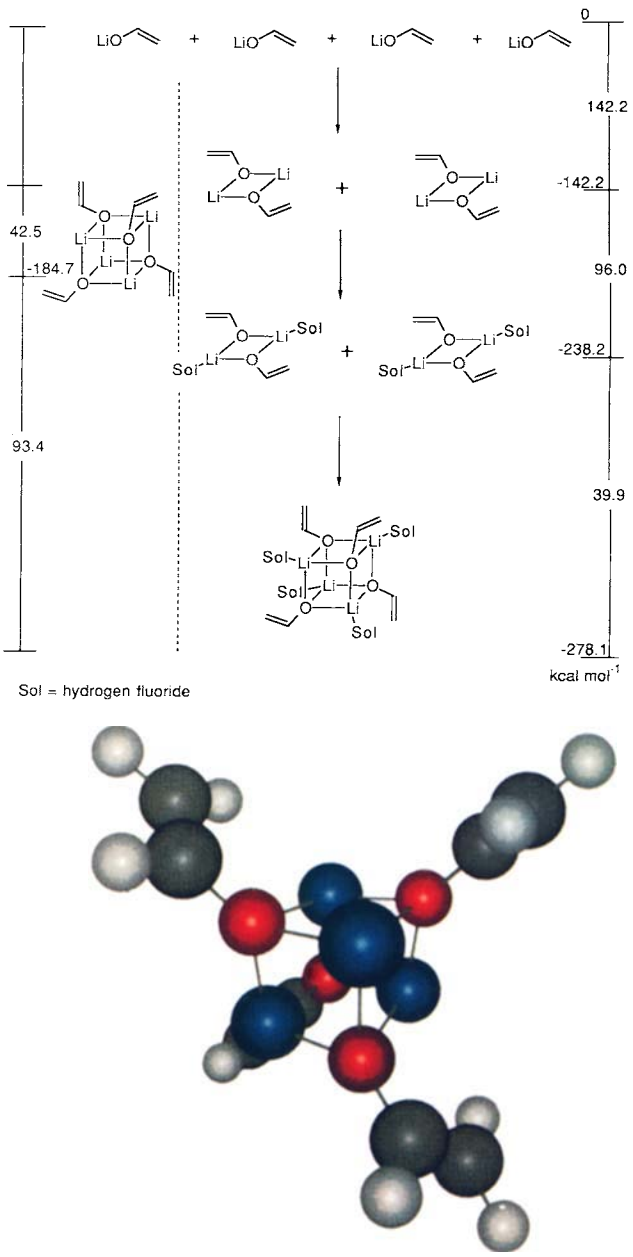
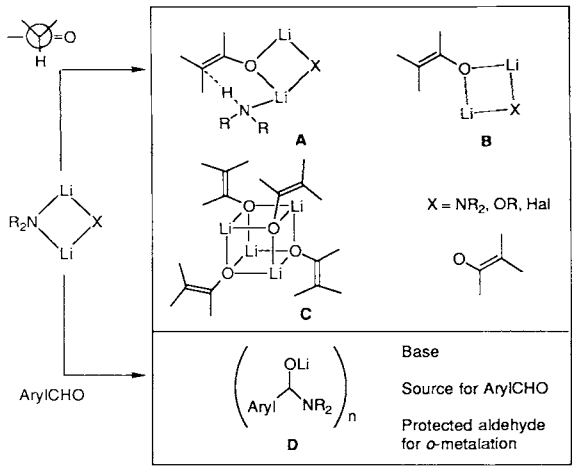


Fig. 21. Calculated (ab-initio 3-21G) aggregation and solvation enthalpies of the Li enolates of acetaldehyde (cf. Table 1) with HF as solvent molecule (Sol) [184]. According to this calculation, 33.5 kcal mol^{-1} of energy is liberated upon complexation of two additional solvent molecules to the dimer $[(EnOLi)_2Sol_2 \rightarrow (EnOLi_2) \cdot Sol_4]$ (En = CH_2=CH); therefore, without consideration of the entropy effect [42c], the difference in the stability between the dimer and the tetramer would be 27 kcal mol^{-1}, the latter being more stable. In THF, this difference is found to be significantly smaller: one often observes both species coexisting (see also Section 2.2). The color picture of the tetramer was generated from the calculated coordinates with the program *MacModel* [184].

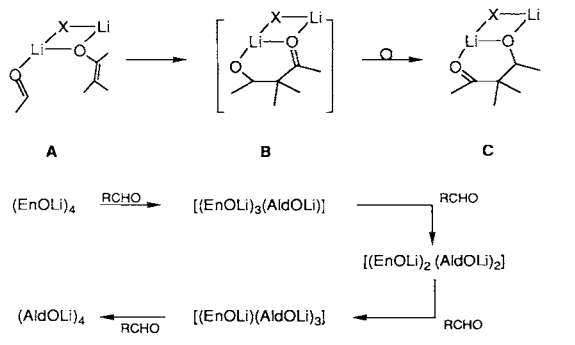
tion of a dimeric Li enolate aggregate with an added aldehyde is much faster than its regeneration from the equilibrium with the tetrameric aggregate. The higher reactivity of the dimer may be attributed to less steric hindrance and more negative charge density, the enolate moiety being "neutralized" by two, rather than three, Li counterions; a monomeric Li enolate would be expected to be even more reactive,[207] and an ate complex should exhibit further increased reactivity (enolate "neutralized" by only 1/2 Li!).[208,209]

It is much easier for the chemist dealing with synthetic and preparative aspects of Li enolate reactions to demonstrate that complex structures rather than a simple reagent

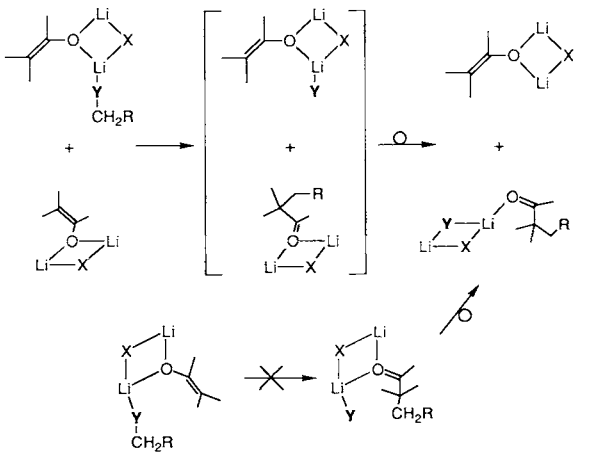
molecule *must* be responsible for an observed result. On the other hand, he or she has very little choice but to speculate exactly which species did it! Little fantasy is required to imagine what a wealth of complications can be caused by aggregations and complexations in processes as fundamental as deprotonation of a carbonyl compound (Scheme 6), aldol addition (Scheme 7), alkylation in the α-position of a carbonyl group (Scheme 8), with (Scheme 9) or without addition of a polar aprotic cosolvent.[216] An almost confusing situation results[217] in which a great variety of structurally different Li enolates of different reactivity may arise in the course of a simple transformation such as the reaction of an enolate with an electrophile[218]—a nightmare for the synthetic chemist, just like the one a crystallographer may experience, who, by pushing the wrong button, generates the chaos shown in Figure 22 instead of a beautiful three-dimensional representation of a structure. After all, it is surprising how well we fared with the simple model, how forgiving the Li enolates are! In the following sections I will describe results to show not only how we might reduce but also how we might exploit the complexity we gained. Once again, it must be emphasized



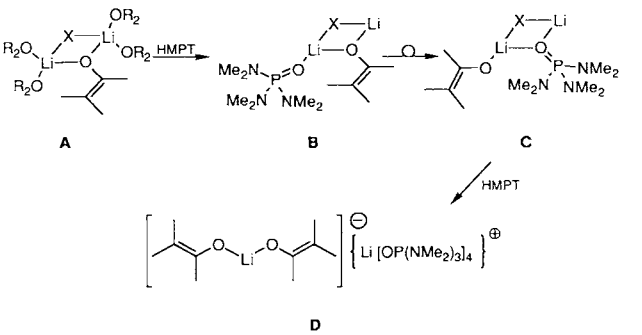
Scheme 6. Reaction of a carbonyl compound with LDA or with an LDA/Li halide or Li alkoxide mixture (cf. the structures in Figs. 2-4, 9, 10). **A**: Dimeric Li enolate or mixed aggregate complexed with a secondary amine. **B**: Pure or mixed aggregate from two LiX units. **C**: Tetrameric aggregate. **D**: Adducts of Li amides with nonenolizable, aromatic aldehydes [210-212].



Scheme 7. Possible reactions of Li enolate aggregates with an aldehyde (cf. structures in Figs. 2, 7, 16). In the process of C-C bond formation, complex **A** is converted, through adduct **B** with the negative oxygen in an "outer position", into the aldolate **C**. The reaction of a Li enolate tetramer $(EnOLi)_4$ may take place over four steps to give the aldolate tetramer! (Cf. the structure in Fig. 7.)



Scheme 8. Formulation of a reaction between two Li enolate aggregates and an alkyl halide to give an α-alkylated ketone and Li halide (cf. the structures in Figs. 11, 20). Because the alkylation of Li enolates occurs with inversion at the alkylating C atom [213], it should not be able to take place in an "intrasupramolecular" ("intraaggregate") fashion (linear S_N2 transition state!) [214].



Scheme 9. Structures that may be formed from a Li enolate by addition of HMPT with enhancement or alteration of reactivity as compared to nonpolar solvent systems. The enolate unit in **A** (enolate inside, cf. Figs. 3-6) can attain increased charge density through complexation of the Li with an HMPT oxygen (**B**), the enolate O atom being still "neutralized" by two $Li^{\oplus}$ (cf. the tetrameric LiCl with HMPT complexation in Fig. 12). Through reorganization, the HMPT oxygen may become part of the aggregate nucleus (**C**), the enolate oxygen outside being "neutralized" only by one $Li^{\oplus}$, which should increase the nucleophilicity/basicity (cf. Fig. 15). In the ate complex **D** (cf. Table 3), the enolate would be even more activated. Very much the same effects are observed with the nonmutagenic cyclic urea DMPU as with HMPT (see Fig. 8 and Ref. [63]) [215].

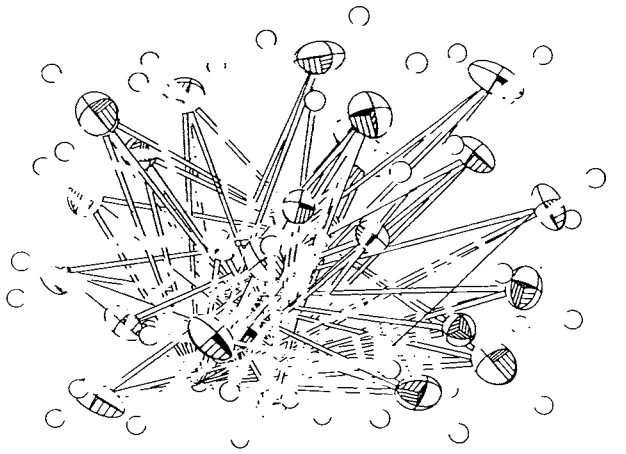
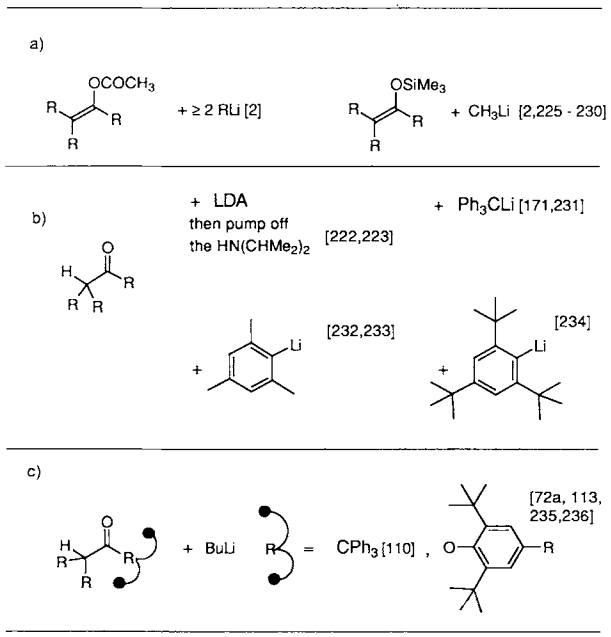


Fig. 22. Unsuccessful ORTEP plot, due to erroneous data input, of the structure of the TriMEDA-complexed amide enolate shown in Fig. 5.

that other polar organometallic compounds behave similarly, so that the discussion of Li enolates will lead to quite general conclusions.[219,220]

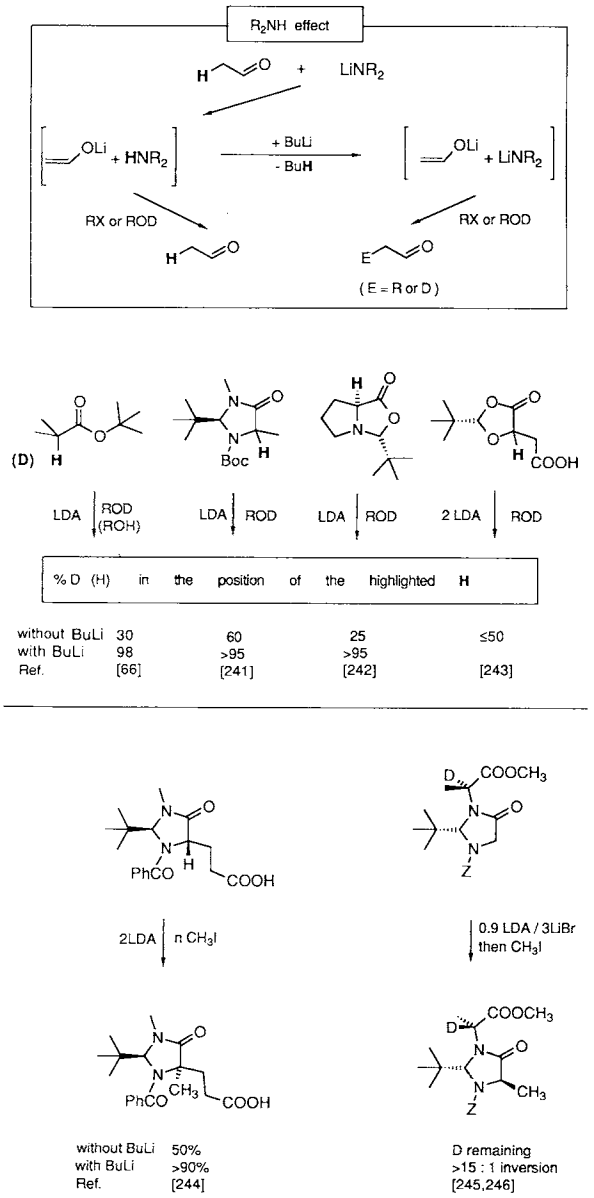
4.1. The Effect of Secondary Amines

It has been known since the beginning of the LDA era[59,221] that the secondary amine concomitantly generated with the Li enolate from a carbonyl compound and LDA *may* have an effect upon the reactivity of the enolate.[67b,222-224] In many reactions with electrophiles the amine-free Li enolate solution gives better results; examples for the generation of amine-free solutions are given in Scheme 10—note that some of these methods are "pre-LDA"!



Scheme 10. Generation of amine-free Li enolate solutions. a) From enol esters and silyl enol ethers. b) From carbonyl derivatives and LDA (pumping off the secondary amine formed), or with sterically hindered, and therefore regioselective, organolithium compounds (with formation of a hydrocarbon). c) From a compound having a sterically hindered, but electronically effective [237] carbonyl group, with butyllithium [238].

Recently, a number of cases have come to light in which totally unexpected results were obtained with Li enolate reactions in the presence of secondary amines, mostly diisopropylamine: Addition of deuterating or alkylating reagents (DX and RX, respectively) does not furnish the desired α-deuterio or α-alkyl carbonyl compound, but a more or less completely α-protonated product, i.e., starting material, and it was shown that the proton stems from the secondary amine.[239] The expected products are often isolated in high yields if butyllithium is added prior to the electrophiles. The amine as a proton source for much too weak bases was observed especially with substrates having more than one acidic proton (effect of the "hidden proton").[240] The general effect is pictured in Scheme 11, which also contains some examples from the recent literature. Obviously, the complexes that we have discovered in crystals[66] (Figs. 3, 5) are also present in solution, and are much more stable than anticipated. Under quenching conditions the "intra-supramolecular" proton transfer from the diisopropylamine to the Li enolate, which are linked together by Li-N complexation and hydrogen bonding,[247,248] competes successfully with the expected intermolecular attack of the electrophile.[249] Formally, huge isotope effects occur in such deuterolysis experiments

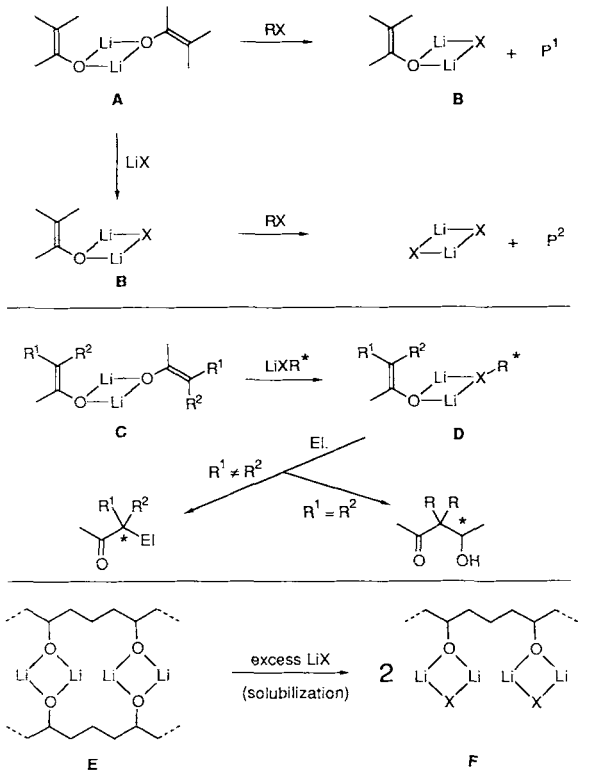


Scheme 11. Reactions of Li enolate-diisopropylamine complexes (in THF). *Top:* In the enolate-amine complex, a (partial) reprotonation occurs under the influence of the electrophile; by removal of the amine with BuLi, the yield of the desired product may be improved. *Middle:* Examples of deuterolyses; only after removal of the NH proton is a good deuterium incorporation achieved; a control experiment with the deuterated precursor and hydrolysis gives a complementary result (D replaced by H only after treatment of the enolate-DNR_2 with BuLi). *Bottom:* Examples for methylation of LDA-generated enolates with iodomethane. *Left:* Only after removal of the R_2NH proton is a high yield of the α-methylglutamic acid derivative obtained. *Right:* The deuterated imidazolidinone derived from glycylalanine is epimerized and alkylated, without loss or scrambling of deuterium over the two α-carbonyl positions, by treatment with LDA/LiBr (LDA alone does not cause a clean conversion, see Section 4.3) and CH_3I (with acetic acid instead of CH_3I as an electrophile, the starting material is recovered without loss of the D and without epimerization!).

when the Li enolate/amine solution in THF is added dropwise to a many thousandfold excess of perdeuteroacetic acid. The "internal return" of the originally removed proton is reminiscent of an effect termed *conducted-tour mechanism* coined many years ago by *Cram* to characterize the stereochemical course of certain ion-pair reactions,[250-252] and of proton-transfer mechanisms[253,254] discussed for active sites of enzymes (cf. serine proteases[255]).

Treatment of an LDA-generated enolate with BuLi is, of course, a drastic cure for removal of the villainous NH proton. Since an LDA/enolate mixture is formed, the product will be exposed to the base LDA; furthermore, an enolate results which may have quite different properties as compared to the original one, due to the presence of LDA (see Section 4.2). This is why the methods collected in Scheme 10 for the generation of amine- and amide-free Li enolate solutions should be kept in mind. To avoid many a complication, the use of sterically more hindered Li amides such as lithium *tert*-butyl(1,1,3,3-tetramethylbutyl)amide (also called LOBA ≡ *l*ithium-*tert*-*o*ctyl-*tert*-*b*utyl-*a*mide[65]) or of the less basic, but also less highly aggregated, disilazanides[256] (LHMDS, KHMDS; cf. the heats of deprotonation in Table 5), producing the poorer complexing $HN(SiMe_3)_2$ in the deprotonation step, is recommended.

The complexes of Li enolates and secondary amines dealt with here are probably also involved in some of the processes discussed in the following section, when achiral enolates are generated by chiral Li amides.



Scheme 12. Addition of LiX to an enolate solution could lead to formation of a mixed aggregate (**A** → **B**), and therefore change the product ratio P^1/P^2. A chiral additive puts an achiral enolate in a chiral environment (**C** → **D**), which may lead to the formation of enantiomerically enriched products. The LiX addition can have a solubilizing effect with a polylithiated derivative (**E** → **F**).

4.2. The LiX Effect in Li Enolate Reactions

Gedanken ohne Inhalt sind leer,
Anschauungen ohne Begriffe sind blind.[*]
Immanuel Kant

If the result of Li enolate reactions, carried out under the usual conditions in nonpolar solvents and at low temperatures, does depend upon the complex processes indicated in Schemes 6-8, then we not only need to worry about the secondary amine being a component of the mixture (Section 4.1); the formation of mixed aggregates may cause the following additional phenomena:

(1) The properties of Li amides used for deprotonations might be influenced by LiX additives, especially with more complex substrates.

(2) An enolate may exhibit different reactivity at the beginning ("pure" aggregate) and at the end ("mixed" aggregate with the LiX formed) of a reaction.

(3) The mode of addition and large excesses of one reactant in small-scale runs may strongly influence the results.

(4) LiX additives that are not part of the stoichiometric equation may decisively change the properties of an enolate.

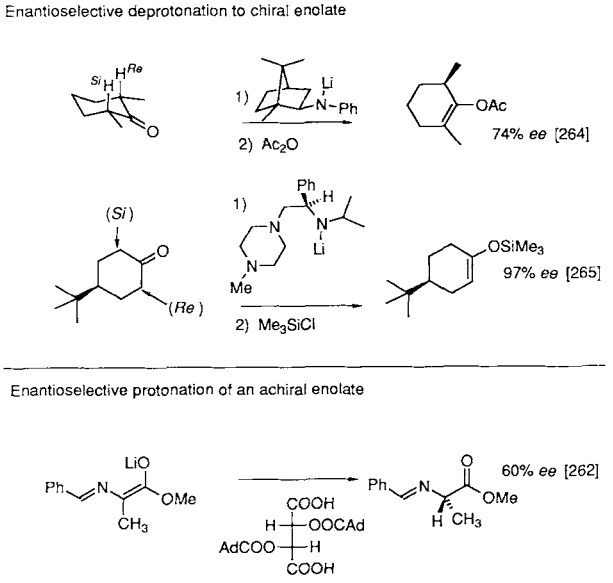
In the three parts of Scheme 12 these effects are exemplified. *Firstly*, a Li enolate dimer may be converted into a mixed dimer by addition of LiX, which is formed in alkylations by alkyl halides or sulfonates. Assuming that the dimeric enolate gives rise to one product, the mixed aggregate of Li enolate and LiX another one; in the absence of interaggregate exchange, this would lead to formation of the two products in a 1 : 1 ratio. On the other hand, addition of excess LiX could convert all of the "pure" into the "mixed" aggregate so that a single product would be formed. *Secondly*, addition of a chiral Li derivative LiXR* to the dimer of an achiral Li enolate should give a chiral mixed aggregate, the enolate component of which has diastereotopic faces or, depending upon the substitution pattern of its double bond, can differentiate enantiotopic faces of a reactant. *Thirdly* (bottom part of Scheme 12), a polylithiated, self-aggregated compound (insoluble) may be converted into a mixed aggregate with added LiX and thus be solubilized (a kind of cross-linking is disrupted).

Of course, the LiX effect as sketched here is oversimplified, perhaps in a single-minded way: especially when added in large amounts, Li halides, thiolates, alkoxides, enolates, and amides will also change the medium itself,[257] rendering it more polar ("salt effect").[150] In addition, formation of ionized species[258] (ate complexes, ion pairs) will be more likely even at low temperatures. Still, the concept of mixed-aggregate formation turned out to be extremely fruitful in the course of our own work, some of which will be outlined in the following sections.

[*] Thoughts without content are empty, intuitions without concepts blind. *Critique of Pure Reason*. Edited and translated by W. Schwarz, Scientia Verlag, Aalen 1982, p. 29.

4.3. Achiral Enolates for the Preparation of Enantiomerically Enriched Products—Making a Virtue of Necessity

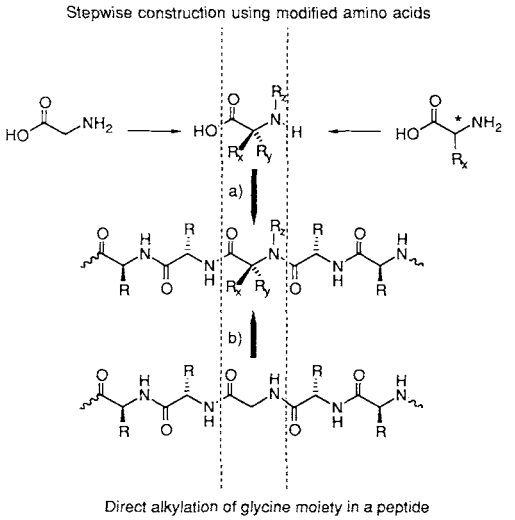
In Section 4.1, methods of avoiding the problems caused by the complexation of Li enolates with secondary amines were discussed. Here, we turn our attention to potentially very useful transformations which depend on the complexation between Li enolate and Li amide. For an enantioselective reaction, instead of coupling an enolate with a chiral auxiliary covalently, which requires a cleavage later on, the components are joined through a complexation, an interaction which is simply broken during aqueous workup! Just like in a chiral solvent,[259, 260] two achiral reactants, such as an enolate and an aldehyde, may thus be coupled to give enantiomerically enriched products (Scheme 12, middle). This procedure is fundamentally different from the use of a chiral Li amide[261] for enantioselective deprotonations or of a chiral acid for protonations[262, 263] (Scheme 13). A number of examples are collected in Table 9. As can be seen, metals other than Li can be employed. Chiral alkoxides are less effective than amides. Usually a Li enolate/$LiNR^*_2$ ratio of 1:3 gives rise to the highest enantiomer excesses.[278] Most of the chiral Li amides used are prepared from 1-phenylethyl amine or from amino acids and are thus readily available. Since there is very little structural information (Fig. 10) about complexes of Li amides with Li enolates, all attempts toward interpretations of these results are highly speculative, and we refrain from reproducing them here.



Scheme 13. Enantioselective protonations/deprotonations involving Li enolates. The chiral reagent (base or acid) selectively attacks enantiotopic groups or faces [266–268]. (With the protonations, the R_2NH effect discussed in Section 4.1 may be involved as well; with the deprotonations, the LiX effect may be operative—carefully excluded only in one case [264, 269].)

5. Alkylations of Sarcosine Units in Peptides—from Expectation to Surprise

What we learned about structure and reactivity of Li enolates was found to be successfully applicable to a seemingly unrelated project. For several years now, our group has been engaged in the development of new methods for the preparation of nonproteinogenic amino acids.[56, 100] These are required for incorporation into peptides whose biological properties are to be modified.[279] Normally, a separate synthesis is necessary for every peptide analogue [Scheme 14, route (a)]. A method by which a glycine unit in a given oligopeptide could be converted into other amino acid moieties by direct *C*-alkylation would not only be much more efficient; it would no doubt provide valuable information about the influence of chirality centers of neighboring amino acid units on the formation of a new stereogenic center in an open-chain peptide[280] [Scheme 14, route (b)].



Scheme 14. Synthesis of modified peptides. a) By stepwise construction from the appropriately modified amino acid building blocks. b) Elaboration of an amino acid by introduction of side chains; many analogous derivatives could thus be obtained from a common precursor peptide.

The notion of generating an enolate in a peptide chain seems to be absurd:

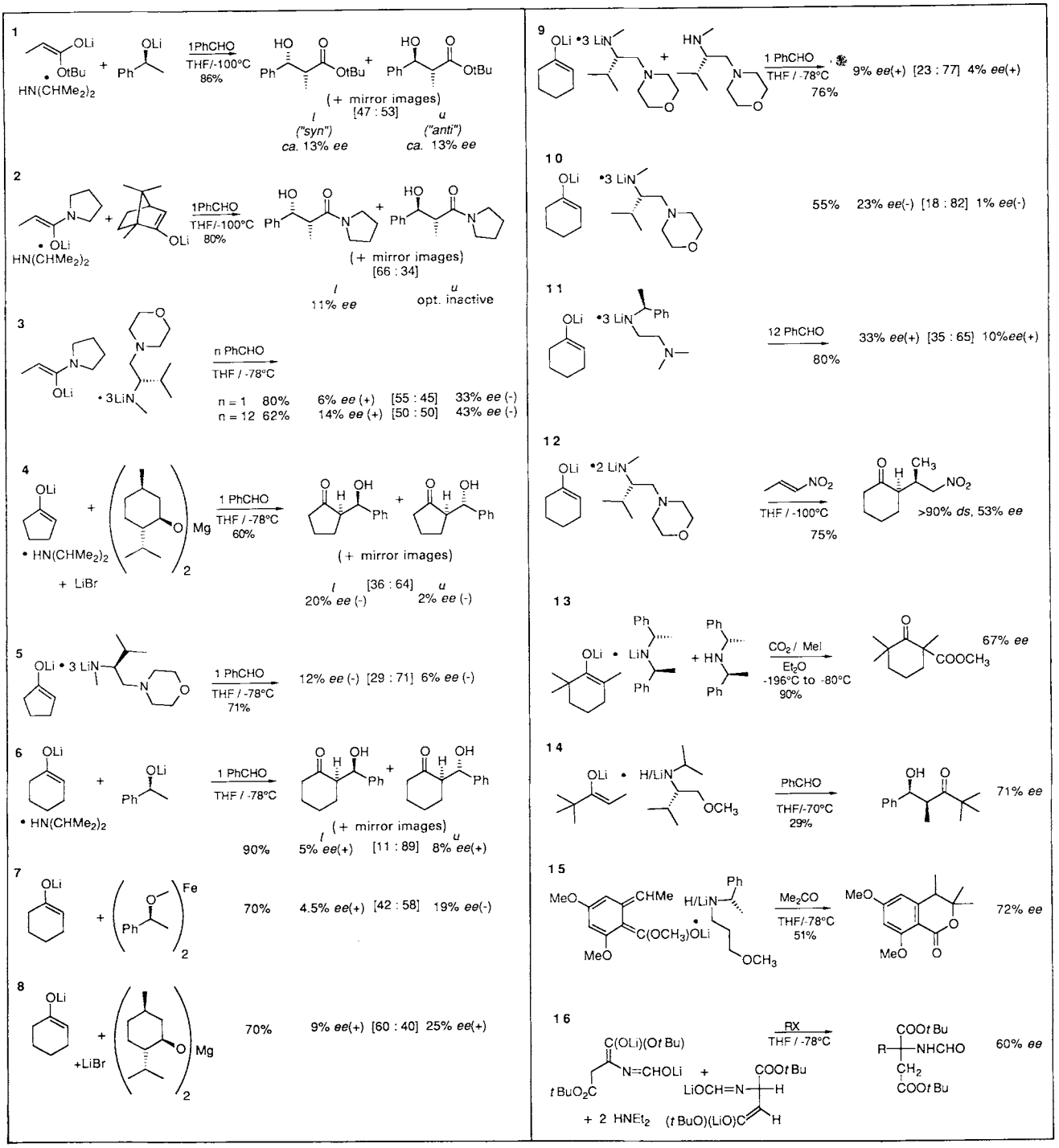
Firstly, there is an acidic amide NH hydrogen ($pK_a < 20$) per amino acid unit to be removed before the CH_2 group of a glycine moiety can be deprotonated (there are even more acidic hydrogens in side-chain functionalized amino acids).

Secondly, strongly basic conditions are bound to be applied for such a CH deprotonation under which epimerizations of stereogenic centers might occur (in an n-oligopeptide a maximum of 2^n different diastereoisomers could be formed!).

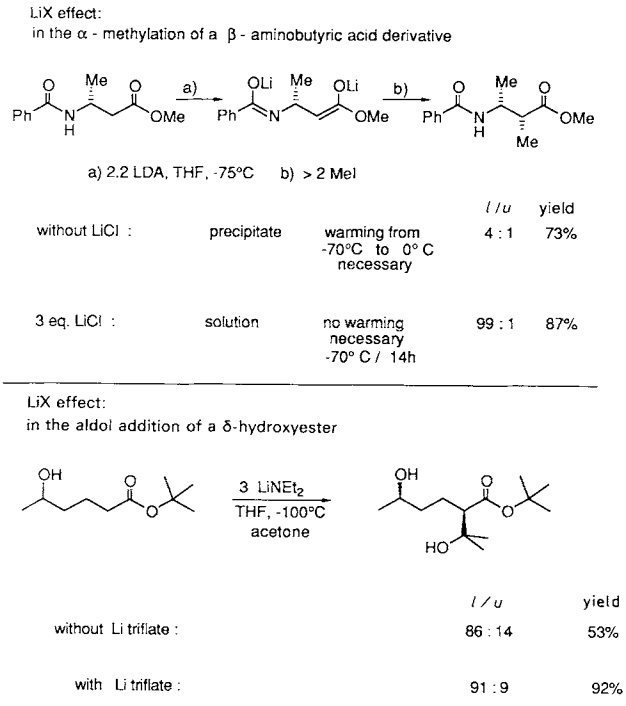
Thirdly, it is usually necessary to generate Li enolates in an aprotic medium at low temperatures, conditions in which an oligopeptide itself, and even more so a polylithiated one, might be expected to have little solubility.

At the outset of our investigations in this area, we did not entertain such reflections; rather, a gifted young chemist[281] did a bold and careful experiment with an already rather large oligopeptide. For reasons of systematization, let us start with the simple cases, reversing the order of events.

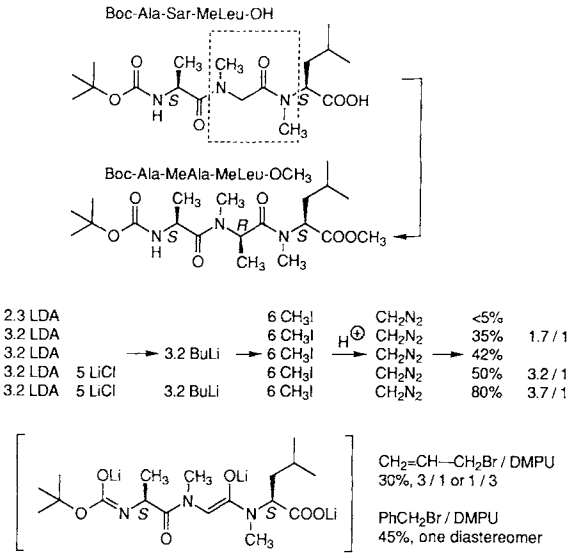
Table 9. Enantioselective aldol additions, Michael additions to a nitroolefin, carboxylation, and alkylation of achiral enolates in the presence of chiral lithium alkoxides or amides. The examples 1–12 and 16 are taken from our own work [53, 91–93, 270–273], whereas we owe the results in entries 13 [274], 14 [275], and 15 [276] to research done by others. Enolate solutions free of amine were obtained either by addition of BuLi to enolates generated with $LiNR_2^*$ or by use of the silyl enol ether/methyllithium procedure. The configurations shown and the enantiomer ratios given were determined by NMR spectroscopy or with chiral HPLC columns [277].



Two nonpeptide examples pictured in Scheme 15 may be used to demonstrate the LiX effect. The (*R*)-*N*-benzoyl-3-aminobutyrate shown in the upper part of Scheme 15 can be alkylated through a dilithium derivative in the 2-position.[41i, 282] At dry-ice temperature the reaction mixture in THF is heterogeneous; warming is necessary to complete the reaction with iodomethane. In contrast, the reaction takes place in homogeneous solution if LiCl[285] is added, with greatly improved result! Other Li salts such as LiBr, $LiClO_4$, $LiOSO_2R$ have similar effects (cf. the lower part[283] of Scheme 15).



Scheme 15. LiX effect on the generation and behavior of two dilithium derivatives [41i, 282, 283]. In the case of the *N*-benzoyl β-amino acid ester the reagent to be alkylated is rendered soluble by addition of LiCl [41i]. In both cases, yields and stereoselectivities are increased. (C=C and C=N configurations here, in Schemes 16-21, and in Fig. 24 are drawn arbitrarily! [284].)



Scheme 16. Diastereoselective alkylations of the sarcosine unit in a Boc-protected tripeptide [286]. For the allylation and benzylation reactions, the cosolvent DMPU [63] had to be added to afford the yields shown.

5.1. Open-Chain Tri-, Tetra-, and Hexapeptides

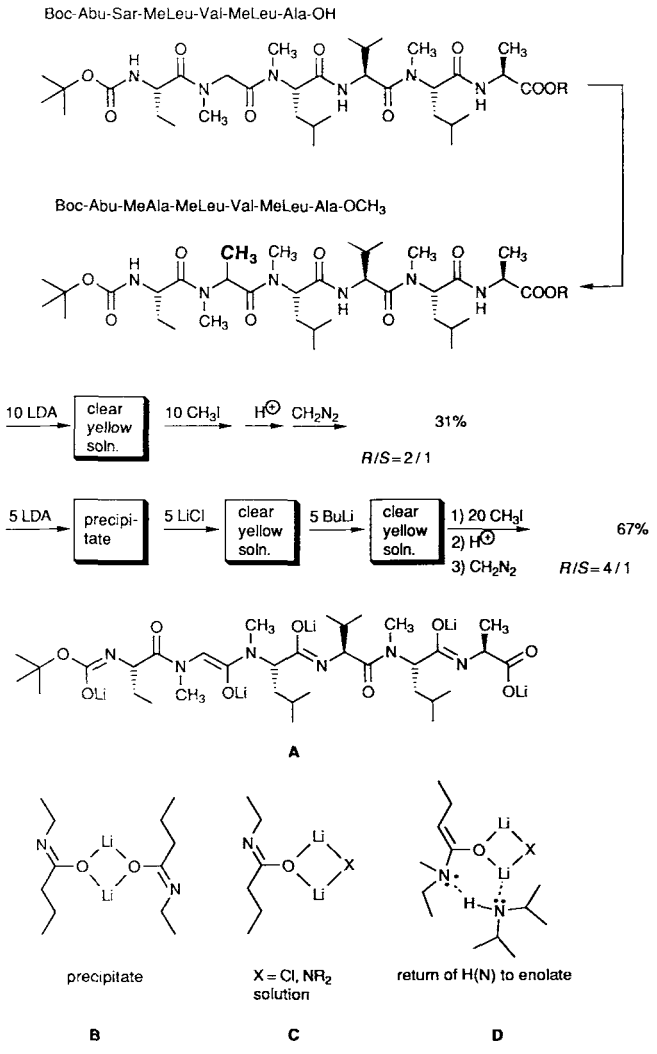
For *C*-alkylations of open-chain peptides we first chose those containing (1) a sarcosine (*N*-methylglycine) substructure (shown in Scheme 16, sarcosine = *N*-methylglycine), (2) a Boc-protected amino end group (Boc = *tert*-butoxycarbonyl), and (3) a nonprotected carboxylic acid end group. Upon mixing of such peptides with the prerequisite number of equivalents of LDA, a more or less dense precipitate is formed. An enolate at the methylglycine (sarcosine) component of the tripeptide shown in Scheme 16 must arise when slightly more than three equivalents of LDA is added, because subsequent addition of iodomethane furnishes a new tripeptide with *N*-methylalanine at the former sarcosine position.

Removal of the diisopropylamine with butyllithium (cf. Section 4.1) led to marginal improvement of the yield, but addition of LiCl *and* BuLi (after LDA deprotonation) led to the isolation of the new peptide in 80% yield. More importantly, the reaction is diastereoselective (*R*-MeAla/*S*-MeAla almost 4 : 1), and it occurs without epimerization at the two stereogenic centers which were present in the starting material! The configuration was proved by comparison with authentic samples.[286-288]

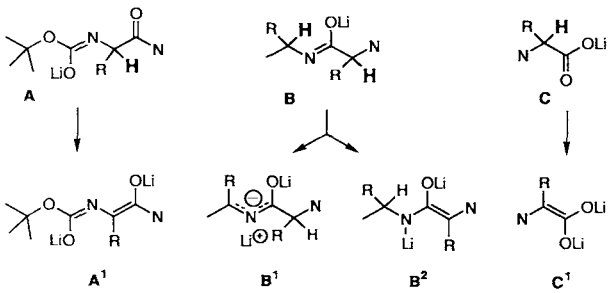
Likewise, with the hexapeptide depicted in Scheme 17, containing four acidic OH and NH hydrogens besides a sarcosine CH_2 group, a precipitate is formed upon addition of the stoichiometric amount of LDA. Twice the calculated amount of LDA[289] or LiCl[285] causes the solid to dissolve.[290] A homogeneous, nonviscous, slightly yellow THF solution results, readily stirred at dry-ice temperature, and typical of polylithiated compounds under these conditions. Methylation again produces, in yields ranging from 30 to 67%, a new *N*-methylalanine unit in the peptide chain, the yield increasing in the presence of LiCl and with diisopropylamine deprotonation by BuLi.[285] Again, the reaction is diastereoselective, with the *R* configuration at the newly created stereogenic center prevailing (by comparison with authentic samples[288]). The hexalithio hexapeptide that ought to give rise to the observed product is shown at the bottom of Scheme 17.

Inspection of the *formulae* in Schemes 16 and 17 reveals that the peptides used have two characteristic features in common: (1) adjacent to each and every stereogenic center a deprotonation has occurred, rendering a certain protection from further deprotonation, i.e., from epimerization (see Scheme 18); (2) the peptides employed carry aliphatic side chains and are thus lipophilic, which should increase the solubility of their Li derivatives in the nonpolar THF. Had these properties been found to be essential for successful application of the above alkylation procedure, the method would be rather limited. The following two examples show that this is not the case.

The Boc-protected alanyl-glycyl-glycyl-glycine was selected as an example of an especially hydrophilic oligopeptide which, in fact, can hardly be retrieved from water. This also led to the discovery of a quite different LiX effect. As evident from the data in Scheme 19, the peptide, which itself is very insoluble in THF at room temperature, and LiCl form an extremely soluble complex. Furthermore, addition of five equivalents of LDA neither causes precipitation nor decomposition; hydrolysis leads to recovery of the peptide in optically active form. The possibility of carrying out reactions with the solutions thus obtained is currently being investigated. While the great solubility of peptide-LiCl complexes in an organic solvent is very surprising, the fact that anhydrous crystalline adducts

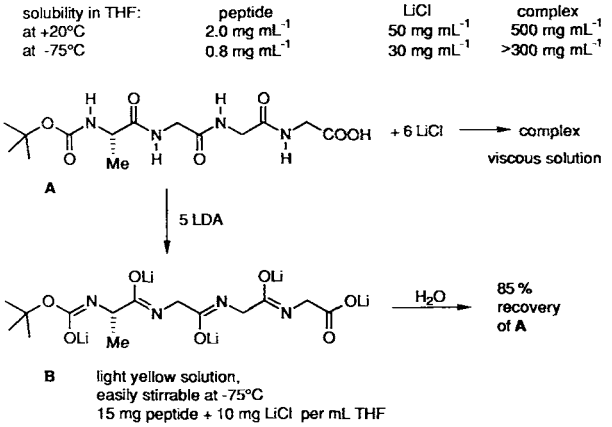


Scheme 17. Fivefold deprotonation of a Boc-protected hexapeptide (consisting of three *N*-methyl and three normal amino acid building blocks) by LDA and diastereoselective methylation at a sarcosine unit [285]. The yields shown were recorded after simple column chromatography and refer to the sum of the two epimers [2-(*R*-MeAla) and 2-(*S*-MeAla)]; the configurations at the other stereogenic centers are the same as in the starting material. **A**, pentalithium derivative; **B**, aggregates of **A**, poorly soluble; **C**, solubilization with LDA or LiCl, probably by formation of mixed aggregates (cf. Figs. 10, 20); **D**, complexation with diisopropylamine results in "reprotonation", i.e., lower yields without subsequent BuLi "treatment" (cf. Fig. 5 and Section 4.1).



Scheme 18. Deprotonation of the carboxylic acid, carbamate, and amide groups of Boc-peptides, as applied to the reactions shown in Schemes 16 and 17, results in protection of the adjacent stereogenic center from epimerization. The highlighted hydrogens are less acidic in these structures than those in which a neighboring anionoid group is absent. The generation of doubly lithiated systems $\mathbf{A}^1$, $\mathbf{B}^1$, $\mathbf{B}^2$, and $\mathbf{C}^1$ from the respective precursors **A**, **B**, and **C** is indeed possible, as shown with simple molecules [126, 248, 291–293], but demands harsher conditions. (Protection of carbonyl groups against metal hydride reduction, and against addition of MeLi, by directed Li enolate formation in di- and tricarbonyl compounds has been well known for a long time [294, 295].

of Li salts with peptides may separate from aqueous solutions has been known since the beginning of this century (*Pfeiffer*'s "Neutralsalzverbindungen der Polypeptide und Eiweisskörper"[298]).[299] Furthermore, the solubilization in water of a protein antigen by addition of LiBr is described in a patent.[300] Some amide, peptide, and urea complexes of Li salts have been subjected to X-ray crystal structure analysis;[301] one such structure is shown in Figure 23.[303]



Scheme 19. Enormous increase in the solubility of a 1:6 mixture of Boc-Ala-Gly-Gly-Gly-OH and anhydrous LiCl in THF compared to that of the components. After removal of the solvent (5 h/10^{-3} torr/20°C), a solid residue is left which contains peptide, LiCl, and THF in the ratio 1:6:2.5. Adding five equivalents of LDA to the mixture of **A** and LiCl, at −75°C, produces a clear solution which probably contains the pentalithio derivative **B** [296, 297].

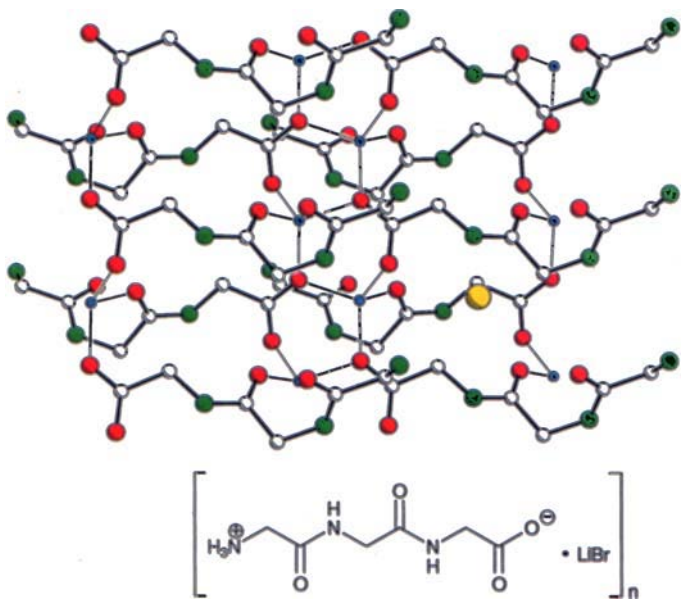


Fig. 23. Crystal structure of the LiBr complex of glycyl-glycyl-glycine [302] (section of the polymeric arrangement; *CSD*: GLYLIB). Cf. the LiX complexes with amides in Table 4, and the structures in Figs. 8, 11, and 16. The "addition ability" of Li salts toward amino acids decreases in the following series: Li > Na > K and I > Br > Cl (after *Pfeiffer*) [299].

5.2. Cyclosporine A

Nescire quaedam magna pars est sapientiae[304][*]

So far, the largest peptide in which we have been able to alkylate a sarcosine unit is cyclosporine A (CyA)[305,306] and some of its analogues.[307-311] CyA contains a series of amino acid moieties which are not protected against epimerization in the way indicated in Scheme 18. CyA is a novel immunosuppressive drug,[312] the discovery and use of which is as important as skilled surgery for the recent rapid developments in organ transplantations. CyA is a cyclic undecapeptide containing seven *N*-methyl amino acids (Fig. 24), four of which are adjacent to each other

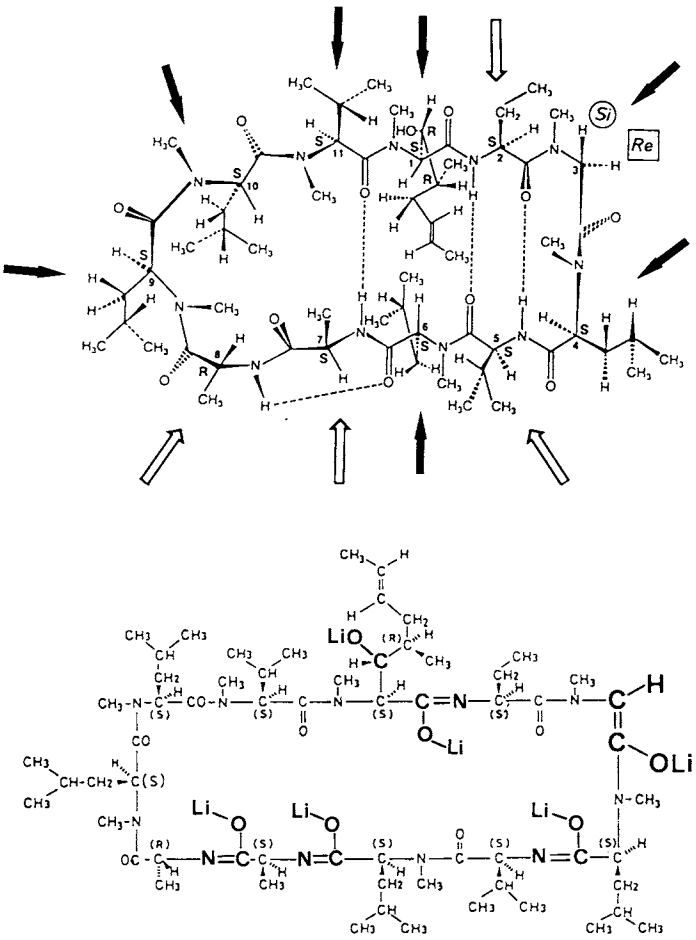


Fig. 24. Cyclosporine A (top) and the hexalithio derivative (bottom). The seven *N*-methyl amino acid building blocks are indicated by solid arrows, the four normal ones by open arrows. The conformation of CyA is identical in the crystal [306] and in solution [130a, 313], except for the orientation of the side chains of amino acids No. 1 and No. 11. There is no structural information available for the Li derivative (*E/Z* configuration at CC and CN double bonds is drawn arbitrarily). The Li derivative exists in THF solution in the presence of diisopropylamine, or LDA, or of LiCl, or mixtures of all three. The yellow solution (≥ 20 g L^{-1}), generated at -75°C, can be warmed up to $+20$°C without decomposition, at least for a short period of time.

(Nos. 9, 10, 11, 1). The amino acid No. 3 is sarcosine, which is followed by another *N*-methyl amino acid, MeLeu. CyA is highly lipophilic and insoluble in water due to the aliphatic side chains and the presence of transannular hydrogen bonds between opposite NH and CO groups in the pleated-sheet-type part of the molecule. In organic solvents CyA exhibits extremely high solubility (>600 mg mL^{-1} in THF at room temperature and >300 mg mL^{-1} at -75°C), and with LiCl a complex is formed, as evidenced gravimetrically or NMR spectroscopically[314] (cf. the LiBr complex of the cyclic decapeptide antamanide in Fig. 25).

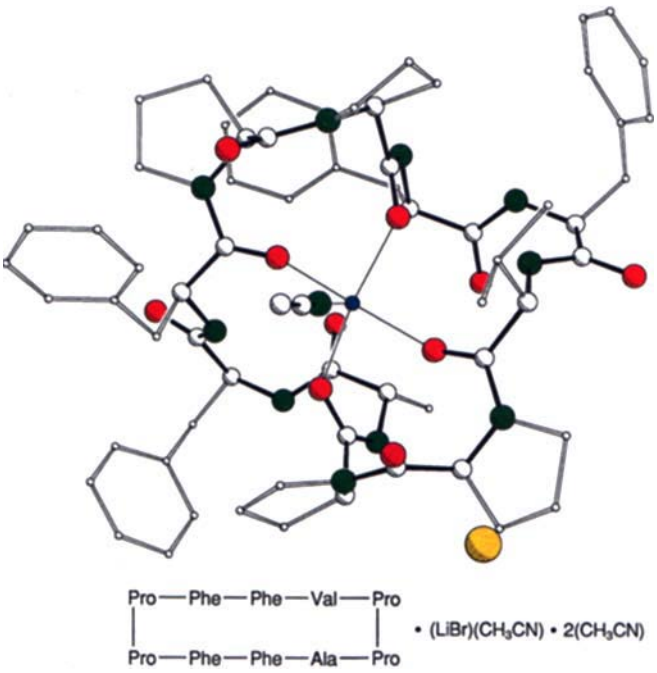
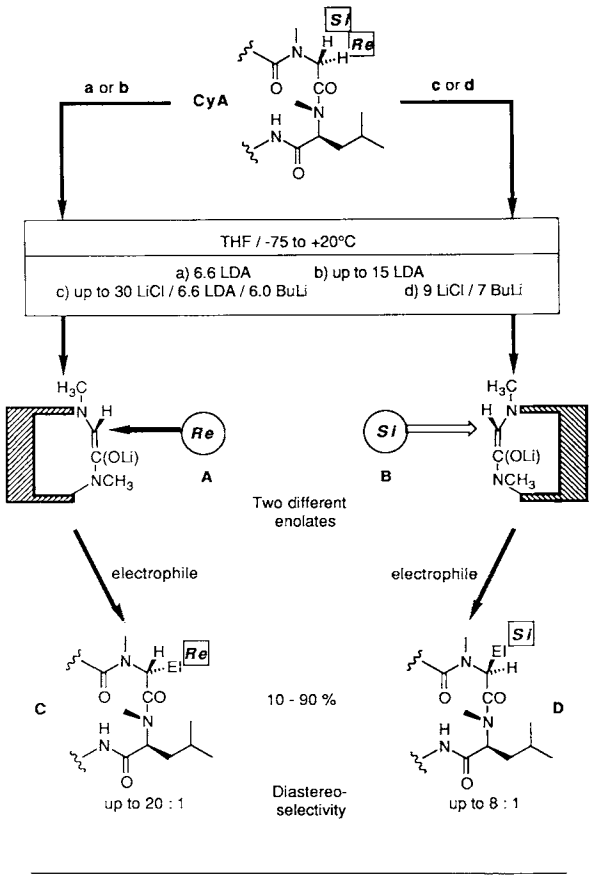


Fig. 25. LiBr complex of antamanide, *cyclo*(Val-Pro-Pro-Ala-Phe-Phe-Pro-Pro-Phe-Phe), crystallized from acetonitrile (*CSD*: ANTAML 10) [315]. The four carbonyl oxygens bound to Li form the base of a nearly square pyramid, with the acetonitrile nitrogen at the apex. The cyclic decapeptide originates from the green death cup mushroom *(Amanita phalloides)* [316]. There are two additional molecules of CH_3CN per cyclic peptide in the crystal.

When treated with the required number of equivalents of LDA (≥ 6) in THF, CyA is deprotonated at the sarcosine unit to give a Li enolate without destruction of the peptide ring. Reactions with electrophiles give derivatives with substituents in the former sarcosine position.[281, 285, 286, 289, 314, 317] With CyA and LDA alone a precipitate or a viscous mixture, which may solidify as a gel, results at -78°C. If an amount of LDA exceeding the six equivalents required (for removal of one OH, one CH_2, and four NH protons) is added (up to 15 equivalents), a clear, yellow, readily stirred solution is obtained, quenching of which with water leads to the recovery of more than 90% CyA. Epimerizations are observed only to a very small extent, and they do indeed occur mainly at the amino acids Nos. 9, 10, and 11, those lacking the protection discussed above. Simple column chromatography readily frees CyA from the impurities thus generated. With electrophiles other than water, products of substitution of the diastereotopic *Re* hydrogen ($\leq 90\%$ *ds*) in the sarcosine unit (Sar^3)

[*] Not knowing is the essence of wisdom.

are formed in yields ranging from 10 to 50%, with a large amount of unreacted CyA being recovered. Some of the substituents that were introduced into CyA by this procedure are indicated in Scheme 20.



El = D, CH_3, $CH_2CH{=}CH_2$, $CH_2COO(t\,Bu)$, CH_2OH, $CH(OH)Ph$, $COOCH_3$, F, SCH_3

Scheme 20. Alkylation of CyA on the sarcosine unit via the Li enolate shown in Fig. 24 [317]. Depending on the conditions of deprotonation either an enolate **A** is generated that is preferentially attacked from the *Re* side, or an enolate **B** with *Si* selectivity (see the products **C** and **D**, respectively) [318]. The highest yields were recorded under "amine-free, LiCl conditions" [c and d], and the best selectivities under the "LDA conditions" [a and b]. CD_3CO_2D, MeI, alkyl bromides, aldehydes, CO_2/CH_2N_2, $FClO_3$, and disulfides were used in excess as electrophiles. The products **C** and **D** can be separated by flash chromatography and isolated in pure form.

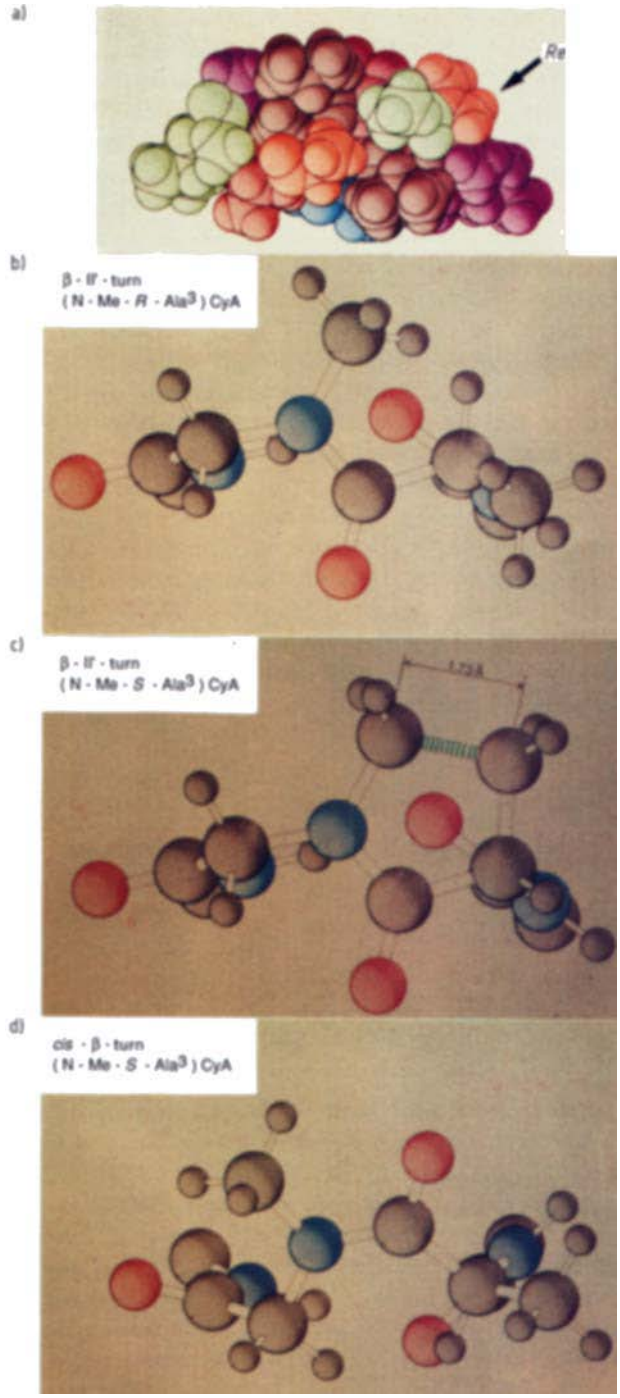


Fig. 26. Space-filling model of CyA generated with the data of the structure analysis, and ball-and-stick model of the partial structure around the β-turn at which the stereoselective alkylation through a Li enolate occurs (Fig. 24, Scheme 20). a) Overview, in which the *Re* hydrogen on sarcosine is emphasized; the *Si* hydrogen and the neighboring NCH_3 group are quasi-1,3-diaxial to each other as viewed by the reader. b) H(*Re*) substituted by CH_3, no steric hindrance [the NMR spectra of CyA and (*N*-Me-(*R*)-Ala³)CyA are superimposable over wide regions]. c) H(*Si*) substituted by CH_3, strong penetration of van der Waals radii of the two CH_3 groups in maintaining the β-II'-turn. d) Equatorial (*Si*)-CH_3 group in a *cis* β-turn, with formation of a *cisoid* peptide bond [the NMR spectra of the (*R*) and (*S*) derivatives differ greatly].

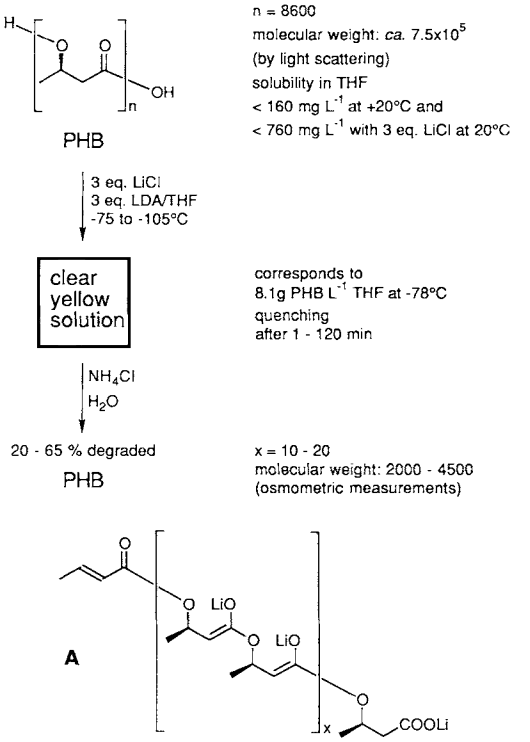
We were overjoyed that the products derived from replacement of the diastereotopic *Si* hydrogen can also be obtained selectively; yields of over 90% may be obtained if the deprotonation of CyA by LDA is carried out in the presence of large amounts of LiCl (up to 30 equivalents), and if the diisopropylamine is removed by BuLi addition. We do not know whether the enolates generated under the two different sets of conditions are configurationally different (*E*/*Z* on C=N and/or C=C) or whether they differ only by different LiX effects exerted by LDA and LiCl. At any rate, the *Re* face of the enolate double bond must be hindered in one case, the *Si* face in the other, by the arrangement of the macrocyclic ring (see Scheme 20).

The pure products are readily isolated by medium-pressure chromatography on SiO_2. Miraculously, CyA ($M_r = 1202$) and the two diastereomeric products of methylation [N-Me-(*R*)-Ala³)CyA and (N-Me-(*S*)-Ala³)CyA,

$M_r = 1216$] clearly separate on a simple analytical silica gel thin-layer plate![319] (The structural assignment of the two methyl derivatives was arrived at by comparison of the NMR spectra with those of authentic samples.[287,288])

Cleavages of the CyA peptide backbone or alkylations of amino acids other than the sarcosine occur only to a very small extent. Upon treatment of CyA with BuLi in the presence of LiCl (Scheme 20, d) appreciable amounts of a butyl ketone may be isolated, if desired, which results from attack at the carbonyl group of amino acid No. 9 (an "unprotected" site!).

The biological activity of the products thus available follows a simple rule: derivatives with substituents in the *Re* position still have immunosuppressive properties comparable to CyA, those substituted in the *Si* position do not. The reason for this is obvious from modeling as shown in Figure 26; the *Re* hydrogen of the sarcosine in CyA occupies a quasi-equatorial position, the *Si* hydrogen a quasi-axial one; introduction of a substituent into the latter position imposes such severe steric hindrance by van der Waals overlap with the NCH_3 group of the adjacent amino acid that the peptide chain must adopt a different conformation, causing the shape of the entire molecule to change.



Scheme 21. Deprotonating solubilization and partial degradation of poly-[(*R*)-3-hydroxybutyrate], PHB, with LDA/LiCl in THF at low temperature. The solubilities described for PHB in THF are upper limits, which have been extrapolated from experiments in volumes of much less than 1 L. The upper limit of the solubility accessible by addition of LDA/LiCl was not investigated. The enolate could also decompose by α-elimination [72] (lithium oxybutyrate end group) instead of β-elimination (crotonate terminal group). There is no indication of a direct attack by LDA on the ester carbonyl groups of the polymer (aminolysis, resulting in formation of carboxamide end groups).

6. Outlook—on to Even More Complex Systems

An experiment is in progress
but it is uncertain
if we are in control
or just observers
Roald Hoffmann[320]

Encouraged by the solubilization of polylithiated organic compounds, such as peptides, by addition of inorganic Li salts, we also investigated other systems. We found, for instance, that when a suspension of the biopolymer PHB (polyhydroxybutyrate, $M_r = 7.5 \times 10^5$), which itself is totally insoluble both in water and THF, was treated with excess LDA in the presence of LiCl at low temperature, a clear, slightly yellow THF solution was obtained. Subsequent quenching with water leads to recovery of up to 65% of a polymer of lower molecular weight (Scheme 21).[321,322] The fact that decomposition of the polyester polyenolate does not take place all the way to the monomer (Li crotonate), but that an unexpectedly long-lived species containing ca. 30 units persists, suggests the answer must have something to do with the structure of this species—which we do not know.[323]

Our excursion into the world of Li enolate aggregate structures and the quest for proof of their involvement in product-forming steps did not only furnish important new knowledge, but led us continuously back to the laboratory. There, we have arrived at systems of a complexity with which we could not have hoped to cope at the outset; they exhibit reactivities which we observe with pleasure and with excitement, but which we again do not understand.

Lesson: Even the synthetic organic chemist must consider very complex structures, supramolecules in *Lehn*'s terminology, in his everyday work. I have nothing to add to the statement of *Lord Todd*:[324]

> Apart from consideration of the hydrogen bond, we organic chemists have really paid little attention to linkages other than the purely covalent. I believe that it will be the duty of organic chemists in the future to study the weak non-bonding interactions which are of enormous importance in the large natural macromolecules. Such studies will lead to a new blossoming of organic chemistry in the future.
>
> *Lord Alexander R. Todd*

My sincere thanks go to the co-workers who have contributed to the work described here; their names are given in the list of references. Collaboration with them was and still is a source of great pleasure for me. I thank my colleague Jack Dunitz for many enlightening discussions. The preparation of this review article would not have been possible without the help and dedication of Silvia Sigrist (typing), Albert K. Beck (list of references), Bernd Lamatsch and Thomas Maetzke (figures), Gerhard Stucky and Geo Adam (schemes and tables), Ulf Misslitz (corrections), Hans-Jörg Gründler (application of the programs WORD® and ChemDraw®), and Edward Dziadulewicz, Robert Fitzi, and Soo Y. Ko (parts of the English version).

Received: September 14, 1988 [A 702 IE]
German version: *Angew. Chem. 100* (1988) 1685

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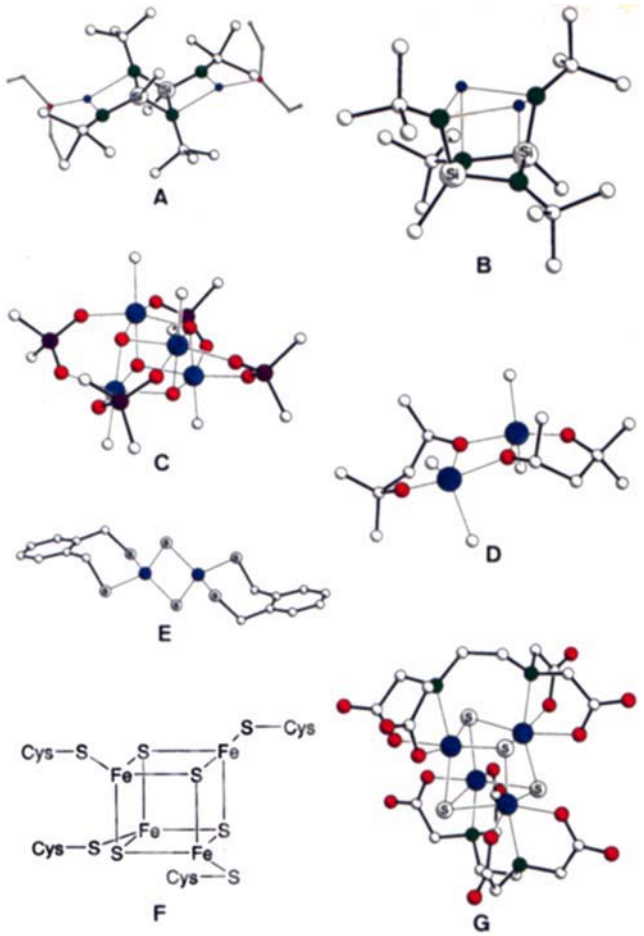

$[(t\mathrm{BuN})_2(\mathrm{CH_3Si})\mathrm{Li}]_2 \cdot 2\mathrm{OEt_2}$ **A**
$[(t\mathrm{BuN})_2(\mathrm{CH_3Si})\mathrm{Li}]_2$ **B**
$[\mathrm{BuSn(O)O_2P(C_6H_{11})_2}]_4$ **C**
$[\mathrm{Me_2TiOC(Me_2)CH_2CH(Me)O}]_2$ **D**
$[(\mathrm{R,S})_2\mathrm{FeS}]_2$ **E**
For **F**, **G**, see text

[116] It might be appropriate at this point to mention that, in the discussion of structures, we draw formulae and use a language not according to the usual conventions in organic chemistry but rather according to those in crystallography. A line between two atoms thereby does not correspond to an electron pair but indicates that their distance is smaller than the sum of the van der Waals' radii. Here, we do not observe the octet rule; otherwise we would have to add a $\oplus$ charge to all the oxygens of the THF molecules bound to Li. We also speak of an X atom not of a $Li^{\oplus}$ cation or an $RO^{\ominus}$ anion! (See also the remarks in the caption of Fig. 1.)

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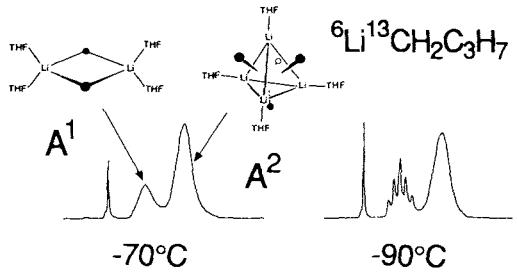

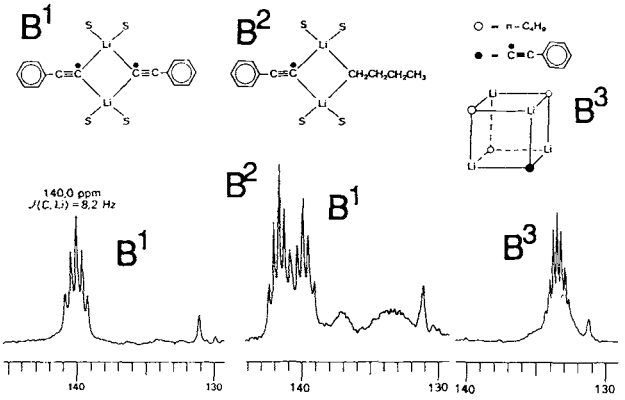

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[207] In the case of Li enehydrazide it was concluded from kinetic measurements of the alkylation that the monomeric species forms product, not the aggregate, though the latter is the predominant species in solution [102c].

[208] See Schemes 5 and 9, Table 3, and Section 2.2.3.

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[210] a) $LiNR_2$ adducts to aromatic aldehydes for *ortho*-metalations: U. Michael, S. Gronowitz, *Acta Chem. Scand. 22* (1968) 1353; D. L. Comins, J. D. Brown, *Tetrahedron Lett. 22* (1981) 4213; D. L. Comins, J. D. Brown, N. B. Mantlo, *ibid. 23* (1982) 3979; b) $LiNR_2$ adducts to aromatic aldehydes for aminative alkylations and reductive aminative coupling with low-valent titanium: D. Seebach, M. Schiess, *Helv. Chim. Acta 65* (1982) 2598; D. Seebach, A. K. Beck, M. Schiess, L. Widler, A. Wonnacott, *Pure Appl. Chem. 55* (1983) 1807–1822; D. Seebach, C. Betschart, M. Schiess, *Helv. Chim. Acta 67* (1984) 1593; C. Betschart, D. Seebach, *ibid. 70* (1987) 2215.

[211] $LiNR_2$ and LiOR adducts [*t*BuOCH(OLi)R] to nonenolizable aldehydes as bases and precursors for the in-situ liberation of an aldehyde: D. Seebach, T. Weber, *Tetrahedron Lett. 24* (1983) 3315; *Helv. Chim. Acta 67* (1984) 1650.

[212] Sulfur analogues [ArylCH(SLi)SR]: D. Seebach, K.-H. Geiss, *Angew. Chem. 86* (1974) 202; *Angew. Chem. Int. Ed. Engl. 13* (1974) 202; K.-H. Geiss, D. Seebach, B. Seuring, *Chem. Ber. 110* (1977) 1833.

[213] L. M. Jackman, B. C. Lange, *J. Org. Chem. 48* (1983) 4789.

[214] L. Tenud, S. Farooq, J. Seibl, A. Eschenmoser, *Helv. Chim. Acta 53* (1970) 2059.

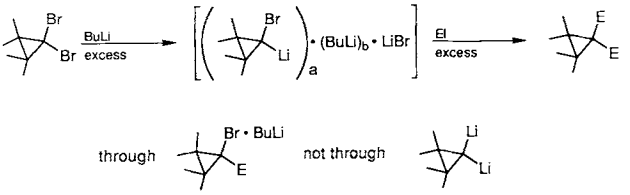
[215] See also the amide complexes in Table 4, urea and amide complexes of Li in crystals [47], and the discussion about LiX effects on peptides in Section 5.

[216] Most of the reaction paths via aggregates shown in Schemes 6–9 had been proposed by us already in 1981 and 1983 [53, 69]; only the complexity, not the principle, is changed if the reaction is formulated for tetrameric aggregates instead of dimeric ones as done here.

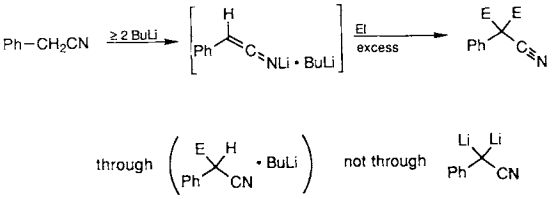
[217] The scenario is even extended if one considers that single-electron transfers (SET) become more probable with increasing degree of aggregation of polar organometallic compounds; a supramolecule can more likely donate an electron (as in the present case), or accept one, than one of its components, because the resulting charge deficiency is distributed over a larger area (higher lying HOMO, lower LUMO). Accordingly, for example, it was recently proved that the tendency of single-electron transfer to occur from a Li amide strongly increases with its degree of aggregation (P. Renaud, M. A. Fox, *J. Am. Chem. Soc. 110* (1988) 5702). An SET mechanism with participation of the aggregate (Fig. 14) was also proposed [56] to explain the reversal of stereoselectivity of reactions of the Li enamides of diketopiperazine–bislactim ethers when going from "normal" electrophiles [99] to C_2Cl_6 (U. Schöllkopf, H.-J. Neubauer, M. Hauptreif, *Angew. Chem. 97* (1985) 1065; *Angew. Chem. Int. Ed. Engl. 24* (1985) 1066).

[218] In the case of participation of aggregates in product-forming steps, different results are possible depending on the use of the respective enolates as racemic mixtures (which can form diastereomeric aggregates) or of enantiomerically pure reagents! Compare the nonlinear dependence of the product *ee* values in numerous enantioselective reactions on the enantiomeric purity of the reagents used. Several examples can be found in the following references: [53]; A. Horeau, *Tetrahedron Lett. 1969*, 3121; C. Agami, C. Puchot, H. Sevestre, *ibid. 27* (1986) 1501; C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc. 108* (1986) 2353; Review on *Kinetic Resolution*, H. B. Kagan, J. C. Fiaud, *Top. Stereochem. 18* (1988) 249.

[219] Two "aggregate effects" may prove this. a) In the reaction of *gem*-dibromocyclopropane with an excess of butyllithium and subsequent addition of an excess of electrophile, products of double substitution

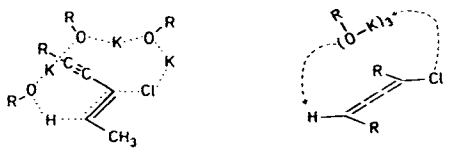


are formed which originally was seen as proof for the occurrence of *gem*-dilithiocyclopropanes. These species, however, could not be detected by NMR spectroscopy of ^{6}Li- and ^{13}C-labeled samples. It turns out that a mixture of bromolithium carbenoid and BuLi is present instead. The added electrophiles react faster with the carbenoid than with BuLi, and "interaggregate" Br/Li exchange leads to the observed result. See flow chart (R. Dammann, *Dissertation Nr. 6277*, ETH Zürich 1978). b) In the reaction of phenylacetonitrile with 2 BuLi (see structure



in Table 2) it is not a dilithium derivative that is responsible for the formation of double substituted products, but a fast "interaggregative" proton transfer during addition of electrophile (P. J. Crowley, M. R. Leach, O. Meth-Cohn, B. J. Wakefield, *Tetrahedron Lett. 27* (1986) 2909). c) Cf. also the discussion in: P. Beak, T. J. Musick, C. Chen, *J. Am. Chem. Soc. 110* (1988) 3538.

[220] Representations from publications by *Schlosser* show what has been concluded from kinetic measurements of the HCl elimination with potassium alkoxides: "Alcoholate Clusters ("Aggregates") and Their Role in Alkyne-Forming Elimination Reaction." M. Schlosser, T. D. An, *Angew. Chem. 93* (1981) 1114; *Angew. Chem. Int. Ed. Engl. 20* (1981) 1039; M. Schlosser, C. Tarchini, T. D. An, R. Ruzziconi, P. J. Bauer, *ibid. 93* (1981) 1116 and *20* (1981) 1041, respectively.



[221] G. Wittig, *Top. Curr. Chem. 67* (1976) 1–14.

[222] M. Schlosser, G. Heinz, *Chem. Ber. 102* (1969) 1944.

[223] D. Seebach, V. Ehrig, M. Teschner, *Liebigs Ann. Chem. 1976*, 1357.

[224] R. P. Woodbury, M. W. Rathke, *Tetrahedron Lett. 1978*, 709.

[225] G. Stork, P. F. Hudrlik, *J. Am. Chem. Soc. 90* (1968) 4462, 4464.

[226] J. K. Rasmussen, *Synthesis 1977*, 91–110.

[227] E. Colvin: *Silicon in Organic Synthesis*, Butterworths, London 1981.

[228] E. W. Colvin: Preparation and Use of Organosilicon Compounds in Organic Synthesis, in F. R. Hartley (Ed.): *The Chemistry of the Metal-Carbon Bond, Vol. 4*, Wiley, New York 1987, Chapter 6, pp. 539–621.

[229] E. W. Colvin: *Silicon Reagents in Organic Synthesis*, Academic Press, London 1988.

[230] W. P. Weber: *Silicon Reagents for Organic Synthesis*, Springer, Berlin 1983.

[231] P. J. Reider, R. S. E. Conn, P. Davis, V. J. Grenda, A. J. Zambito, E. J. J. Grabowski, *J. Org. Chem. 52* (1987) 3326.

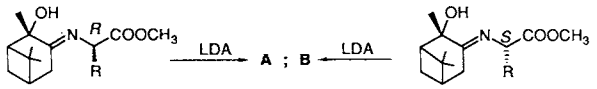
[232] A. K. Beck, M. S. Hoekstra, D. Seebach, *Tetrahedron Lett. 1977*, 1187.

[233] D. Seebach, T. Weller, G. Protschuk, A. K. Beck, M. S. Hoekstra, *Helv. Chim. Acta 64* (1981) 716.

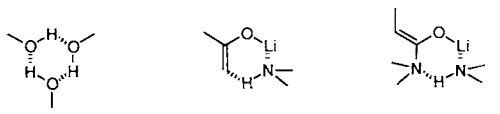
[234] M. Yoshifuji, T. Nakamura, N. Inamoto, *Tetrahedron Lett. 28* (1987) 6325.

[235] C. H. Heathcock, M. C. Pirrung, S. D. Young, J. P. Hagen, E. T. Jarvi, U. Badertscher, H.-P. Märki, S. H. Montgomery, *J. Am. Chem. Soc. 106* (1984) 8161, and earlier papers of the same group cited therein.

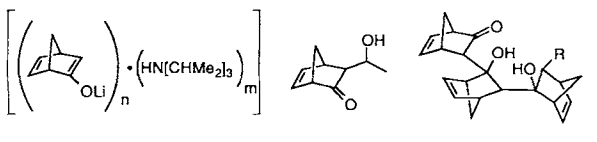
[236] R. Häner, D. Seebach, *Chimia 39* (1985) 356; D. Seebach, R. Häner, T. Vettiger, *Helv. Chim. Acta 70* (1987) 1507.
[237] T. Hassel, D. Seebach, *Helv. Chim. Acta 61* (1978) 2237, and earlier papers of our group cited therein.
[238] P. Beak, D. B. Reitz, *Chem. Rev. 78* (1978) 275–316; P. Beak, W. J. Zajdel, D. B. Reitz, *ibid. 84* (1984) 471–523.
[239] In this case alkylated diisopropylamine can be formed under conditions, under which pure diisopropylamine would not be alkylated (−80°C, in THF); thus, one must conclude that the amine is activated by the Li enolate for the alkylation to the tertiary amine! (See [244].)
[240] a) The effect of the "hidden proton" has been observed in substrates with several acidic sites also in the absence of secondary amines; see, e.g., the results of protonation of Schiff bases of penicillamine benzyl esters: R. A. Firestone, N. Schelechow, D. B. R. Johnston, B. G. Christensen, *Tetrahedron Lett. 1972*, 375; R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, B. G. Christensen, *J. Org. Chem. 39* (1974) 437; R. A. Firestone, B. G. Christensen, *J. Chem. Soc. Chem. Commun. 1976*, 288. b) Doubly deprotonated species—bis(enolates)—can be more stable than the corresponding simply deprotonated ones; see the following newer papers and the references cited therein: K. G. Bilyard, P. J. Garratt, R. Hunter, E. Lete, *J. Org. Chem. 47* (1982) 4731; K. Furuta, A. Misumi, A. Mori, N. Ikeda, H. Yamamoto, *Tetrahedron Lett. 25* (1984) 669. Solvation and chelation (see Tables 4,5) can invert the normal order of acidity: S. M. Bachrach, *J. Am. Chem. Soc. 108* (1986) 6406. But also here, as a warning, we must point to the intraaggregate effects mentioned in [219].
[241] E. Dziadulewicz, postdoctoral fellow, ETH Zürich 1987/88, hitherto unpublished results.
[242] D. Seebach, M. Boes, R. Naef, W. B. Schweizer, *J. Am. Chem. Soc. 105* (1983) 5390.
[243] P. Strazewski, C. Tamm, *Helv. Chim. Acta 69* (1986) 1041; P. Strazewski, *Dissertation*, Universität Basel 1986.
[244] J. D. Aebi, D. Seebach, *Helv. Chim. Acta 68* (1985) 1507.
[245] R. Polt, D. Seebach, *Helv. Chim. Acta 70* (1987) 1930; *J. Am. Chem. Soc. 111* (1989), in press.
[246] Cf. the protonations and alkylations of Schiff base enolates formed from amino acids and hydroxypinanone; under otherwise identical conditions, the epimeric precursors give rise to two enolates, **A** and **B**, that behave very differently (both should have the (*E*) configuration of the enolate double bond!); A. El Achqar, M.-L. Roumestant, P. Viallefont, *Tetrahedron Lett. 29* (1988) 2441.



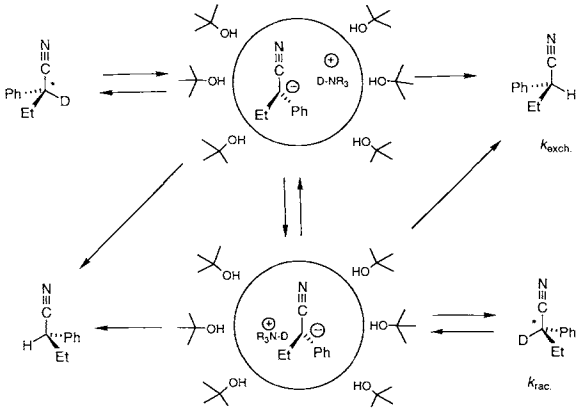
[247] Cf. the cooperative hydrogen bonds [76] in many biologically important structures in which, for example, three hydrogen bonds are arranged in a cyclic array, **A**, with the complexes **B** and **C** (Figs. 3, 5, Table 2). Here, as there, the bond strength is greater than anticipated from simple O···HO, N···HN or πC···HN hydrogen bonds. Much stronger are hydrogen bonds between ions, and between ions and neutral molecules, see [250, 251, 252c].



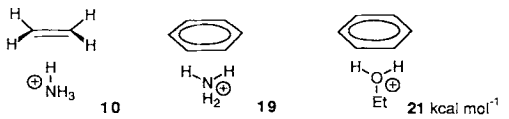
[248] The effect of the complexation of Li carboxylate (or the [RR'C=CO_2Li]Li derivative) with the secondary amine and the return of the proton in attempted deuterations of doubly metalated toluic acids as well as aliphatic or alicyclic carboxylic acids was already discussed at the beginning of the 1970s: P. L. Creger, *J. Am. Chem. Soc. 92* (1970) 1396; P. E. Pfeffer, L. S. Silbert, J. M. Chirinko, Jr., *J. Org. Chem. 37* (1972) 451.
[249] Reports on the observation of such effects in carbonyl additions, which occur much faster than nucleophilic substitutions, are not known to us. The enolate **A** generated with LDA, e.g., adds smoothly to acetaldehyde to give the expected product **B** (84%), while with CH_3I a 3:1 product **C**, R = CH_3, is generated in ca. 50% yield, which was attributed to the existence of tetrameric aggregates [183].



[250] D. J. Cram: *Fundamentals of Carbanion Chemistry*, Academic Press, New York 1965. In spite of the protic medium, the rate of racemization ($k_{rac.}$) is greater than that of the D/H exchange ($k_{exch.}$) via an ion pair. The formulae show the "conducted tour mechanism" (*Cram*), $k_{rac.}:k_{exch.} = 20:1$. Cf. also: A.-M. Weidler, G. Bergson, *Act. Chem. Scand. 18* (1964) 1487; K. Bott, *Tetrahedron Lett. 1965*, 4569.



[251] There are very strong hydrogen bonds formed between ammonium or oxonium ions and π systems: C. A. Deakyne, M. Meot-Ner (Mautner), *J. Am. Chem. Soc. 107* (1985) 474 (measurements and ab-initio calcula-



tions), cf. also [257]. Hydrogen bonds between an amine NH and the fluorenyl carbanion: S. Buchholz, K. Harms, M. Marsch, W. Massa, G. Boche, *Angew. Chem. 101* (1989) No. 1; *Angew. Chem. Int. Ed. Engl. 28* (1989) No. 1. Intramolecular hydrogen bonds between an OH group and an indenyl carbanion: P. Ahlberg, B. Johnsson, I. McEwen, M. Rönnqvist, *J. Chem. Soc. Chem. Commun. 1986*, 1500.
[252] Recent reviews on hydrogen bonds see [75, 76] and: a) A. C. Legon, D. J. Millen, *Acc. Chem. Res. 20* (1987) 39; b) E. B. Wilson, Z. Smith, *ibid. 20* (1987) 257; c) H. A. Staab, T. Saupe, *Angew. Chem. 100* (1988) 895–909; *Angew. Chem. Int. Ed. Engl. 27* (1988) 865–879.
[253] C. F. Bernasconi, D. E. Fairchild, C. J. Murray, *J. Am. Chem. Soc. 109* (1987) 3409, and earlier papers of this group cited therein.
[254] Theoretical Studies of Proton Transfers: S. Scheiner, *Acc. Chem. Res. 18* (1985) 174–180.
[255] S. Sprang, T. Standing, R. J. Fletterick, R. M. Stroud, J. Finer-Moore, N.-H. Xuong, R. Hamlin, W. J. Rutter, C. S. Craik, *Science (Washington, DC) 237* (1987) 905; C. S. Craik, S. Roczniak, C. Largman, W. J. Rutter, *ibid. 237* (1987) 909.
[256] See [47, 61, 82], Table 5, and papers about basicity [LDA (pK_a 35.7)/$LiN(SiMe_3)_2$ (pK_a 29.5)] and about aggregation in solution: B. Y. Kimura, T. L. Brown, *J. Organomet. Chem. 26* (1971) 57; R. R. Fraser, T. S. Mansour, *J. Org. Chem. 49* (1984) 3442.
[257] Effect of $LiClO_4$ on the Diels-Alder reaction: R. Braun, J. Sauer, *Chem. Ber. 119* (1986) 1269. In the presence of $LiClO_4$ the equilibrium constant of the deprotonation of tropolone with pyridine in Et_2O is raised by a factor of 12500; this finding was related to ion pairs and aggregates of the Li salt: Y. Pocker, J. C. Ciula, *J. Am. Chem. Soc. 110* (1988) 2904. Influence of $LiClO_4$ on the *C*- vs. *O*-alkylation of Li enolates, see [138]; on the addition of MeLi to ketones: E. C. Ashby, S. A. Noding, *J. Org. Chem. 44* (1979) 4371; on the S_N2 reaction of MeLi with vinyloxiranes: J. C. Saddler, P. L. Fuchs, *J. Am. Chem. Soc. 103* (1981) 2112.
[258] Mixtures of LiBr and a tertiary amine can be applied for the α-alkylation of special base-labile and/or polymerization-prone carbonyl compounds. In these cases "complexes" such as **A** and **B** are proposed as the reactive species (cf. the data in [251]). **A**: O. Tsuge, S. Kanemasa, M. Yoshioka, *J. Org. Chem. 53* (1988) 1384. **B**: M. A. Blanchette, W.

Choy, J. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett. 25* (1984) 2183; M. W. Rathke, M. Nowak, *J. Org.*

Chem. 50 (1985) 2624; T. Rosen, C. H. Heathcock, *J. Am. Chem. Soc. 107* (1985) 3731. Cf. also an enantioselective version: T. Yamashita, H. Mitsui, H. Watanabe, N. Nakamura, *Bull. Chem. Soc. Jpn. 55* (1982) 961.

[259] D. Seebach, H. Dörr, B. Bastani, V. Ehrig, *Angew. Chem. 81* (1969) 1002; *Angew. Chem. Int. Ed. Engl. 8* (1969) 982; D. Seebach, H.-O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nüssler, H.-A. Oei, M. Schmidt, *Helv. Chim. Acta 60* (1977) 301; D. Seebach, W. Langer, *ibid. 62* (1979) 1701.

[260] Cf. also chiral ethylenediamine derivatives of proline (with and without alkoxide group) for the enantioselective addition of Li compounds and of tin enolates to aldehydes (in part very high *ee*), see references cited in T. Mukaiyama: *Organic Synthetic Reactions*, Tokyo Kagaku Dojin, Tokyo 1987 (ISBN 4-8079-0286-5), Chapter 11.3 and 13.2, respectively. (An English translation of this book published in Japanese, is being prepared. Its title will be *Challenges in Synthetic Organic Chemistry*.) Chiral binaphthyl-substituted ethylenediamine for enantioselective addition of alkyllithium to aldehydes: J.-P. Mazaleyrat, D. J. Cram, *J. Am. Chem. Soc. 103* (1981) 4585.

[261] J. K. Whitesell, S. W. Felman, *J. Org. Chem. 45* (1980) 755.

[262] L. Duhamel, J.-C. Plaquevent, *J. Am. Chem. Soc. 100* (1978) 7415. Review: L. Duhamel, P. Duhamel, J.-C. Launay, J.-C. Plaquevent, *Bull. Soc. Chim. Fr. 1984*, II 421-430.

[263] H. Hogeveen, L. Zwart, *Tetrahedron Lett. 23* (1982) 105.

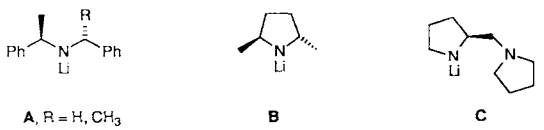
[264] N. S. Simpkins, *J. Chem. Soc. Chem. Commun. 1986*, 88.

[265] R. Shirai, M. Tanaka, K. Koga, *J. Am. Chem. Soc. 108* (1986) 543.

[266] Further enantioselective protonations of achiral enolates and N-analogues with chiral acids or in the presence of chiral amines/Li amides: [178b, 262, 263] and L. Duhamel, S. Fouquay, J.-C. Plaquevent, *Tetrahedron Lett. 27* (1986) 4975; U. Gerlach, S. Hünig, *Angew. Chem. 99* (1987) 1323; *Angew. Chem. Int. Ed. Engl. 26* (1987) 1283; *Tetrahedron Lett. 28* (1987) 5805.

[267] Diastereoselective protonations: H. E. Zimmerman, *Acc. Chem. Res. 20* (1987) 263-268; ... of nitronates: D. Seebach, A. K. Beck, T. Mukhopadhyay, E. Thomas, *Helv. Chim. Acta 65* (1982) 1101; T. M. Williams, R. Crumbie, H. S. Mosher, *J. Org. Chem. 50* (1985) 91; M. Eyer, D. Seebach, *J. Am. Chem. Soc. 107* (1985) 3601; U. Brändli, M. Eyer, D. Seebach, *Chem. Ber. 119* (1986) 575.

[268] Further enantiooselective deprotonations have been performed, e.g., with the bases **A**-**C** (see also Table 9 and N. S. Simpkins, lecture held at the Society of Chemical Industry Symposium "Chirality Recognition in Synthesis", London, March 17, 1988). For **A**, see [261, 263, 264] and



A, R = H, CH_3 **B** **C**

J. A. Marshall, J. Lebreton, *Tetrahedron Lett. 28* (1987) 3323; *J. Am. Chem. Soc. 110* (1988) 2925; L. Duhamel, A. Ravard, J.-C. Plaquevent, D. Davoust, *Tetrahedron Lett. 28* (1987) 5517; For **B** see [26]; For **C**, see M. Asami, *Chem. Lett. 1984*, 829; *Tetrahedron Lett. 26* (1985) 5803; M. Asami, H.Kirihara, *Chem. Lett. 1987*, 389; S. K. Hendrie, J. Leonhard, *Tetrahedron 43* (1987) 3289.

[269] When the precursor of the achiral enolate is a mixture of enantiomers and a chiral base is used for the deprotonation, a kinetic resolution may be responsible for the optical activity of the product; this has to be considered especially in cases of yields below 50%, see for example: M. B. Eleveld, H. Hogeveen, *Tetrahedron Lett. 27* (1986) 631, and review article cited in [218].

[270] M. Simpson, *Diplomarbeit*, ETH Zürich 1982.

[271] T. Mukhopadhyay, Postdoctoral fellow at the ETH Zürich 1981-1982.

[272] D. Wasmuth, *Dissertation Nr. 7033*, ETH Zürich 1982.

[273] D. Seebach, D. Wasmuth, *Angew. Chem. 93* (1981) 1007; *Angew. Chem. Int. Ed. Engl. 20* (1981) 971.

[274] H. Hogeveen, W. M. P. B. Menge, *Tetrahedron Lett. 27* (1986) 2767.

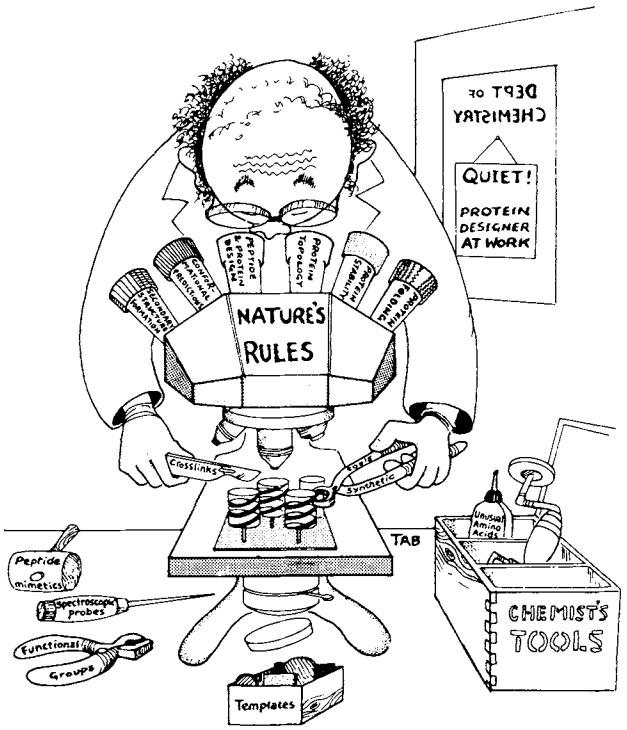
[275] A. Ando, T. Shioiri, *J. Chem. Soc. Chem. Commun. 1987*, 1620; cf. also *ibid. 1987*, 656.

[276] A. C. Regan, J. Staunton, *J. Chem. Soc. Chem. Commun. 1983*, 764; cf. also T. A. Carpenter, G. E. Evans, F. J. Leeper, J. Staunton, M. R. Wilkinson, *J. Chem. Soc. Perkin Trans. I 1984*, 1043; A. C. Regan, J. Staunton, *J. Chem. Soc. Chem. Commun. 1987*, 520. It is not clear from these papers if and which excess of $LiNR_2$ has been used. Cf. also the complexes of Li toluic acid dianion derivatives and diisopropylamine [248].

[277] With the aldol-type products (Nos. 1-11), chiral shift reagent $[Eu(dmc)_3]$ and the Mosher method or Pirkle columns [93] were used. With the nitroketone (No. 12), $Eu(tfc)_3$ was used, the product being compared with that of an authentic racemic sample [173] by NMR [93].

[278] It has not been investigated to what extent the adducts **D** shown in Scheme 6 are involved in the aldol additions to benzaldehyde (Nos. 1-11 from Table 9), which proceed most selectively by using a large excess of aldehyde (Nos. 3, 11).

[279] a) A. F. Spatola in B. Weinstein (Ed.): *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins, Vol. 7*, Marcel Dekker, New York 1983, pp. 267-357.—See also the articles by *Benner, Fersht*, and *Kaiser* in: S. A. Benner (Ed.): *Redesigning the Molecules of Life*, Springer-Verlag, Berlin 1988. b) M. Mutter, *Trends Biochem. Sci. 13* (1988) 260. I thank Professor *Mutter* for kindly allowing us to reproduce the following cartoon (drawn by the graphic division of the journal *Trends in Biochemical Sciences* ("TIBS") after a draft of Prof. *Mutter*).



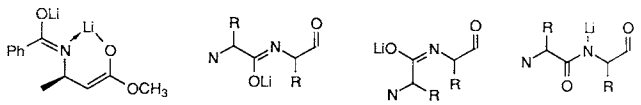
[280] Cf. the path via the cyclic dipeptide derivatives, Scheme 11 (bottom right) and [245].

[281] R. Naef, ETH Zürich 1983, hitherto unpublished results.

[282] D. Seebach, H. Estermann, *Tetrahedron Lett. 28* (1987) 3103.

[283] K. Narasaka, Y. Ukaji, K. Watanabe, *Chem. Lett. 1986*, 1755.

[284] The configuration of the CC and CN double bond of the enolate drawn in Scheme 15 is, as with all deprotonated peptides in this section (Schemes 15-19 and 24), chosen arbitrarily (or better, by the "technique of illustration"). There are no structural investigations of such species known to us. There is probably no doubt about the position of the Li at the more electronegative heteroatom oxygen (**A**-**C** vs. **D**). Of the four possible geometric isomers of the butyric acid derivative, **A** seems to be especially "attractive". Besides the *Z* isomer **B**, the *E* isomer **C** may be also considered for the lithiated peptides. See also entry 16 in Table 9.



A (*E,E*) **B** (*Z*) **C** (*E*) **D**

[285] The first experiments on solubilization and alkylation of polylithiated open-chain peptides in the presence of LiCl have been performed in our laboratory by *S. Shoda* (Postdoctoral fellow at the ETH Zürich 1984-1986).

[286] H. Gründler, Part of the projected *Ph. D. thesis*, ETH Zürich.

[287] a) R. M. Wenger, *Helv. Chim. Acta 67* (1984) 502; b) *Angew. Chem. 97* (1985) 88-96; *Angew. Chem. Int. Ed. Engl. 24* (1985) 77-85; *Progr. Chem. Org. Nat. Prod. 50* (1986) 123-168; *Prog. Allergy 38* (1986) 46-64; R. M. Wenger, T. G. Payne, M. H. Schreier, *Prog. Clin. Biochem. Med. 3* (1986) 157-191.

[288] I sincerely thank Dr. *R. M. Wenger* of Sandoz AG, Basel, for the temporary acceptance of co-workers of my group into his laboratory, for

numerous discussions about oligopeptides and about cyclosporine, and for authentic samples and help in the identification of our products. Dr. *Wenger* has also kindly provided us with the color prints of Fig. 26.

[289] The solubilizing effect of an excess of LDA on polylithiated peptides was first observed in our laboratory by *C. W. Murtiashaw* (Postdoctoral fellow at the ETH Zürich 1983–1984).

[290] Probably other highly aggregated lithium derivatives can also be solubilized in this way, e.g., the geminal enediolates $R_2C{=}C(OLi)_2$, derived from carboxylic acids, for which "polymerization degrees" of up to 250 in THF were reported [126].

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[292] D. A. Evans, P. J. Sidebottom, *J. Chem. Soc. Chem. Commun. 1978*, 753.

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[299] One can imagine that the complexation of Li with peptides is linked to the application of Li salts in the long-term treatment of depressions; the mechanism is unknown to date, see [33] and: F. N. Johnson: *The History of Lithium Therapy* and *The Psychopharmacology of Lithium*, Macmillan Press, London 1984.

[300] T. H. Haskell, S. Hanessian, US Patent 3405218 (Oct. 8, 1968); *Chem. Abstr. 68* (1968) 89875p.

[301] See [47] and references [113, 122, 123, 135] therein.

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[304] P. T. d'Holbach (pseudonym: J. B. Mirabaud): *Système de la nature ou des lois du monde physique et du monde moral* (First edition 1770, London).

[305] Cyclosporine A (CyA): A. Rüegger, M. Kuhn, H. Lichti, H.-R. Loosli, R. Huguenin, C. Quiquerez, A. von Wartburg, *Helv. Chim. Acta 59* (1976) 1075.

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[307] CyC: R. Traber, M. Kuhn, A. Rüegger, H. Lichti, H.-R. Loosli, A. von Wartburg, *Helv. Chim. Acta 60* (1977) 1247.

[308] CyB,D,E: R. Traber, M. Kuhn, H.-R. Loosli, W. Pache, A. von Wartburg, *Helv. Chim. Acta 60* (1977) 1568.

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[318] With all other El groups shown, except $COOCH_3$, the new amino acid has *R* configuration in **C**, and *S* configuration in **D**. By the change of the CIP order of priority, the afore mentioned assignment is inverted with the aminomalonic acid moiety ($El = COOCH_3$), a demonstration that the pro-*R*/pro-*S* specification is not constitutionally invariant! In the products with El = F and $El = SCH_3$ the newly introduced substituents have highest priority, so that **C** is *R* and **D** *S*. Generally, substitution of the C^{Re} ligand on a tetrahedral center $XABC_2$ by a new group D (→ XABCD) will lead to *R*-specification in exactly 50% of all cases, depending upon whether D is No. 1, 2, 3, or 4 in the priority sequence!

[319] R_f values with 10% MeOH in Et_2O: (*R*)-Ala^3 0.56, (*S*)-Ala^3 0.51, CyA 0.47.

[320] Taken from the poem "Flag of Poland" in *The Metamict State*, Poems by Roald Hoffmann, University Presses of Florida 1987.

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[323] a) There are indications, that LiCl formed in situ increases the solubility of polybenzamides in an aprotic solvent (e.g., DMF) ("solubility mediator"): F. Schultze-Gebhart in B. von Falkai (Ed.): *Synthesefasern*, Verlag Chemie, Weinheim 1981, Chapter II, p. 452; Z. A. Rogowin: *Chemiefasern*, Thieme Verlag, Stuttgart 1982, Chapter 30, p. 375. b) The solubilization and reaction of polyamides with electrophiles by deprotonation of the amide groups with NaH in the aprotic polar solvent DMSO has recently come into use to modify the properties of polymers: M. Takayanagi, T. Katayose, *J. Polym. Sci. Polym. Chem. Ed. 19* (1981) 1133; D. R. Moore, L. J. Mathias, *J. Appl. Polym. Sci. 32* (1986) 6299; M. Takayanagi, S. Ueta, W.-Y. Lei, K. Koga, *Polym. J. 19* (1987) 467. c) The effect of the deprotonation, and solubilization with LiX, is reminiscent of the xanthate-method in the production of artificial silk from cellulose: M.-L. Kehren, A. Reichle: *Cellulose-Chemiefasern* in *Ullmanns Enzyklopädie der technischen Chemie, 4th ed., Vol. 9*, Verlag Chemie, Weinheim 1975, pp. 213–226.

[324] Taken from a speech given in Frankfurt, see [130a].