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Aggregated Intermediates in the Aldol Reaction Sequence. Crystal Structure of the Open Dimer of LiTMP·TMEDA

Paul G. Williard* and Qi-Yong Liu

Department of Chemistry, Brown University
Providence, Rhode Island 02912

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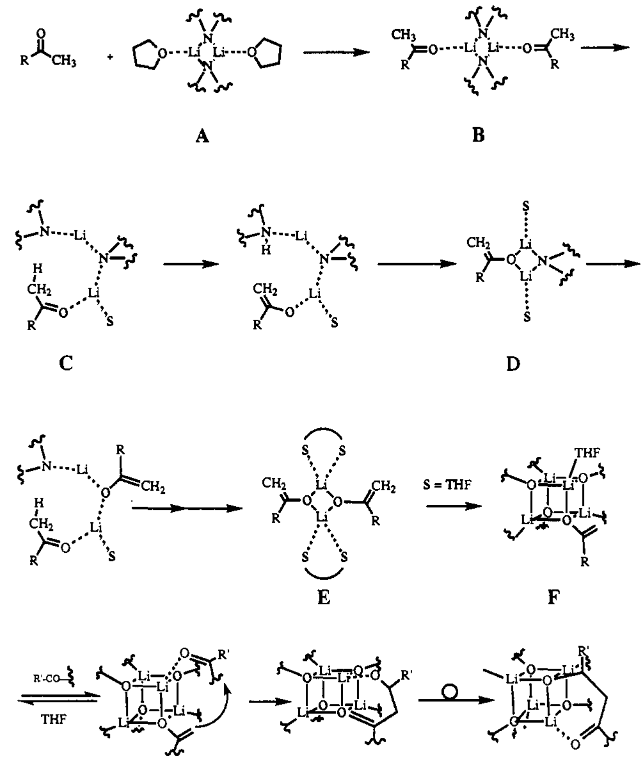
Recent crystallographic, spectroscopic, theoretical, and experimental evidence points to a more complete sequence of aggregated intermediates in the aldol and related enolate reactions than previously delineated.[1] Given the central importance of the aldol and related reactions to synthetic organic chemistry,[2] it is necessary to revise and to expand our models for these reactions in light of recent results.

A depiction of an aldol reaction as a sequence of tetrameric intermediates was put forth by Seebach et al. nearly 10 years ago.[3] At that time structural evidence had been accumulated both in solution by NMR and in the solid state by X-ray diffraction analysis for a tetrameric, tetra-THF-solvated enolate aggregate shown as intermediate F in Scheme I.[4] Structural evidence for the additional intermediates in Scheme I was lacking although a number of authors have suggested that aggregated intermediates are involved in enolate reactions.[5] An accumulation of structural information by X-ray diffraction analysis over the past several years from our laboratory and elsewhere prompts us to expand the sequence of intermediates originally proposed by Seebach to include the enolization reaction. Hence the reaction sequence depicted Scheme I emerges as a more complete model, incorporating all structural evidence to date.

At the outset of enolate formation, it is necessary for a carbonyl substrate to become associated with a dimeric, lithium amide base shown as intermediate A. The recent extensive NMR studies of Collum et al. confirm that a bis-solvated dimer A is a major form of both lithium diisopropylamide (LDA) and lithium hexamethyldisilazide (LiHMDS) in THF solution.[6] Crystallographic studies of the THF-solvated dimers of both LDA and LiHMDS are known.[7] Solution spectroscopic studies by Lochmann as well as more recent crystallographic studies confirm the existence of intermediate B in which the carbonyl substrate substitutes for the solvent in the dimeric HMDS bases.[8] A convenient descriptive name for intermediates such as B is a preenolization complex.

Scheme I. Aggregated intermediates in the aldol reaction for which structural evidence/analogy exists[a]



[a] A, bis-solvated amide base dimer; B, preenolization complex; C, open dimer; D, mixed anion aggregate; E, enolate dimer; F, enolate tetramer; G, pre-aldol complex; H, tetrameric aldolate product.

For the enolization reaction to take place, intermediate B must expose a basic nitrogen to allow proton transfer to occur. This process is likely to occur by fragmentation of the central Li–N core of the preenolization complex to produce an open dimer C. Justification for the open dimeric intermediate such as C is based upon (a) Collum's observation of open dimers of lithium tetramethylpiperidide in solution; (b) our own independent isolation and characterization by X-ray diffraction of the first example of an open dimer, depicted in Figure 1, as TMEDA-solvated lithium 2,2,6,6-tetramethylpiperidide (**1**), LiTMP·TMEDA;[9] (c) the theoretical work of Schleyer in which a somewhat similar open dimeric intermediate is proposed for the addition of an alkyllithium reagent to a carbonyl substrate; and (d) a body of experimental evidence suggesting the favorable geometry of an eight-membered ring for proton transfer.[10] In fact, our isolation and characterization of the open dimer depicted

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(9) Crystal parameters for **1**: monoclinic space group, $P2_1/n$; $a = 12.726(3)$ Å, $b = 13.195(4)$ Å, $c = 16.531(4)$ Å, $\beta = 91.10(10)°$; $V = 2775(1)$ Å^3; $z = 4$; $d_{calc} = 0.98$ g cm^{-3}; μ(Mo Kα) = 0.06 mm^{-1}; Intensity data $0 \leq h \leq 14$, $0 \leq k \leq 14$, $-18 \leq l \leq 18$; $2\theta_{max} = 47.1°$; full matrix structure refinement on F^2 using SHELXL-92 (Sheldrick, G. *J. Appl. Crystallogr.*, in press); $R(1) = 0.061$ for 2059 $F_o > 4\sigma(F_o)$ and 0.114 for all 4089 data, $wR(2) = 0.186$, GOF = 0.953. The (TMP)N–Li–N(TMP)–Li infrastructure of this open dimer is comparable with that of tetrameric, unsolvated LiTMP; see: Lappert, M. F.; Slade, M. J.; Singh, A.; Atwood, J. L.; Rogers, R. D.; Shakir, R. *J. Am. Chem. Soc.* **1983**, *105*, 302–4.

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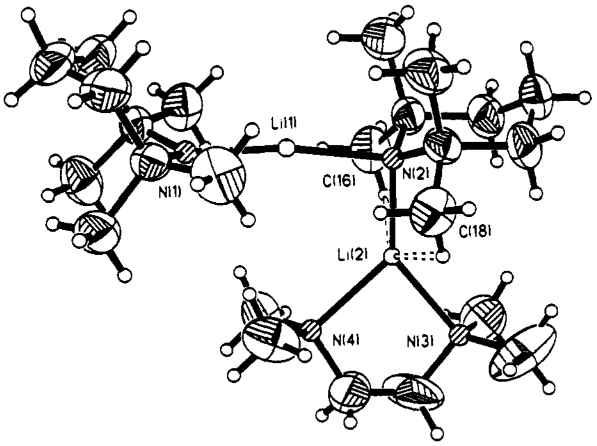

Figure 1. Crystal structure of the TMEDA-solvated, open dimer of lithium 2,2,6,6-tetramethylpiperidide, LiTMP·TMEDA. Some significant structural parameters are N(1)–Li(1) = 1.885(5) Å; N(2)–Li(1) = 2.049(5) Å; N(2)–Li(2) = 1.949(5) Å; H(16a)–Li(2) = 2.247 Å; H(18a)–Li(2) = 2.316(5) Å; N(1)–Li(1)–N(2) = 172.6(3)°; and Li(1)–N(2)–Li(2) = 98.8(2)°.

in Figure 1 provided the key link that allowed us to construct the sequence depicted in Scheme I.

Following the proton transfer in the open dimer C, a mixed anion aggregate D incorporating an equivalent amount of enolized carbonyl substrate and amide base forms. Structural evidence for the mixed aggregate D comes from our laboratory.[11] Recent experimental results in which a 1:1 stoichiometric ratio of Li enolate and a chiral Li amide base are utilized to increase the optical purity of certain enolate reaction products provide additional evidence that mixed enolate/amide base aggregates are forming and reacting in solution.[12] Mixed anion aggregates incorporating Li amide bases and enolizable substrates are also reported by Boche as quasi-dianion complexes (QDACS) and other authors.[13] Complete enolization of a carbonyl substrate under normal reaction conditions requires that the mixed anion aggregate D unblock another Li–N contact[14] via an open dimer and proceed to a dimeric[15] or tetrameric enolate aggregate E or F depending upon the solvent. The ligand denoted as S in the intermediates C through E can be the secondary amine generated from the amide base[16] or the bulk reaction solvent such as THF.

The tetrameric enolate aggregate F is well-known from Jackman's NMR studies[4b] and from Seebach's crystal structure.[4c] We provided structural analogy for the intermediate G as a tetrapinacolone-solvated, tetrameric pinacolonate aggregate, although our original structure as well as unpublished homologues incorporates sodium cations rather than lithium.[17] Unsuccessful attempts to obtain a crystal structure corresponding to intermediate G with the lithium cation have been made.[18] The first lithium aldolate crystal structure was reported as a tetramer corresponding to the final intermediate H in Scheme I although this aldolate was obtained in the absence of ethereal solvents.[19] It is noteworthy that more recent structural results as well as calorimetric studies in solution by Arnett suggest that metal aldolate products are likely to exist as aggregates.[20] Hence it is likely that a diversity of aldolate aggregate structures will be found but that very few of these will be monomeric.

Future structural results are likely to provide an even more detailed sequence of aggregated intermediates in the aldol reaction than that presented in Scheme I. It is noteworthy that the original monomeric transition state model for the Ivanov reaction as commonly applied to the aldol reaction has served as the basis for design and control of the stereochemistry of enolate reactions.[21] This Zimmerman–Traxler model has spawned a plethora of conformational variations. However, it is important to note that most enolate reactions in solution and especially in the solid state are expected to proceed through aggregated intermediates.[22] Hence it seems unlikely that complete predictability and stereochemical control of simple alkali metal enolate reactions will be possible until a complete characterization of the aggregated intermediates emerges. It is also to be anticipated that the enolization, aldol, and related reactions in solution proceed through a complex network of interrelated, aggregated intermediates rather than a single linear, sequential channel of monomeric intermediates and that these intermediates will depend upon the specific local concentration as the reaction proceeds. To date the most complete reaction model of these intermediates is given in Scheme I.

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Supplementary Material Available: Crystal data and structure refinement and tables of atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates and isotropic displacement parameters for **1** (7 pages). Ordering information is given on any current masthead page.

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