

265. Mechanistic Implications of the Tetrameric Cubic Structure of Lithium Enolates

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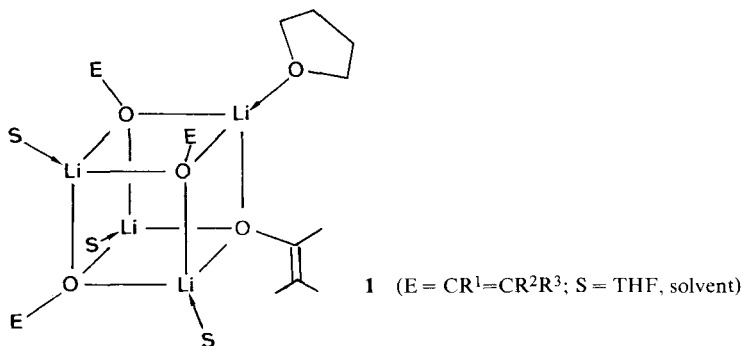
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Summary

The tetrameric cubic structure established for lithium enolates in the solid state is used as a model to discuss several facets of enolate chemistry: solubility, effects of cosolvents, addition to aldehyde and acid chloride, influence of mixed aggregates on diastereo- and enantioselectivities.

There is increasing evidence that lithium enolates, the most widely used class of d^2 -reagents in organic synthesis, form solvated, cubic, tetrameric aggregates of the type **1**. For the solid state this type of structure is definitely established for two crystalline lithium enolates and is strongly indicated for several others by their stoichiometry (see the preceding paper [1]). In aprotic solvents only aggregated species²⁾ are detected by NMR. spectroscopy [2]; even during reactions with electrophiles these aggregates are preserved and appear to be the actual reacting species, as



¹⁾ Part of the projected Ph.D. thesis of R. A., ETH Zürich.

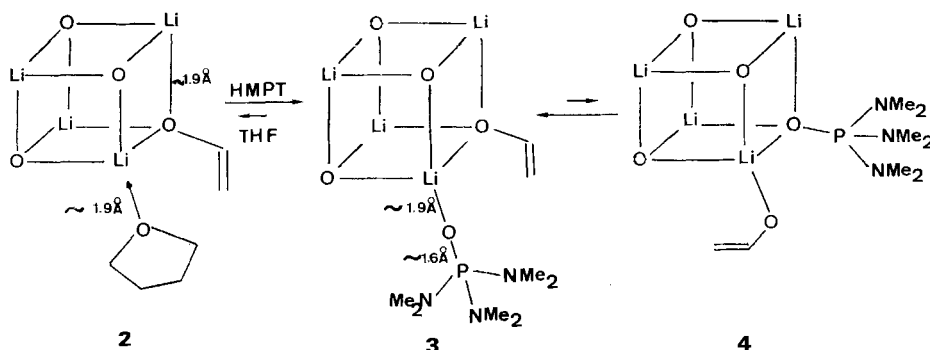
²⁾ Usually tetrameric, although in dimethoxyethane (glyme) the Li-enolate of isobutyrophenone is dimeric according to NMR. relaxation-time measurements [2]. In dimethyl sulfoxide solution LiCH₂CN occurs as a 'non-electron deficient' tetrameric aggregate [3]. Thus, what is said here about enolates probably applies - *mutatis mutandis* - also to lithiated nitriles and similar species containing electronegative heteroatoms.

indicated by reaction rates, which are first-order - and not broken-order³⁾ in enolate concentration [5].

In this paper we show from a few examples how lithium enolate chemistry can be interpreted in terms of *supermolecules*⁴⁾ of type **1**; the discussion is frankly speculative, but at least some of our proposals should be amenable to experimental testing.

The Li_4O_4 -cube owes its stability mainly to electrostatic attraction between the small Li^+ -cations and the negatively charged O-atoms of the enolate anions, each ionic center being adjacent to three counter-ions⁵⁾. A donor heteroatom of a neutral solvent molecule occupies the fourth coordination site at each Li-atom. The Li_4O_4 -cube is thus covered by a lipophilic surface layer that makes the cube soluble in organic solvents such as dimethyl ether, 2-methyl-tetrahydrofuran (MTHF), tetrahydrofuran (THF), and mixtures of these with pentane even at temperatures as low as -145° [8]. In the usual aprotic, weakly polar solvents, *i.e.* under conditions of poor anion solvation⁶⁾, replacement of a charged atom in the cube by an uncharged atom is energetically unfavorable; so is a disaggregation. On the other hand, the O-atom of a highly polar solvent molecule such as hexamethyl phosphoric amide (HMPT) should be a better ligand than the O-atom of an ether (see **2** \rightarrow **3** in Scheme 1) and should displace the latter from a corner of the cube. It might then even exchange corners with an enolate O-atom to form an isomeric cube **4**⁷⁾. The enhancement of reactivity and increase in O- vs. C-ambidoselectivity⁸⁾ of lithium enolates in the presence of cosolvents such as HMPT [2] [12] is compatible with the increased ease of access⁸⁾ to both the O- and the C (β)-atom of the enolate moiety in **3** and **4**.

Scheme 1



³⁾ Potassium enolates show different behaviour, *e.g.* the *O*-alkylation of the K-enolate of dibenzoyl methane with dimethylsulfate in DMSO is 0.24-order [4].

⁴⁾ 'Dans la chimie supramoléculaire, on crée de nouvelles entités, les supermolécules, en associant non plus des atomes mais les molécules elles-mêmes' [6].

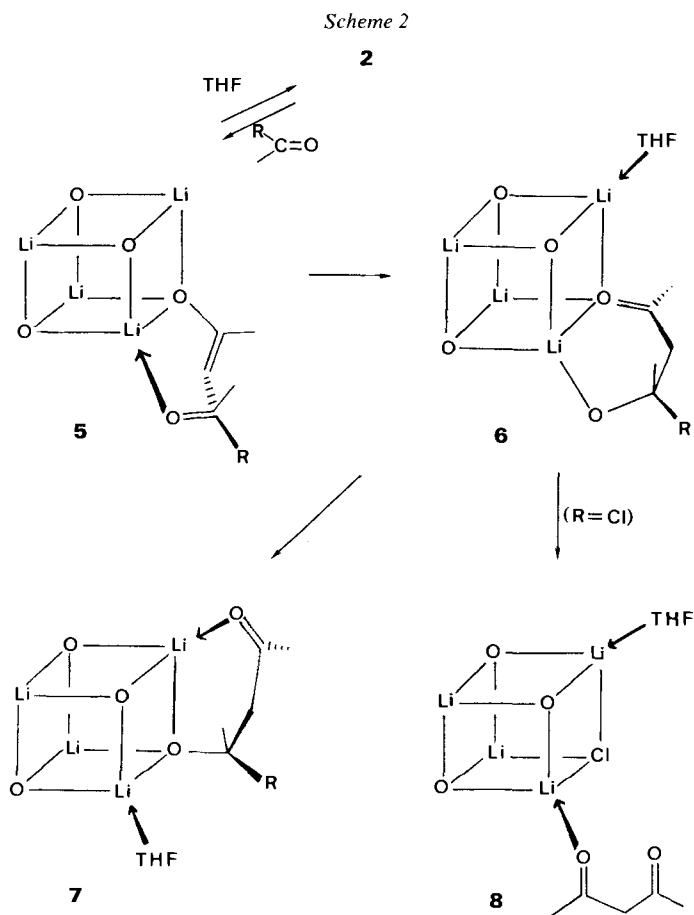
⁵⁾ Polymer-bound lithium enolates [7] cannot possibly form tetrameric aggregates and indeed exhibit some atypical properties.

⁶⁾ ... when not even crown ethers or cryptands can separate alkali cations from their counter-ions [9].

⁷⁾ Isomeric tetramers have been observed by NMR. spectroscopy [2].

⁸⁾ In THF, Li-enolates strongly favour alkylation [10] and acylation [11] on the C-atom, the more easily accessible atom of the enolate regardless of its 'hardness' or 'softness'.

The first step in the reaction of a Li-enolate cube with an electrophile should be substitution of one of the four complexing solvent molecules by the electrophile itself. This is shown in *Scheme 2* for a carbonyl substrate (see **2** → **5**). Formation of a C, C-bond between the enolate C(β)-atom and the carbonyl C-atom would then lead to **6** with the unfavorable arrangement of a neutral carbonyl O-atom (the former enolate-O-atom) *in* and a negative oxide O-atom (the former carbonyl-O-atom) *out*. If the carbonyl electrophile was an aldehyde or ketone, the two O-atoms will switch positions to give **7**; if the electrophile was an acid chloride (R = Cl), a chloride ion will be expelled from the tetrahedral intermediate and move into a corner of the cube (see **8**). The transition state between **5** and **6** may formally resemble the six-membered ring chair arrangement often invoked in discussions of the aldol reaction⁹). However, the environment encountered by an incoming sub-



⁹) The two long Li,O-bonds (ca. 2 Å) make such chairs rather different in shape from cyclohexane chairs, a difference which is often overlooked. For leading references on the stereochemistry of aldol reactions see [1] and [2] in the preceding paper [1].

strate, shown in the *Figure*, suggests that the stereochemical course of such reactions is not the result of a 1:1 rendezvous between the electrophile and one enolate, but rather depends on the influence of all three adjacent enolates. The possible implications of this for enolate chemistry are so complex and multifarious that they cannot be discussed here, but they undoubtedly contribute an additional richness to the conceptual palette of the organic chemist.

For example, the products **7** and **8** are mixed aggregates of the type $[\text{enolate}_3\text{Li}_4\text{X}]^{10}$, reagents which differ from the $[\text{enolate}_4\text{Li}_4]$ aggregates involved in the first step. Thus, quite different products could be formed with a given electrophile, depending on whether it is present in small concentration or in excess¹¹). Another consequence is that an asymmetric synthesis could be induced in a mixed aggregate containing an achiral and a chiral enolate held in the same cube. Examples of this may have been observed, inadvertently¹²).

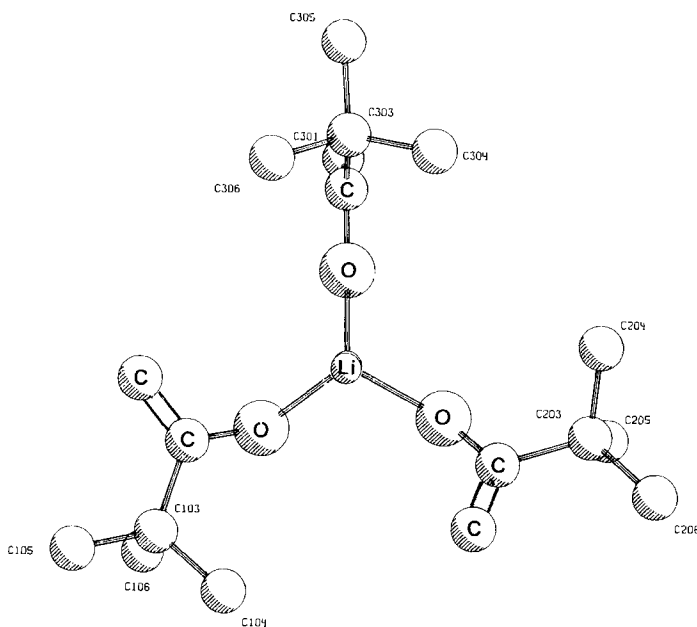


Figure. View on a Li-corner of the cube (formed from Li-enolates of pinacolone [1]) as experienced by an approaching electrophile (note the non-equivalence of the three enolates)

¹⁰) Addition of LiCl to $[\text{enolate}_4\text{Li}_4]$ leads to the formation of $[\text{enolate}_3\text{Li}_4\text{Cl}]$ characterized by NMR spectroscopy [2]. Compare with the so-called 'ate-complexes' of alkyllithium derivatives with halides [12] [13]. For one such reaction, the final product may be LiBr, which has been shown ebullioscopically to have an aggregation number of 3-4 in diethyl ether [13a]. - For K, Rb, and Cs *t*-butyl alcoholates, tetrameric cubic structures were found by powder X-ray analysis [13b].

¹¹) In fact, the related tetrameric aggregates of type $[\text{Alkyl}_4\text{Li}_4 \text{ solvent}_4]$ give drastically different results when reacted with 1, 2, 3, or 4 mol-equiv. of an electrophile; for example, see the 'strange' ratios recommended for enantioselective additions of alkyllithium reagents to aldehydes in the presence of chiral auxiliaries [14].

¹²) At least in our laboratory [15].

The change in perspective from looking at lithium enolates as monomers to considering them as cubic or other well defined aggregates necessitates careful re-examination of much of their chemistry. Insofar as their reactions actually occur between partners at *in* or *out* positions on the Li_4O_4 -cube, it may even be possible to isolate crystalline intermediates of enolate reactions. If this turns out to be the case, the reaction path would be open to exploration by crystal structure analysis [16]. Experiments in this direction are under way.

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