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Structure of an unsymmetrical heptalithium cage complex containing aldolate and enolized aldolate dianion

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This manuscript is dedicated to Professor Gilbert Stork on the occasion of his 90th birthday and his abiding interest in enolates

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ABSTRACT

The solid state structure of a lithium mixed anion aggregate, **1**, containing aldolate, enolized aldolate, and unenolized ketone, which are all derived from pinacolone, is described. Theoretical calculations (semi-empirical PM3 and ab initio HF/6-31G*) are used to quantify the relative stabilities of a model aldolate and also enolized aldolate isomers. Ab initio calculations indicate isomers with a cubane core, for both aldolates and enolized aldolate anions, are stabilized over open ring or ladder derivatives. The highly unsymmetrical structure of **1** incorporates three distinct components, i.e., two bridging monomeric enolized aldolates, an open monomeric enolized aldolate, and a monomeric aldolate. The composition of **1** is consistent with origination from an aldolate tetramer.

1. Introduction

Interest in enolate anions has been fueled by their ease of use as carbon–carbon bond forming units.[1] Alkylation or aldol-type addition reactions utilizing lithium enolates are the most widely used carbon–carbon forming reactions in organic synthesis and especially in the preparation of biologically active molecules.[2] The structure of lithium enolates has been widely studied with a view to understanding their formation and also importantly their selectivity.[3] To date little attention has been paid to the structure of aldolate intermediates. We now report a most unusual structure of a mixed anion complex containing unenolized ketone, aldolate, and enolized aldolate dianion.

2. Experimental section

2.1. General

Diisopropylamine (10 mmol) was mixed with 2 mL of hexane and cooled to 0 °C before addition of ^{n}BuLi (10 mmol, 1.6 M solution in hexanes). The viscous solution was stirred for 15 min and placed in a −20 °C freezer for 4 h. Precipitation of the salt was followed by removal of the solvent via syringe. The solid was washed with hexane (2×10 mL) and the solvent again syringed off. After addition of 10 ml of hexane the mixture was cooled to 0 °C and pinacolone (10 mmol) added dropwise. Upon warming the solution to 25 °C the clear solution was reduced to half volume in vacuo. Crystalline **1** was deposited after 12 h at 25 °C.

PM3 calculations were performed using the Spartan molecular modeling package. All ab initio calculations were run at the HF/6-31G* level.

3. Results and discussion

Complex **1**, $[\{^t\mathrm{BuCOCH_2C}(^t\mathrm{Bu})\mathrm{MeOLi}\}\cdot\{^t\mathrm{BuC(OLi){=}CHC}(^t\mathrm{Bu})\mathrm{MeOLi}\}_3\cdot\{^t\mathrm{BuCOMe}\}]$, was prepared as described in the experimental section. An X-ray crystallographic study of **1** reveals a cage complex containing seven lithium atoms, one pinacolone, one aldolate, and three enolized aldolate components (Fig. 1).[4]

Although the structural chemistry of lithium has great variety the structure of **1** is exceptional in its own right.[5] The very unsymmetrical nature of **1** combined with the fact that two distinct anion types are present leads to a very unusual framework. All three components of **1** are listed in Scheme 1. A simpler view is seen in Fig. 2 where only the lithium and oxygen atoms are shown. There

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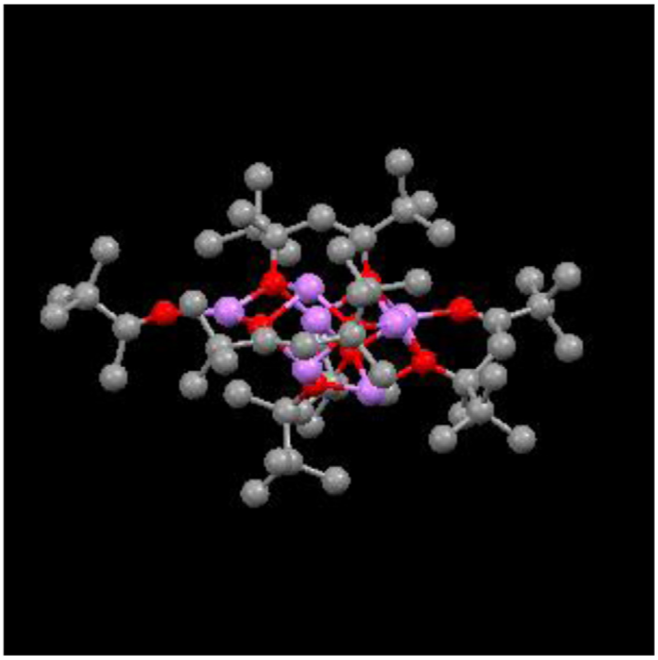


Fig. 1. Molecular structure of **1** with hydrogen atoms omitted for clarity.

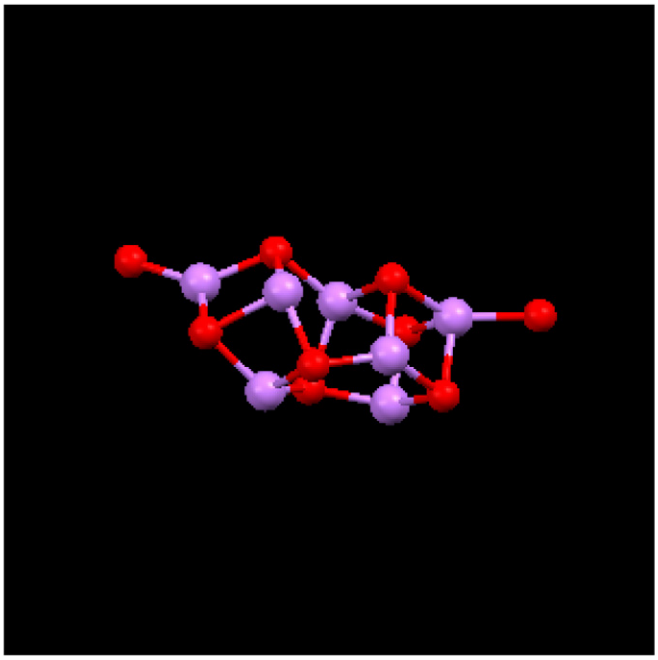
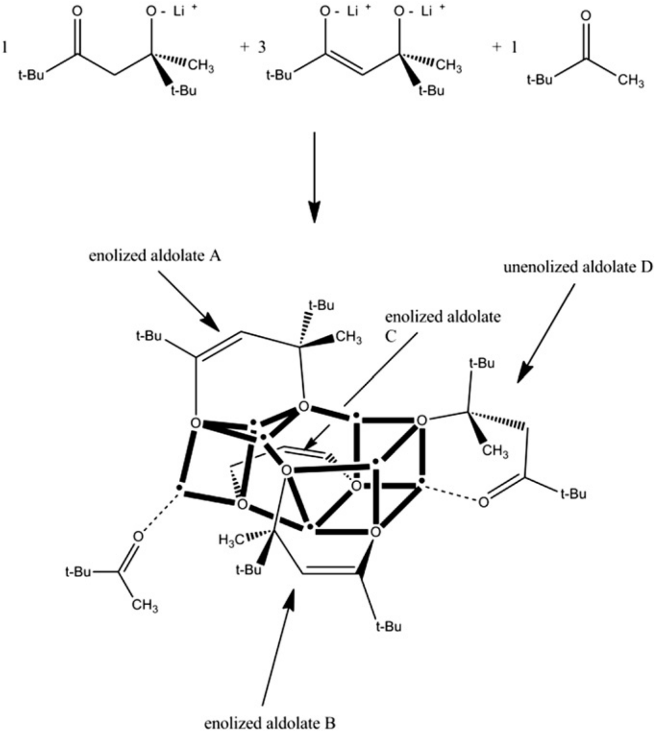


Fig. 2. Core structure of **1** showing only lithium and oxygen atoms.



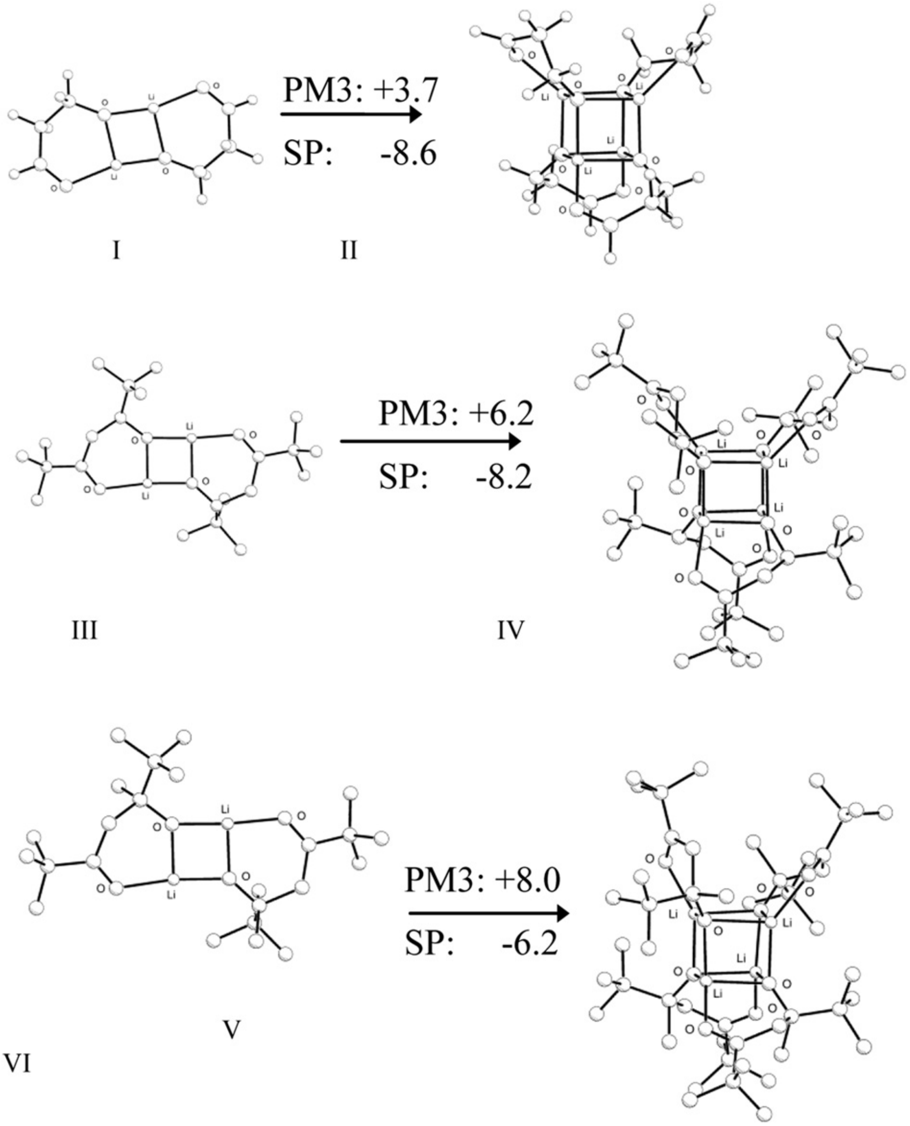
Scheme 1. Drawing of **1** showing component anions.

are 5×3 coordinate lithiums and 2×4 coordinate lithiums. Salient features of this structure are the six four membered Li–O–Li–O rings. Angles within the rings range between 74.4° and 101.0° with the average being 88.2°. Such rings are the fundamental building blocks in almost all alkali metal structures. Other stabilizing features of **1** are the three interconnected trimeric rings Li(1)–O(2)–Li(2)–O(7)–Li(5)–O(8), Li(5)–O(6)–Li(6)–O(1)–Li(7)–O(8), and Li(2)–O(4)–Li(4)–O(6)–Li(6)–O(2). The bond angles in these rings vary from 87.1° to 139.3° with an average angle of 109.7°. Similar trimers have been documented for a variety of lithium species.[6] Any explanation of the formation of **1** by analysis of the bond lengths is complicated by the profusion of short contacts between the carbon chains and some of the lithium atoms.[6e] Another important aspect of **1** is that each anionic oxygen is tetracoordinate, bonding to three lithium atoms. Pentacoordinate oxygen is very rarely found in lithium complexes.[7]

We do not wish to speculate on the mechanism of formation of **1**, since several alternatives can be envisioned. However, it is surprising that no tetrameric cube is formed, or that no cube-shaped unit is present within **1**. This is in contrast to the known capability of both enolates[8] and aldolates[9] to form tetrameric cubic structures. Although a section of the structure appears to be nearly cubic it is missing one edge of the cube. It is also composed of three distinct anions and therefore cannot be described as a broken cube.[10]

Theoretical calculations using the PM3 semiempirical method were employed to investigate the probable structures of lithiated aldolates and lithiated enolized aldolate dianions. Relative stabilities are quoted on a per lithium basis.

Calculations were conducted for dimers and cubic tetramers on three aldolate systems with increasing steric bulk: (i) HCOCH$_2$CH$_2$OLi (**I** and **II**), (ii) ^{t}BuCOCH$_2$CH(^{t}Bu)OLi (**III** and **IV**), and (iii) ^{t}BuCOCH$_2$CH(^{t}Bu)MeOLi (**V** and **VI**), using PM3 semiempirical[11] and ab initio[12] methods (Scheme 2). Although the semiempirical calculations located minima for the cubanes, the relative heats of formation predict a significant preference for the dimers (3.7, 6.2, and 8.0 kcal/mol for **I**, **III**, and **V**, respectively).[13] These results are not consistent with the experimental finding that compound **IV** is a cubane in the solid state.[9] We have recently found combining PM3 geometry optimizations with single point ab initio calculations at the HF/6-31G* level, can be a useful technique for determining relative stabilities of lithium structures.[14,15] This method was used on the aldolate structures **I**–**VI** and resulted in a reversal of the PM3 stability order (8.6, 8.2, and 6.2 kcal/mol for **II**, **IV**, and **VI**, respectively). Both semiempirical and ab initio calculations indicate increasing destabilization of the cubanes with increasing steric bulk of the aldolate. However, even the very bulky aldolate **VI** is predicted to be significantly stabilized over the dimers.



Scheme 2. PM3 optimized structures of the aldolates. The thermicity of the reactions (kcal/mol per lithium) is calculated from the PM3 heats of formation and the ab initio single point (SP) absolute energies of the dimers and tetramers. Hydrogen atoms are omitted from **II**, **IV**, **V**, and **VI** for clarity.

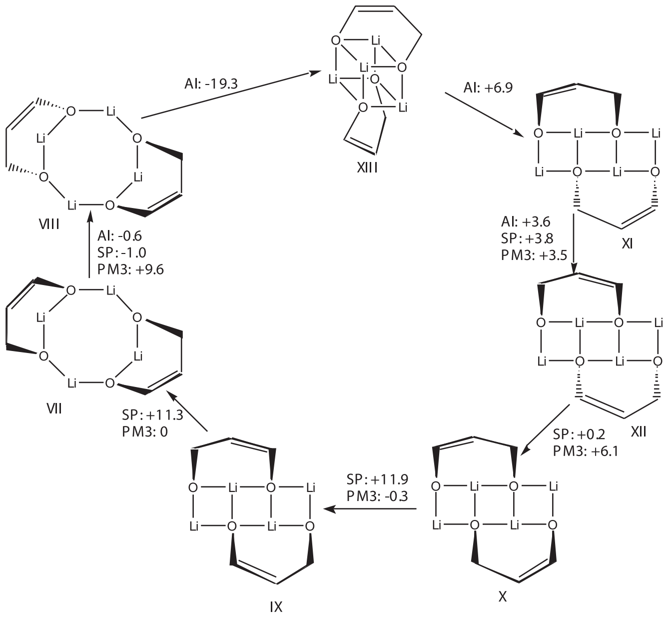
For comparison, the aldolates **I** and **II** were geometry optimized by ab initio methods at the HF/6-31G* level (see Supplementary data—Table 6). As expected, the tetrameric cubane **IIa** was determined to be highly stabilized in favor of the dimer **Ia** (10.8 kcal/mol), showing consistency with the PM3/single point calculations. A comparison of the core dimensions between the PM3 and ab initio geometry optimized structures of **I**/**II**/**Ia** and **IIa** is detailed in Table 7 in the Supplementary data. In addition, structural data is given from the crystallographically characterized aldolate $[\{^t\mathrm{Bu}\text{-}\mathrm{COCH_2CH}(^t\mathrm{Bu})\mathrm{OLi}\}_4]$ **2**, and its calculated **IV**.

Both computational methods show similar Li–O (formal and dative) bond lengths, with an average difference of 0.05 Å. The Li–O–Li and O–Li–O angles (associated with the formal bonds) in the PM3 geometry optimizations are significantly nearer 90° than the corresponding ab initio structures, with an average difference between the methods of 4.7°. Excellent agreement is found between the X-ray data for **2** and the ab initio optimized structure of the model aldolate **IIa**, with an average difference of only 0.04 Å for the Li–O bond lengths and 0.3° for the internal cubane angles. The PM3 optimization of **IV** gave reasonable agreement with the X-ray data for the Li–O bond lengths, with average difference of 0.12 Å, and the internal cubane angles were found to have an average difference of 6.6°.

From this data it appears that the semiempirical PM3 calculations give reasonable geometry optimizations but that the heats of formation are unreliable in predicting the relative stabilities of the aggregates. Using the absolute energies from single point ab initio calculations on the PM3 geometries, much better agreement is found with the geometry optimized ab initio structures. These results indicate tetramerization energies decrease with increasing steric bulk of the aldolate but are still favored over dimerization even for the very bulky aldolate derived from pinacolone (**V**/**VI**).

Since no structural data is known for these compounds,[16] three isomers were investigated by PM3 and ab initio methods: four rung ladders, open eight membered rings and cubanes; all of which are known to exist for lithium complexes.[5] The ladders and the rings were studied with the carbon chains in both cis and trans positions with respect to each other. Additionally, the ladders were optimized with the double bond associated with either the inner or outer rung oxygens. A summary of the results is shown in Scheme 3 and quantified in Table 8 in the Supplementary data.

Interestingly, no ab initio minima could be located for the ladders with the chains in a cis configuration, **IX** and **X**. Instead these geometries optimized to the cubane **XIII**. In contrast, the PM3 calculations located minima for **IX** and **X** but starting geometries



Scheme 3. Relative stabilities of the possible dimeric isomers of an enolazied aldolate. Energies are quoted in kcal/mol for the ab initio (AI). Single point (SP) and semi-emperical (PM3) calculations.

resembling the cubane **XIII** reverted to one of the ladder conformations. This complicates any direct comparisons between the computational methods. Nevertheless, the lowest energy isomer predicted from ab initio is clearly the cubane dimer **XIII**. Such cubane Li_4X_4 (X=C, N, O) cores are common for lithium compounds.[5] Furthermore, the alkoxide dianion complex [{(salen) $Li_2\cdot$hmpa}$_2$] (H_2salen=*N*,*N*′-ethylenebis (salicylideneimine)), has been determined to contain a rigid cubane core in both solution and the solid state.[17]

Thus, the cubic tetramer structure, which is typical for lithium enolates, and probably for smaller aldolates as well, is not accessible when both the reactant enolate and the reacting carbonyl compound are bulky. More studies, such as diffusion NMR[18] will be required to determine whether **1** represents the main component in solution as well, and, if not, what other aggregates are present.

4. Conclusion

Theoretical calculations (PM3/6-31G* and 6-31G*) indicate that both the aldolate and enolized aldolate complexes prefer to adopt cubane frameworks. The driving force for this structural motif will be to maximize the number of Li—O(anion) contacts.

Complex **1** can be broken into four separate units, two bridging monomeric dianions (associated with Li1 and Li6) and (associated with Li4 and Li5), an open dianion (associated with Li2 and Li7) and an aldolate monomer (associated with Li3). A possible reason for the formation of such a structure could be that it is the thermodynamic product due to a reduction in the steric interferences incurred in the homoleptic tetramers. However, the calculations indicate that the homoleptic tetramers are viable structures. Sequential lithiation of the aldolate tetramer will result in Li—O bond breaking in the cubane, to allow association of the incorporated metal with either two, three or four oxygen atoms. Each anionic oxygen in the cage remains tetracoordinate. In a similar vein, Snaith has recently suggested that the mixed anion aggregate $[(Ph_2NLi)_2\cdot\{Ph(C_6H_4Li)NLi\}_2\cdot(^nBuLi)_2\cdot(Et_2O)_4]$ represents an intermediate in the *ortho*-metalation of diphenylamine.[19]

No dilithiated aldolate has been crystallographically characterized previously and only one lithium aldolate has been reported.[9] Nevertheless, both species have proven to be useful anions for organic transformations.[1,3,20] Since an unenolized ketone is present in the structure (O9), either excess pinacolone was present or, more likely, not all of the pinacolone was enolized. This latter situation accounts for the presence of aldolate and dianion in place of enolate. A quantitative yield of crystals was not determined due to the uncertainty in the efficiency of crystallization. Another point to note is the temperature for reaction and crystallization. Ambient temperature and reduction of the solution under vacuum may lead to a variety of products since as is well known enolization and aldol additions are commonly performed at low temperature (≈ -78 °C). Attempts at a rational synthesis of **1** have thus far been unsuccessful. It is possible that the formation of **1** was critically dependant on the conditions used in its preparation. We are currently investigating the possibility of sequentially deprotonating lithium aldolate tetramers in a rational manner.

Complex **1** represents an interesting addition to enolate structural chemistry. From previous investigations it is clear that enolization and subsequent aldol addition reactions involve complex aggregates.[3] This is certainly affirmed by **1**, which is complex not only in its structural arrangement but also in that it contains distinct anion types. Hence we suggest that structural results as reported herein and as noted above represent a preliminary glimpse of the complex, aggregated organolithium structures that are routinely present in solutions of enolates and their related reaction products. Some additional possibilities are depicted in Scheme 3.

Acknowledgements

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Supplementary data

Full crystallographic details including atomic coordinates, thermal parameters, bond lengths and angles, atomic displacement parameters, quantitative results of semi-emperical and ab initio calculations. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.10.047.

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