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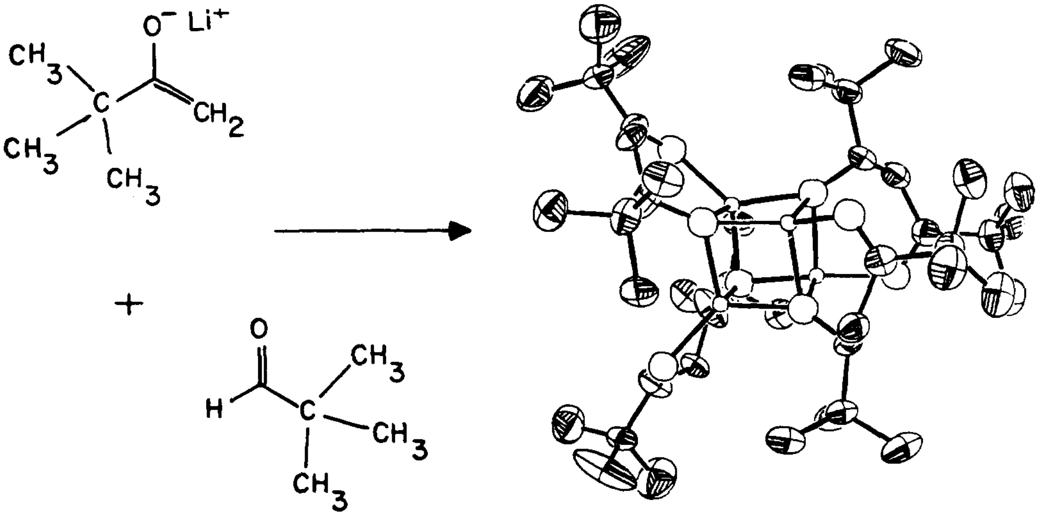
X-RAY CRYSTAL STRUCTURE OF A LITHIUM ALDOLATE - A TETRAMERIC AGGREGATE

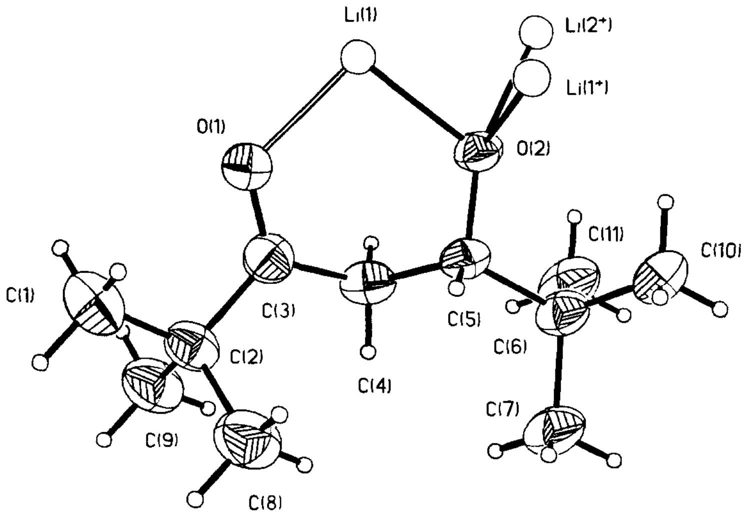
Paul G. Williard* and Joseph M. Salvino
Department of Chemistry, Brown University, Providence, RI 02912

Abstract: The aldol adduct formed from addition of pivalaldehyde to the lithium enolate of pinacolone crystallized directly from the reaction mixture and was subjected to x-ray diffraction analysis.

The utility of the aldol reaction in organic synthesis is undeniable. A number of recent reviews aptly summarize the current state of knowledge concerning this and related reactions.[1] In most cases, comparative product analysis provides the basis for thinking about the reactions' mechanistic and stereochemical aspects. However, some kinetic analyses as well as a molecular mechanical interpretation[2] of the aldol reaction are reported. Recent x-ray diffraction analyses of lithium anions[3] from this and other labs led us to consider a crystallographic study of the aldol reaction. Hence, we now report the first single crystal, x-ray structure determination of a lithiated aldol intermediate.



Reaction of the lithium enolate of pinacolone with pivalaldehyde proceeds at 0° C in pentane to give a clear, colorless solution of the aldol product. Cooling this solution to -28° C overnight produces crystals suitable for diffraction analysis.[4] Structure determination[5] reveals that this aldol is a tetrameric aggregate in the solid state. The figure above depicts this tetramer. The small circles represent lithium atoms and the large circles are oxygens. An expanded view of one-fourth of this tetramer is given on the following page along with bond lengths and angles.



Representative Lithium Aldol Product

Bond lengths[a,b] (Å)	
Li(1)-O(1)	1.973(5)
Li(1)-O(2)	1.941(4)
O(1)-C(3)	1.224(3)
O(2)-C(5)	1.383(3)
C(2)-C(3)	1.519(4)
C(3)-C(4)	1.510(4)
C(4)-C(5)	1.559(4)
C(5)-C(6)	1.557(4)
Li(1+)-O(2)	1.953(5)
Li(2+)-O(2)	1.913(5)

Bond angles[a] (deg.)	
O(1)-Li(1)-O(2)	97.3(2)
Li(1)-O(1)-C(3)	122.2(2)
Li(1)-O(2)-C(5)	121.3(2)
O(1)-C(3)-C(2)	120.3(2)
O(1)-C(3)-C(4)	119.3(2)
O(2)-C(5)-C(4)	110.1(2)
O(2)-C(5)-C(6)	112.7(2)
C(2)-C(3)-C(4)	120.4(2)
C(3)-C(4)-C(5)	110.0(2)
C(4)-C(5)-C(6)	112.8(2)

Dihedral angles[a] (deg.)	
Li(1)-O(1)-C(3)-C(2)	152.6(8)
Li(1)-O(1)-C(3)-C(4)	-28.0(2)
Li(1)-O(2)-C(5)-C(4)	39.6(3)
Li(1)-O(2)-C(5)-C(6)	166.5(9)
O(1)-C(3)-C(4)-C(5)	67.9(6)
C(3)-C(4)-C(5)-O(2)	-71.5(6)
C(1)-C(2)-C(3)-O(1)	-8.4(2)
C(4)-C(5)-C(6)-C(7)	-66.3(3)

Perpendicular displacement (Å) from least squares plane[c]

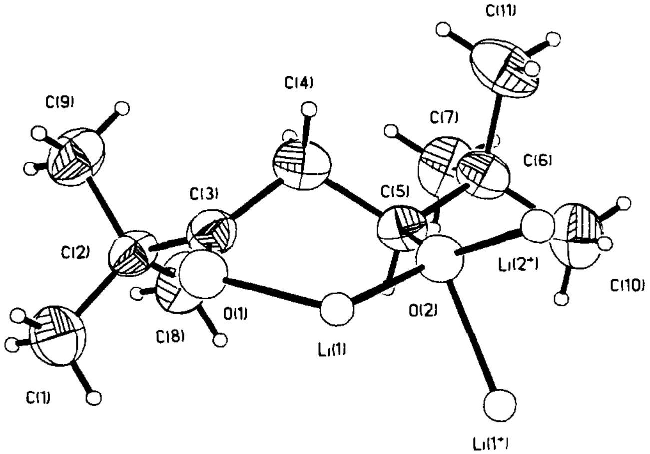
Li(1) = -0.13; O(1) = 0.09; O(2) = -0.01; C(3) = 0.20; C(4) = -0.44; C(5) = 0.29;
C(1) = 1.65; C(2) = 0.95; C(6) = 0.02; C(7) = 0.64; C(8) = 1.98; C(9) = -0.07; C(10) = 0.66; C(11) = -1.49;

[a] Values given represent the specific fragment of the crystallographic asymmetric unit depicted. Numbers in parentheses are the standard deviations of these values.

[b] Second lithium atoms generated by the transformation (-x, y, 0.5-z).

[c] The plane, defined by the equation $(-7.449 \cdot x + 7.808 \cdot y + 14.745 \cdot z = 2.6416)$, is the least sqaures plane through the six atoms Li(1), O(1), O(2), C(3), C(4), and C(5).

The monomeric aldol unit on the previous page is rotated by ≅90° about a horizontal axis and is replotted below. This perspective emphasizes the disparity between the traditional chair (or boat) conformation of carbocyclic 6-membered rings and that which is observed for the lithium chelate. Noteworthy features of this plot are the near planarity of Li(1), O(1), O(2), C(3), and C(5) as shown by the relative displacements from a least squares plane and the contracted bond angle for O(1)-Li(1)-O(2). While chelation is clearly important in this partial structure and in the tetrameric aggregate as a whole, the resemblance of this partial structure to the transition state of the aldol reaction[6] remains speculative.



The tetrameric aggregate exhibits approximate S_4 symmetry. A horizontal rotation-inversion axis passes through the conters of the side faces of the cube in the perspective shown. Clearly S_4 symmetry is not be possible for chiral aldols, although tetrameric aggregation is certainly not excluded. Recent NMR studies of organolithium compounds[7] and measurements of colligative properties of enolate solutions[8] suggests that crystallographically determined aggregates are the same as those in solution. The reactivity of enolate anions may ultimately be related to the aggregation state of these species since these aggregates may be the reactive intermediates themselves.[9]

Diastereoselection in the aldol reaction is definitely related to enolate geometry.[1] Since this simple aldol product cannot exhibit diastereoisomerism, nothing can be deduced about the topography of its formation. Perhaps a better understanding of aldol reaction topography will arise when more is learned about the stereochemical features of the aggregates which take part in the reaction. This knowledge may also lead to a more rational choice of chiral auxiliaries for effecting enantioselection in the aldol reaction.

In light of this crystal structure, the aldol reaction mechanism proposed by Seebach, Amstutz and Dunitz[10] is extraordinarily perspicacious. No doubt future experimental work will elucidate additional details of this mechanism.

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4. The aldolate crystallized in the monoclinic space group C 2/c with unit cell parameters a = 21.039(12) Å, b = 12.153(7) A, c = 20.230(8) A and β = 99.53(4)°. The crystallographic asymmetric unit consists of a species of formula $(C_{11}H_{21}O_2Li)_2$. The unit cell contains eight such species and produces a calculated density of 1.00 g/cm^{-3}. A total of 3400 reflections were recorded in the range $3.5° \leq 2\theta \leq 45°$ by the $\theta:2\theta$ scan routine routine using MoKα radiation (λ =0.71069 A). A total of 2639 unique reflections were observed using the criteria $[F_0 \geq 2.5\sigma(F_0)]$.

5. Direct methods (SHELXTL 4.1) solved the structure. All non-hydrogen atoms were refined anisotropically. Hydrogens were located by Fourier difference synthesis, constrained to ride on an attached atom, and refined isotropically. The final agreement factors are R = 0.0629 and R_w = 0.0726 for 318 independent variables. Some disorder was noted for one of the t-butyl groups and for one of the methylene groups. Site occupation factors were refined for the disordered groups. Crystallographic parameters have been deposited with the Cambridge Crystallographic Data Center, Lensfield Road, Cambridge, England.

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