corresponds to log P_{CE} = 4.7 and 27 for PS1(18C6) and PS2-(12C4), respectively.

The experimental data can be interpreted nicely by a model developed in our group recently. From this interpretation a 2:1 stoichiometry of the complexes in the membrane phase was deduced, for both 12-crown-4- and 18-crown-6-containing carriers.

Experimental Section

The ^{1}H NMR spectra were recorded with a Bruker WP-80 spectrometer with $(CH_3)_4Si$ or $CHCl_3$ as an internal standard.

Materials. The synthesis of (hydroxymethyl)-18-crown-6 (**8**) has been carried out according to known procedures.[18-20] (Hydroxymethyl)-12-crown-4 (**9**) was obtained from Janssen, dibenzo-18-crown-6 was from Merck Schuchardt, and both were used without further purification. *o*-Nitrophenyl *n*-octyl ether (Fluka) was distilled before use. Potassium perchlorate (Brocades) was used without purification. The polymeric film Accurel was obtained from Enka Membrana.

(4-Bromobutyl)chlorodimethylsilane (3). 4-Bromo-1-butene (6.0 g, 0.05 mol), chlorodimethylsilane (7.1 g, 0.075 mol), and the catalyst (10 μL of 0.1 M $H_2PtCl_6 \cdot 6H_2O$ in 2-propanol) were dissolved in 20 mL of toluene and stirred under nitrogen at 85 °C for 18 h. Toluene was evaporated under reduced pressure, and the residue was distilled at reduced pressure (34-36 °C at 2.3 mmHg). Yield 7.2 g (63%); ^{1}H NMR ($CDCl_3$) δ 3.4 (t, J = 6.5 Hz, 2 H, CH_2Br), 1.9 (quintet, J = 6.5 Hz, 2 H, CH_2CH_2Br), 1.8-1.3 (m, 2 H, $CH_2CH_2CH_2Br$), 1.0-0.7 (m, 2 H, SiH_2C), 0.4 (s, 6 H, SiH_3C).

4-Bromobutyl-Terminated Poly(dimethylsiloxanes) (6 and 7). (4-Bromobutyl)chlorodimethylsilane (**3**) (4.45 g, 19.4 mmol) was dissolved in 25 mL of petroleum ether (bp 60-80 °C) and added slowly to a stirred solution of the silanol-terminated siloxane (8.8 mmol) and *N*,*N*-diisopropylethylamine (1.14 g, 8.8 mmol) in 25 mL of petroleum ether under nitrogen atmosphere at 0 °C. Stirring was continued for 1 h. The solid salts were removed by filtration, and subsequently, the solvent was evaporated. The excess of chlorodimethylsilane was removed by distillation at reduced pressure (80-90 °C at 2.4 mmHg) to yield **6** and **7** (70-90%). ^{1}H NMR ($CDCl_3$) δ 3.4 (t, J = 6.5 Hz, 4 H, CH_2Br), 1.9 (quintet, J = 6.5 Hz, 4 H, CH_2CH_2Br), 1.8-1.3 (m, 4 H, $CH_2CH_2CH_2Br$), 0.7-0.4 (m, 4 H, $SiCH_2$), 0.1 (s, $SiCH_3$).

Crown Ether Terminated Poly(dimethylsiloxanes) (10-12). The hydroxymethyl crown ether (**8** or **9**) (4 mmol) was dissolved in 10 mL of dry THF, and 1.5 equiv of NaH, previously washed with petroleum ether (bp 60-80 °C), was added. While this solution was refluxed, a solution of 0.9 equiv of **6** or **7** in 15 mL of dry THF was added slowly. The reaction mixture was refluxed overnight. After quenching with ethanol, the solvent was evaporated. The residue was dissolved in $CHCl_3$, and the salts were removed by filtration. The filtrate was washed with H_2O and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Yield 50-70%; ^{1}H NMR ($CDCl_3$) δ 3.8-3.2 (m, OCH_2), 1.8-1.0 (m, $CH_2CH_2CH_2$), 0.8-0.4 (m, $SiCH_2$), 0.1 (s, $SiCH_3$).

Apparatus. The permeation cell consisted of two identical cylindrical compartments (half-cell volume, 45 mL; effective membrane area, 9.8 cm^2). Each compartment contained four baffles, which are flat strips set radically along the wall of the compartments. The baffle width was one-tenth of the diameter of the cell. A flat-bladed turbine positioned at the center was driven by a magnet outside the compartment at a stirring rate of 1000 rpm. The use of baffles with turbine impellors secured a large top-to-bottom circulation, creating well-mixed solutions without significant concentration gradients. The diameter of the turbine was one-third of the diameter of the compartment. The compartment was double-walled for thermostating using a thermostated water bath (Tamson, TC). The membrane was positioned between the cylindrical compartments containing the two aqueous phases. The supported liquid membrane consisted of a solution of carrier in *o*-nitrophenyl *n*-octyl ether immobilized in a porous polypropylene film (Accurel; thickness, d_m = 100 μm; porosity, θ = 64%). A 0.1 M potassium perchlorate solution was used as the source phase, and doubly distilled and deionized water was used as the receiving phase. The amount of transported potassium perchlorate was determined by measuring the conductivity of the receiving phase (Philips PW 9527 conductivity meter and a Philips PW 9512/61 electrode with a cell constant of 0.74 cm^{-1}).

Registry No. **1**, 5162-44-7; **2**, 1066-35-9; **3**, 52112-26-2; **4**, 4029-00-9; **6**, 123640-18-6; **8**, 17455-13-9; **9**, 294-93-9; **10**, 123640-20-0; **11**, 123640-19-7; K, 7440-09-7; *o*-nitrophenyl *n*-octyl ether, 37682-29-4.

(18) Krespan, C. J. G. *J. Org. Chem.* **1974**, *39*, 2351-2356.
(19) Howe, R. J.; Malkin, T. *J. Chem. Soc.* **1951**, 2663-2667.
(20) Dishong, D. M.; Diamond, C. J.; Cinoman, M. I.; Gokel, G. W. *J. Am. Chem. Soc.* **1983**, *105*, 586-593.

Structure-Energy Relations for the Aldol Reaction in Nonpolar Media

Edward M. Arnett,* Franklin J. Fisher, Michael A. Nichols, and Anthony A. Ribeiro[1]

Contribution from the Department of Chemistry and Duke NMR Center, Duke University, Durham, North Carolina 27706. *Received June 12, 1989*

Abstract: A complete thermochemical analysis is presented for the aldol reaction of lithiopinacolonate with pivalaldehyde in hexane at 25 °C and in cyclohexane at 25 and 6 °C. Reactions were performed in the presence and absence of tetrahydrofuran, tetramethylethylenediamine, and dimethoxyethane. Solution structures of the reactants and products were determined by using colligative property techniques (vapor pressure osmometry and freezing point depression) to measure the degrees of aggregation and by using ^{6}Li and 2D ^{6}Li-^{1}H heteronuclear Overhauser enhancement (HOESY) NMR. Titration calorimetry was used to determine the heats of reaction of pivalaldehyde with the hexameric lithiopinacolonate, the tetrameric and dimeric enolate·ligand complexes, and heats of interaction of the hexameric enolate with the ligands. It is shown that the tetrameric lithium aldolate product does not complex with any of the three ligands in hydrocarbon solution. A complete description of experimental techniques is given, and most of the data have been confirmed by two complete and independent repetitions. However, attention is drawn to an erroneous, and presently unexplained value (ΔH_{rxn} = -30.19 kcal/mol) reported in our previous communication for the aldol reaction of the uncomplexed hexameric lithiopinacolonate with pivalaldehyde in hexane at 25 °C. To our knowledge, the present article is the first complete structure-energy analysis of an aldol reaction under conditions approaching those used in modern synthesis. The results emphasize the importance of caution in proposing detailed mechanisms for this important reaction.

Base-promoted reactions of carbonyl compounds and their nitrogen equivalents are by any accounting the most important class of modern synthetic reactions. Within this family, the aldol reaction has become one of the most powerful means for forming carbon-carbon bonds.[2] Although now over 150 years old,[3] it has only been since the early 1970s[4] that the aldol reaction has as-

(1) Duke Nuclear Magnetic Resonance Center, 152 Jones Building, Duke University Medical Center.

(2) (a) Carey, F. A.; Sunberg, R. J. In *Advanced Organic Chemistry*, 2nd ed.; Plenum Press: New York, 1983; Part B, Chapter 10. (b) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*, Vol. II; Durst, T.; Buncel, E., Eds.; Elsevier: Amsterdam, 1983; Part B.

0002-7863/90/1512-801$02.50/0

sumed a position of such stature. Prior to that, it was run in protic media at room temperature, or higher, and was usually accompanied by so many side reactions (e.g. elimination and polymerization) that its value was badly compromised.

The modern aldol reaction[5] is run at low temperatures in nonpolar solvents, usually ethers, and has increasingly used sterically hindered lithium amide bases to form the enolate. The addition of an aldehyde or ketone to the lithium enolate produces the lithium aldolate product instantly, even at −80 °C. The two carbons that are joined in the aldol process usually become chiral, resulting in a mixture of diastereomeric products. An especially useful feature of the reaction is the potential conversion of the first-formed "kinetic product" into a more stable "thermodynamic" diastereomer when remaining in the basic reaction solution or raising the temperature.

A series of beautifully designed stereochemical experiments[2b,5b-f] have clarified the empirical basis for diastereoselective reactions and have helped in the development of useful guidelines and "rules of thumb" for predicting the stereochemical outcome under different conditions. These product-distribution studies have been interpreted in terms of postulated transition-state structures,[2b,5b-f,6] which usually picture a monomeric enolate and the carbonyl addend bound in a cyclic structure that is organized by chelation to the metal counterion.

Recently, it has become clear that alkali enolates are actually highly aggregated in low-polarity solvents under synthetic aldol reaction conditions. Driving forces for aggregation are primarily electrostatic;[7] it is now generally agreed that the carbon–lithium bond of methyllithium is almost entirely ionic,[8] and even potassium enolates may be hexameric in hydrocarbon solutions.[9] In fact, it now appears that only very low concentrations of monomeric enolate ions exist in nonpolar solvents at low temperature and that they may very well not be the true reactive intermediates in most aldol or alkylation reactions. Several careful studies[10] of complex systems involving organolithium compounds indicate that the aggregated species may be the true reactive intermediates. In these cases, it can be envisioned that the product stereochemistry is determined by attack on the faces of these aggregates. If this scenario is correct, then the great predictive success of lithium enolate chemistry must be attributed to its rich empirical data base rather than to any special insight provided by the monomeric transition-state models.[11]

In sharp contrast to the many synthetic studies of enolate reactions, there have been relatively few rigorous physical organic investigations carried out on relevant systems under synthetic conditions. In addition to the seminally important X-ray studies[12] that provide unequivocal evidence of hexameric, tetrameric, and dimeric structures of the crystalline enolates, there are several reports using NMR and colligative properties in which the degrees of aggregation and solution structures were determined.[13] Furthermore, studies have shown that amine molecules produced from the original deprotonation of the ketone may be part of the aggregates,[10h,i,14] as well as solvate molecules of ether or halide ions[10d,g,12,13a,15] produced during alkylation reactions. The complexity of these aggregates and their rapid rates of interconversion have provided a formidable barrier to complete mechanistic analysis.

Previous investigations in this laboratory have deliberately avoided most of these problems by using resonance-stabilized dicarbonyl enolates in DMSO solution.[16] Even under these conditions where simple equilibria between ions and ion pairs may be demonstrated, the abnormal behavior of lithium enolates compared to their sodium or potassium cognates suggested the presence of higher lithium aggregates.

In view of these complexities, we were intrigued by Williard's report of the hexameric structure of lithium pinacolonate crystals as precipitated from hexane solution,[12a] the corresponding tetrameric lithium aldolate product resulting from reaction with pivalaldehyde in hydrocarbon solution,[17] and Seebach's reported X-ray crystal structures of THF[18] and TriMEDA[10i] solvated lithiopinacolonate. Williard's studies provided the first unequivocal structural information on the reactant and product for a simple aldol reaction under modern synthetic conditions and provided us with the occasion for a thermochemical investigation, which we have reported in a preliminary account.[19]

(3) (a) Kane, R. *Ann. Physik Chem.* **1838**, *44*, 55. (b) Kane, R. *J. Prakt. Chem.* **1838**, *15*, 129.

(4) Neilson, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1–403.

(5) For reviews of the modern aldol reaction: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654. (b) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47–63. (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1982; Vol. 13. (d) Heathcock, C. H. *Science* **1981**, *214*, 395–399. (e) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, Chapter 2. (f) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32. (g) Hajos, Z. G. In *Carbon–Carbon Bond Formation*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; Vol. 1, Chapter 1. (h) Mukaiyama, T. *Org. React.* **1982**, *28*, 203–331. (i) Braun, M. *Angew. Chem.* **1987**, *26*, 24–37. (j) Masumune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30. (k) Heathcock, C. H. In *Current Trends in Organic Synthesis*; Nazaki, H., Ed.; Pergamon Press: New York, 1983; pp 27–43.

(6) (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923. (b) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828–5835. (c) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367–1371. (d) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199–2204. (e) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70. (f) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162–7173. (g) Li, Y.; Paddon-Row, M. N.; Houk, K. M. *J. Am. Chem. Soc.* **1988**, *110*, 3684–3686.

(7) (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737–2769. (b) Jackman, L. M.; Smith, B. D. *J. Am. Chem. Soc.* **1988**, *110*, 3829–3835.

(8) (a) See: Kaufmann, E.; Raghavachari, K.; Reed, A. E.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 1597–1607 and footnotes 29–35 therein. (b) Bushby, R. J.; Steel, H. L. *J. Organomet. Chem.* **1987**, *336*, C25–C32.

(9) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 3345–3346.

(10) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258. (b) Hope, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932–948. (c) Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 4494–4499. (d) Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, *107*, 2805–2806. (e) Seebach, D. In *Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research*, Houston, TX, 1984; Welch Foundation: Houston, TX, 1984. (f) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805–1810. (g) DePue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524–5533. (h) Strazewski, P.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 1041–1051. (i) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373–1393.

(11) Aggregated aldol transition states have been proposed in the following: (a) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622. (b) Heathcock, C. H.; Lampe, J. *J. Org. Chem.* **1983**, *48*, 4330. (c) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539–5541.

(12) For reviews of X-ray crystal structures of organolithium compounds: (a) Footnotes 3, 4, 6, and 7 in Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462–468. (b) Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 354–450 and references therein. (c) Reference 10e. (d) Schade, C.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1987**, *27*, 169–272 and references therein. (e) *J. Organomet. Chem.* **1988**, *350*, 327–330.

(13) For reviews and studies of organolithium solution structures: (a) Footnotes 2–4 in DePue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5518–5524. (b) Footnotes 8 and 10 in ref 10g. (c) Footnotes 4 and 5 in ref 9.

(14) (a) Tamm, C.; Gamboni, R. *Helv. Chim. Acta* **1986**, *69*, 615–620. (b) Miller, D. J.; Saunders, W. H., Jr. *J. Org. Chem.* **1982**, *47*, 5039–5041. (c) Helmchem, G.; Grottemeirer, G.; Schmierer, R.; Selim, A. *Angew. Chem.* **1981**, *93*, 209.

(15) (a) Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954–4962. (b) Jackman, L. M.; Haddon, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 3687–3692.

(16) (a) Arnett, E. M.; DePalma, V. M. *J. Am. Chem. Soc.* **1976**, *98*, 7447–7448. (b) Arnett, E. M.; DePalma, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 5828–5829. (c) DePalma, V. M.; Arnett, E. M. *J. Am. Chem. Soc.* **1978**, *100*, 3514–3525. (d) Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759–6767. (e) Arnett, E. M.; Maroldo, S. G.; Schriver, G. W.; Schilling, S. L.; Troughton, E. B. *J. Am. Chem. Soc.* **1985**, *107*, 2091–2099. (f) Arnett, E. M.; Harrelson, J. A. *J. Am. Chem. Soc.* **1987**, *109*, 809–812. (g) Arnett, E. M.; Harrelson, J. A. *Gazz. Chim. Ital.* **1987**, *117*, 237.

(17) Williard, P. G.; Salvino, J. M. *Tetrahedron Lett.* **1985**, *26*, 3931–3934.

(18) Amstutz, R.; Schwiezer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617–2621.

(19) Arnett, E. M.; Fisher, F. J.; Nichols, M. A.; Ribeiro, A. A. *J. Am. Chem. Soc.* **1989**, *111*, 748–749.

The present article provides the experimental details of our thermochemical, vapor pressure osmometric, and ^6Li-^1H HOESY NMR studies, along with additional cryoscopic measurements that prove that the X-ray structures of the crystalline reactants and product were also the principle structures in hydrocarbon solution. Further evidence is also given below for the effects of added solvates and other ligands on the thermochemistry and structures involved in the reaction.

Experimental Section

Materials and General Procedures. All chemicals whose purification is not explicitly mentioned in this section were purified by standard methods.[20] Purity was checked by ^1H NMR, melting point, and boiling point, where applicable. Tetrahydrofuran (THF, Fisher), and cyclohexane (Fisher)/1% bis[2-(2-methoxyethoxy)ethyl] ether (Kodak) were distilled from the sodium/benzophenone ketyl. Hexane (Mallinckrodt) was stored over 4-Å molecular sieves and used without further purification. Benzene-d_6 (Aldrich) and cyclohexane-d_{12} (Aldrich) were used directly from their commercially sealed ampules. All manipulations were carried out under argon by using standard techniques,[21] or in a Vacuum Atmospheres HE-43-2 dry box equipped with a VAC HE-493 purification system. Water content of the solvents was checked by either a Mettler DL-18 or a Labindustries Aquametry I Karl Fisher titrator. Proton and ^{13}C NMR spectra were recorded on either a IBM NR-80, a Varian XL-300, a JEOL FX-90Q, a General Electric GN-300, or a GN-500 NMR spectrometer at ambient temperature (~25 °C), unless otherwise noted. Chemical shifts are reported in ppm relative to the residual carbons or protons of the solvent.[22]

Purification of Lithium Bis(trimethylsilyl)amide (LiHMDS). Various forms of the kinetic base LiHMDS were used in these studies. The solution in hexanes (1 M, Aldrich) was found to be most convenient. However, we have experienced some irreproducible calorimetric results that have been traced to different commercial batches of the base.[23] The purest form of LiHMDS used was obtained from the solid (Aldrich, 99.8%), which was sublimed at <70 °C (10^{-2}–10^{-3} Torr) to remove possible lithium halide impurities. The white crystalline material was then stored under vacuum in a dry box prior to use. All cyclohexane solutions utilized this form of the base.

Syntheses of the Lithium Pinacolonates and Aldolate. The lithium enolate of pinacolone (I) was prepared by the addition of 2.5 mL (20 mmol) of 3,3-dimethyl-2-butanone (Aldrich) to 20 mL of a 1 M LiHMDS solution in hexanes at 0 °C. Crystals were isolated upon cooling to −78 °C and purified by washing with *n*-pentane. Volatiles were removed under vacuum, and the enolate salt was transferred to a dry box for further manipulation: ^1H NMR (C_6D_6, 80 MHz) δ 3.99 (d, J = 1 Hz, 1 H), 3.86 (d, J = 1 Hz, 1 H), 1.17 (s, 9 H); $^{13}C(^1H)$ NMR (C_5H_{12}, D_2O external, 22.5 MHz) δ 178 (CO), 78 (=CH_2), 39 (*tert*-butyl C), 31 ((-CH_3)$_3$).

Lithiopinacolonate·THF was prepared in a manner identical with that described above, with 3 mL of THF added to solution before precipitation. White crystals were isolated: ^1H NMR (500 MHz, C_6D_{12}, 12 °C) δ 3.78 (m, 4 H), 3.54 (s, 1 H), 3.48 (s, 1 H), 1.73 (m, 4 H), 1.06 (s, 9 H); $^{13}C(^1H)$ NMR (125.7 MHz, C_6D_{12}, 12 °C) δ 176 (CO), 76 (=CH_2), 68 (-CH_2O), 38 (*tert*-butyl C), 31 ((-CH_3)$_3$), 26 (-CH_2CH_2-).

The lithium salt of 5-hydroxy-2,2,6,6-tetramethyl-3-heptanone (III) was prepared and isolated as described:[17,24] ^1H NMR (80 MHz, C_6D_6) δ 3.63 (dd, J = 13.9, 4.3 Hz, 1 H), 3.23 (d, J = 12.93 Hz, 1 H), 1.98 (dd, J = 14.7, 7.0 Hz, 1 H), 1.17 (s, 9 H), 1.01 (s, 9 H); $^{13}C(^1H)$ NMR (125.7 MHz, C_6D_{12}, 12 °C) δ 223 (C=O), 81 (-COLi), 46 (*tert*-butyl C), 43 (-CH_2-), 38 (*tert*-butyl C), 26 ((-CH_3)$_3$).

Calorimetry. All heats of reaction were determined at 6 and 25 °C with a Tronac Model 1250 solution calorimeter operated in the 450 isoperibol mode. The basic operation of the instrument has been described previously.[25] Solutions of lithiopinacolonate (0.1–0.4 M) in hexane and cyclohexane were prepared with LiHMDS and transferred via a gas-tight syringe to an argon-purged Dewar-calorimeter vessel. Hydrocarbon solutions containing 1 equiv of the basic ligands, THF, tetramethylethylenediamine (TMEDA), and dimethoxymethane (DME) were prepared similarly. Both titration and batch (ampule-breaking) calorimetric techniques were used to introduce precise amounts of pivaldehyde into the calorimeter vessel. Clean, linear thermograms demonstrated that the exothermic reactions were complete and instantaneous. Heats of reaction, in kilocalories/mole, were calculated by the standard method.[25]

Heats of interaction of the basic ligands with lithiopinacolonate in hexane (25 °C) and cyclohexane (6 °C) were determined in a similar fashion. At 25 °C, the thermograms obtained were sloping curves, from which the heat of reaction could only be estimated. These types of thermograms suggest that slowly equilibrating processes are occurring.[25] However, at 6 °C the thermograms were clean, and only in the case of DME was there evidence of an equilibrium process.

Product Studies for Aldol Addition Reactions. In order to insure that the measured heat changes were those of only the aldol addition reaction, the system was modeled for NMR analysis. A lithium enolate solution in hexane was prepared at 25 °C and 0.5 equiv of pivalaldehyde was added. The reaction was worked up by addition of (trimethylsilyl)-imidazole as described by House.[26] NMR analysis of the crude product showed only the presence of silylated enolate, aldol product,[26] and HMDS. The reaction was also carried out with milligram quantities of reagents in cyclohexane-d_{12} in an NMR tube. Quantitative formation of III was observed. Identical results were obtained in the presence of 1 equiv of the ligands.

Vapor Pressure Osmometry (VPO).[27] Aggregation numbers for I and III and solutions with 1 equiv of the basic ligands in cyclohexane were determined with a Wescor 5500-XR vapor pressure osmometer. The osmometer was operated at 37 °C in a VAC dry box under purified argon. The normal experimental protocol was altered for use with air-sensitive compounds. All solutions were prepared within the dry box and used immediately. Calibration curves were generated using triphenylmethane and biphenyl as standards, with linear least-squares analyses of the plots yielding correlation coefficients of at least 0.9900. Several published results[7b,28] were duplicated by using this technique. The aggregation number of the enolate or aldolate salt in the presence of a ligand was determined by first measuring its value without the ligand and then repeating the experiment after addition of 1 equiv of the ligand. The presence of THF, DME, TMEDA, and HMDS could not be detected in cyclohexane due to their similar vapor pressures. Therefore, VPO can only be used to detect *changes* in the aggregation number when the added ligand interacts with the organolithium salt.[29] Aggregation numbers determined by VPO carry an estimated 10% uncertainty.[30]

Cryoscopic Measurements. Cryoscopy was performed with an apparatus similar to that of Mair et al.[31] The solution temperature was measured by a YSI precision thermistor connected to a Wheatstone bridge. Freezing curves were obtained in analog form on a Sargent Welch SRG chart recorder, or digitally with a Keithley 175 voltammeter. Calibration curves were obtained with use of solutions of triphenylmethane, biphenyl, and benzophenone. Linear least-squares correlation coefficients of these plots were at least 0.9900. A cryoscopic constant of 22.0 ± 1 °C kg/mol was obtained for cyclohexane.[32,33]

Cyclohexane solutions of the lithium enolate or aldolate were prepared in a dry box with use of the solid salts and transferred via gas-tight

(20) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: New York, 1980.

(21) Shriver, D. F.; Drezdzon, M. A. *The Manipulation of Air-Sensitive Compounds*, 2nd ed.; Wiley: New York, 1986.

(22) Proton resonances: $CDCl_3$ = 7.24 ppm, C_6D_6 = 7.15 ppm, C_6D_{12} = 1.38 ppm.

(23) The impurities in question could not be detected by ^1H NMR. We do not suspect a lithium halide since addition of LiBr did not change the ΔH_{rxn} in a control experiment. Also, the preparation and purification of these commercial solutions is proprietary information of the Aldrich Chemical Co.

(24) We found that cyclohexane solutions of III were stable at 25 °C for <1 h and at 12 °C for 15–20 h. After these limiting periods, NMR analysis showed a significant amount of the elimination product, *trans*-2,2,6,6-tetramethyl-4-hepten-3-one: ^1H NMR (80 MHz, C_6D_{12}) 7.02 (d, J = 15.3 Hz, 1 H), 6.36 (d, J = 15.6 Hz, 1 H), 1.13 (s, 9 H), 1.08 (s, 9 H).

(25) (a) Hansen, L. D.; Lewis, E. A.; Eatough, D. J. Instrumentation and Data Reduction. In *Analytical Solution Calorimetry*; Grime, J. K., Ed.; Wiley: New York, 1985. (b) Eatough, D. J.; Izatt, R. M.; Christensen, J. J. Titration and Flow Calorimetry: Instrumentation and Data Calculation. In *Comprehensive Analytical Chemistry*; Jespersen, N. D., Ed.; Elsevier Press: New York, 1982; Vol. XII. (c) Eatough, D. J.; Christensen, J. J.; Izatt, R. M. In *Experiments in Thermometric Titrimetry and Titration Calorimetry, Revised Ed.*; Brigham Young University Press: Salt Lake City, UT, 1974.

(26) House, H. O.; Dzuba, L. J.; Gall, M.; Olmstead, H. E. *J. Org. Chem.* **1969**, *34*, 2324.

(27) For a basic description of osmometry, see: Lott, P. F.; Millich F. *J. Chem. Educ.* **1966**, *43*, A191–A208 and A295–A312.

(28) Brown, T.; Kimura, B. *J. Organomet. Chem.* **1971**, *26*, 57.

(29) Interaction of the ligand with the lithium salt cannot be determined solely from VPO when there is no change in aggregation number.

(30) We have submitted a description of our error analysis as supplementary material.

(31) Mair, B. J.; Glasgow, A. R., Jr.; Rossini, F. D. *J. Res. N.B.S.* **1941**, *26*, RP1397.

(32) Mp 6.5 °C; lit. K_f = 20.0–20.3 °C kg/mol. Kaye, G. W. C.; Laby, T. H. *Tables of Physical and Chemical Constants and Mathematical Formulas*, 11th ed.; Longmans, Green and Co.: New York, 1956.

(33) Solutions of the basic ligands were found to have freezing points within experimental error of those calculated from K_f.

Table I. Heats of Reaction for the Aldol Reaction of Lithiopinacolonate (I) to Pivaldehyde (II) in Hexane and Cyclohexane at 6 and 25 °C[a]

ligand added[b]	ΔH_{rxn} in hexane (25 °C) (kcal/mol)		ΔH_{rxn} in cyclohexane (kcal/mol)	
	ref 19	this work	25 °C	6 °C
none	−30.19 ± 0.76[c]	−21.54 ± 1.64	−21.79 ± 0.57	−21.59 ± 0.59
THF	−17.94 ± 0.36	−16.00 ± 1.12[d]	−16.75 ± 0.26[d]	−16.35 ± 0.42[d]
TMEDA	−20.85 ± 0.72	−18.89 ± 1.08	−19.16 ± 0.67	−19.52 ± 0.48[e]
DME	−19.05 ± 0.44	−18.04 ± 0.46	−17.94 ± 0.33	−19.49 ± 0.51[f]

[a] Errors are reported as standard deviation. [b] One equivalent added. [c] This number is incorrect; see Results. [d] Includes $\Delta H_{dilution}$ for THF (+0.74 kcal/mol). [e] Includes $\Delta H_{dilution}$ for TMEDA (+0.87 kcal/mol). [f] Includes $\Delta H_{dilution}$ for DME (+1.66 kcal/mol).

syringe to the cryoscopic cell. Lithiopinacolonate precipitates from cyclohexane solution upon cooling below 7 °C. Cryoscopic titration plots[34] were obtained by direct addition of the ligand to the enolate solution in the cryoscopic cell.

^{6}Li-Labeled Compounds. [^{6}Li]HMDS·THF was prepared by the addition of 0.6852 g (114 mmol) of ^{6}Li shavings,[35] 15 mL of *tert*-butyl chloride (Kodak) (137 mmol, 1.2 equiv), and 36 mL of HMDS (Aldrich) (171 mmol, 1.7 equiv) to 50 mL of THF in a round-bottom flask under argon. The mixture was placed into a Bransonic 2200 ultrasonic cleaning bath and sonicated for 12–18 h.[36] The bath temperature was kept at 5–15 °C by occasional additions of ice. The solvent was removed under vacuum, hexane was added, and the mixture was centrifuged to separate unreacted ^{6}Li metal and ^{6}LiCl. The supernatant liquid was removed by syringe and cooled to −78 °C to yield crystalline [^{6}Li]HMDS·THF.[37] Upon recrystallization and removal of volatiles under vacuum, a pure white solid (1.24 g, 7.0 mmol, 6.1% yield) was obtained: ^{1}H NMR (C_6D_6, 80 MHz) δ 3.7 (m, 4 H), 1.3 (m, 4 H), 0.4 (s, 18 H).

THF-free [^{6}Li]HMDS was prepared by deprotonation of the amine by [(trimethylsilyl)methyl][^{6}Li]lithium. $^6LiCH_2Si(CH_3)_3$ was prepared from ^{6}Li metal and (trimethylsilyl)methyl chloride by using a procedure adapted from Brown.[38] No attempt was made to purify the solid alkyllithium compound. After isolation, it was immediately dissolved in pentane and excess HMDS was added at −78 °C. Crude [^{6}Li]HMDS solid was isolated after prolonged cooling at −78 °C and sublimed to remove halide impurities.

[^{6}Li]I·THF and [^{6}Li]III were prepared as described earlier with use of a [^{6}Li]HMDS·THF/pentane solution. [^{6}Li]I and samples containing 1 equiv of TMEDA or DME were prepared with use of THF-free [^{6}Li]HMDS. Solutions of each in 1 mL of the deuterated solvent were prepared inside the dry box in 5-mm tubes and flame-sealed immediately after removal.

Variable-Temperature ^{6}Li NMR. ^{6}Li NMR spectra were recorded on a General Electric GN-500 spectrometer at 73.6 MHz. The ^{6}Li 90° pulse width was determined by the usual method.[39] The temperature inside of the probe was measured by a thermocouple and is accurate to ±0.5 °C. Samples were permitted to equilibrate at 9, 16, 25, 37, and 50 °C for 10 min prior to data acquisition. All ^{6}Li chemical shifts are relative to an internal saturated ^{6}LiO-*t*-Bu/C_6H_6 standard in a sealed capillary tube (δ = 0 ppm).

^{6}Li and ^{1}H spectra of cyclohexane-d_{12} solutions of [^{6}Li]I and those containing DME or TMEDA showed only slight decomposition of the samples from 9 to 25 °C. However, after data acquisition at 37 and 50 °C, the sample showed significant and total decomposition of the sample, respectively.

^{6}Li-^{1}H Heteronuclear Overhauser Enhancement (HOESY) NMR.[40] NMR spectra were recorded on a General Electric GN-500 spectrometer equipped with a broad-band 10-mm probe and a Nicolet 1280 computer. NMR frequencies are listed above. The ^{6}Li chemical shifts for the 2D spectra are relative to an external 2 M LiOH/D_2O standard (δ = 0 ppm). The observed ^{13}C and ^{6}Li 90° pulses were adjusted by using the usual method.[39] The ^{1}H decoupler 90° pulse width was adjusted by using the DEPT sequence, looking for the null of methylene and methyl ^{13}C signals.[41]

Scheme I. The Aldol Addition of Lithiopinacolonate (I) to Pivalaldehyde (II)

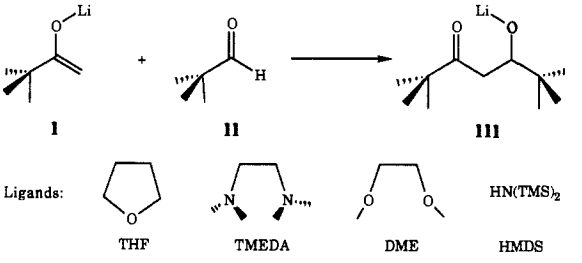


Table II. Heats of Interaction of Lithiopinacolonate (I) with Ligands in Cyclohexane and Hexane at 6.3 and 25 °C, Respectively

ligand added	$\Delta H_{interaction}$ (kcal/mol)[a]		
	cyclohexane		hexane:
	6 °C	25 °C	25 °C
THF	−6.17 ± 0.46[b]	−5.85 ± 0.50[b]	−7.43 ± 1.15
TMEDA	−2.98 ± 0.38[b]	−2.71[b,c]	<3[c]
DME	−3.52 ± 0.52[b]	−3.55[b,c]	<3[c]

[a] Errors are standard deviation. [b] Includes $\Delta H_{dilution}$ for ligands (see Table I). [c] Heats could only be estimated due to equilibrium effect on thermograms.

Table III. Aggregation Numbers (n) for Lithiopinacolonate and the Lithium Aldolate Product (III) at 37 °C by VPO[a]

ligand added[b]	nI[c]	nIII[c]
none	6.4	4.1
THF	4.5	4.3
THF[d]	4.1	
TMEDA	5.2[e]	4.3
DME	5.5[e]	3.9
HMDS	6.6	3.8

[a] Aggregation numbers carry an estimated 10% uncertainty. [b] One equivalent of ligand added prior to measurement. [c] Concentration 0.1–0.3 M. [d] Prepared as crystalline I·THF. [e] Calculated as av n(I) − Δn (from addition of ligand).

We used a sample of *n*-butyllithium (Alfa, ~2.5 M) in cyclohexane-d_{12} in the development of the HOESY experiment.[42] It has been found to exist as a hexamer in cyclohexane by cryoscopic[43] and isopiestic measurements.[44] The ^{6}Li-^{1}H NOE spectrum was similar to that obtained by Schleyer and Bauer et al. in THF-d_8 at −96 °C.[45] The only cross-peaks observed were those from the α- and β-protons. The proton assignments were made from 1D ^{1}H decoupling, ^{1}H-^{1}H COSY, and ^{1}H-^{13}C HETCOR experiments. We have submitted these spectra and experimental conditions as supplementary material.

The ^{6}Li-^{1}H HOESY experiments used a ^{6}Li observe pulse of 36 μs and a decoupler pulse of 60 μs. On the basis of previous work,[45] the fixed mixing interval was set to 1.8 s and the delay to at least 6 s. The phase cycling was based on that of Yu and Levy.[46] All 2D plots are presented in absolute value mode.

(34) For an example: Kallman, N.; Collum, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 7455–7472.
(35) ^{6}Li metal (95.5%) was obtained from Oak Ridge National Laboratory, Oak Ridge, TN.
(36) This procedure was adapted from Einhorn, J.; Luche, J. L. *J. Org. Chem.* **1987**, *52*, 4124–4126.
(37) NMR integration showed 1 equiv of THF per lithium amide base. A crystal structure for a related compound, LiHMDS·Et_2O, has been reported: Lappert, M. F.; Slade, M. J.; Singh, A. *J. Am. Chem. Soc.* **1983**, *105*, 302–304.
(38) Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664–4670.
(39) Martin, M. L.; Martin, G. L.; Delpuech, J. J. *Practical NMR Spectroscopy*; Heyden: London, 1980; p 267.
(40) For a review of this technique: Bauer, W.; Schleyer, P. v. R. *Magn. Reson. Chem.* **1988**, *26*, 827–833 and references therein.
(41) Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon Press: Oxford, 1987; pp 154–157.
(42) The NMR sample was prepared as described in ref 45.
(43) Brown, T. L. *Acc. Chem. Res.* **1968**, *1*, 23.
(44) Magerison, D.; Newport, J. P. *Trans. Faraday Soc.* **1963**, *59*, 2058.
(45) Bauer, W.; Clark, T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 970–977.
(46) Yu, C.; Levy, G. C. *J. Am. Chem. Soc.* **1984**, *106*, 6533–6537.

Table IV. Aggregation Numbers (n) for Lithiopinacolonate (I) and the Lithium Aldolate Product (III) in Cyclohexane As Found by Cryoscopy at 6 °C

ligand added[b]	nI[c]	nIII[c]
none	precipitated	4.3 ± 0.5
THF	3.5 ± 0.7	4[e,f]
THF[d]	3.9 ± 0.8	
TMEDA	2[e,g]	4[e,f]
DME	2[e,g]	4[e,f]
HMDS	precipitated	4[e,f]

[a] Aggregation numbers carry an estimated 10% uncertainty. [b] One equivalent of ligand added prior to measurement. [c] Concentration ~ 0.1 M. [d] Prepared as crystalline I·THF. [e] Determined by cryoscopic titration plots. [f] None of the ligand was found to participate in the aggregate. [g] One equivalent of ligand was found to participate in the aggregate.

Results

Heats for the aldol addition (see Scheme I) of lithiopinacolonate (I) to pivalaldehyde (II) are given in Table I. The first point which should be noted is the discrepancy between our recent values and those we reported earlier[19] for the reaction in hexane. While most of the values are acceptable given the air-sensitive nature of the enolate and aldolate, the difference of 8.5 kcal/mol in the first entry presents a serious error. We suspect that the source of this error was the presence of impurities in the commercial LiHMDS solution[23] that was used. It must also be pointed out that these measurements were made 2 years apart by different workers, and we now know much more about the purification and handling of LiHMDS, I, and III. Therefore, the data presented here are more accurate than those presented in our previous communication.[47]

The percentage of reaction ($\%_{rxn}$) was varied from 6 to 75% to determine its effect upon the ΔH_{rxn}. In all cases, the ΔH_{rxn} was independent of the $\%_{rxn}$ within experimental error.

Heats of interaction ($\Delta H_{interaction}$) for the basic ligands with I and III are given in Tables II and V. Due to equilibrium effects at 25 °C, $\Delta H_{interaction}$ of TMEDA and DME with the enolate could only be estimated since the reactions did not go to completion. However, only minimal equilibrium effects were seen in cyclohexane at 6 °C, and an accurate measurement of $\Delta H_{interaction}$ could be made.

Tables III and IV list the aggregation numbers for the lithium enolate (I) and aldolate (III) as determined by colligative property techniques. VPO and cryoscopy are complementary techniques that yield aggregation numbers, but the use of cryoscopic titration[34] can provide information relating to the participation of ligand molecules in the aggregate.

Cryoscopic titration curves for the addition of the basic ligands to I and III are given in Figures 1 and 2. Theoretical lines on the plots correspond to various possible aggregation numbers (n) of the organolithium compound. The points for these lines were calculated by using eq 1 or 2, where eq 1 corresponds to ligand interaction with the lithium salt, and eq 2 does not. Cryoscopic measurements carry an estimated 10% uncertainty.

$$\text{calcd mmolality} = ([\text{LiSalt}\cdot l\ \text{ligand}]/n) + [\text{ligand}] - [\text{LiSalt}] \quad (1)$$

$$\text{where } [\text{LiSalt}\cdot l\ \text{ligand}] = [\text{LiSalt}]$$

$$\text{calcd mmolality} = ([\text{LiSalt}]/n) + [\text{ligand}] \quad (2)$$

Although they were conducted at different temperatures, VPO and cryoscopy yielded identical results except in the cases where TMEDA and DME were the ligands. As will be discussed in the next section, this is due to a temperature-dependent equilibrium between aggregation states in solution.

Discussion

Introduction. Considering the wide range of aldol reactions used in many complicated synthetic procedures, the reaction pictured in Scheme I is disarmingly simple. However, we will see that even this example is much more complicated than it appears on paper. Although the classical studies of organolithium aggregation were published as many as 25 years ago,[48] only recently has its impact on synthetic processes started to be fully appreciated. As a result, very few of the commonly postulated mechanisms for the aldol reaction include the aggregated species. In this study we have been able to correlate, for the first time, solid-state and solution structures for the lithium enolate and aldolate product with corresponding thermodynamic data. The reaction of choice was found to be ideal for these types of studies since the aggregation state of the enolate could be varied and controlled by judicious choice of ligand and temperature. In the following discussion, we will first examine how the solution structures of the lithium enolate and aldolate were elucidated using colligative properties and NMR experiments. These will be compared with the crystal structures where possible. Thermochemical results will then be correlated with the aggregation states of the enolate and aldolate.

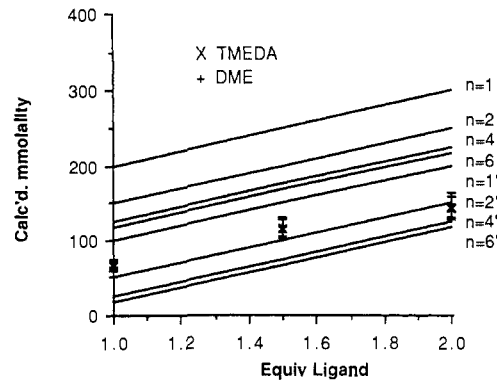


Figure 1. Cryoscopic titration plot for lithiopinacolonate (I) in the presence of 1.0–2.0 equiv of ligands. Aggregation numbers (n) with an asterisk correspond to values calculated by use of eq 1. Those with no asterisk were calculated by eq 2. Errors are approximately 10%.

Vapor Pressure Osmometry. From Table III, it can be seen that the lithium aldolate product (III) exists as a tetramer (n = 4) in cyclohexane at 37 °C, regardless of the ligand present. However, the aggregation state of lithiopinacolonate (I) in cyclohexane is highly dependent upon the presence of ligands. With no ligands or HMDS (a product of ketone deprotonation) present, the enolate was found to be hexameric (n = 6). In the presence of THF, the enolate exists as a tetramer (n = 4). These solution structures essentially correspond to the solid-state X-ray crystallographic structures that were determined by Williard,[12a,17] Seebach,[18] and their co-workers.

The most interesting cases were those where DME and TMEDA were used as ligands for the lithium enolate. Upon addition of 1 equiv of DME or TMEDA, the aggregation number of the enolate was reduced by 0.9 and 1.2, respectively. Since there is no literature precedent for a pentameric aggregate of a simple enolate (or to our knowledge any pentameric organolithium aggregates), these aggregation numbers of 5 suggest an equilibrium between various aggregation states in solution. We can reasonably conclude that the higher aggregate of the equilibrium is a hexamer, while the lower aggregate is undetermined by VPO, but might possibly be tetrameric or dimeric. This question had to be settled by cryoscopy (see below).

With VPO, the aggregation numbers for the lithium enolate and aldolate have been determined in cyclohexane at 37 °C. As discussed earlier (see the Experimental Section), VPO yields *no* information as to whether the ligand interacts with the lithium salt, except where DME and TMEDA reduced the aggregation number of the enolate.

Cryoscopy and Cryoscopic Titration. Aggregation numbers obtained by cryoscopy and cryoscopic titration are given in Table

(47) These data were also published in ref 5a. We have informed Professor Seebach of the error.

(48) For an historical perspective of the development of organolithium aggregation studies: ref 12b and Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon Press: New York, 1974; Chapter 1.

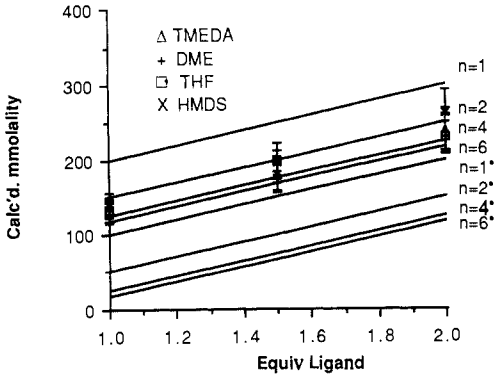


Figure 2. Cryoscopic titration plot of the lithium aldolate product (III) in the presence of 1.0–2.0 equiv of ligands. Aggregation numbers (n) with an asterisk correspond to values calculated by use of eq 1. Those with no asterisk were calculated by using eq 2. Errors are approximately 10%.

IV. In the absence of ligands, the aldolate was found to be tetrameric. However, cryoscopic studies of I in the absence of ligands were precluded by its precipitation from solution. This obstacle was overcome by the use of cryoscopic titration. Figure 1 shows the cryoscopic titration plots for the addition of TMEDA and DME to a cyclohexane solution of the enolate. The experimental data points lie within error of an aggregation state of 2 (dimer) *with* incorporation of one equiv of ligand. Presumably, this dimeric structure is analogous to that determined by Seebach et al.[10i] for the solid I·TriMEDA complex.

The cryoscopic titration plot for the aldolate in the presence of the ligands is given in Figure 2. All of the experimental points lie within the set of theoretical lines corresponding to *no* ligand interaction. Since III was found to be a tetramer when no ligands were present in solution, the scatter of the points around the theoretical line $n = 4$ is a manifestation of the experimental error, rather than a *non*-ligand-assisted disaggregation.[49]

^{6}Li NMR. From the VPO and the cryoscopic data obtained in cyclohexane it was found that lithiopinacolonate (I) exists in an equilibrium between the predominately dimeric (at 6 °C) and hexameric (>37 °C) aggregates in the presence of 1 equiv TMEDA and DME. Direct observation of this equilibrium was attempted, unsuccessfully, using ^{7}Li NMR and UV spectroscopy.

The only direct evidence for the hexamer–dimer equilibrium was obtained by ^{6}Li NMR. The ^{6}Li NMR spectra obtained for the various aggregation states of lithiopinacolonate in cyclohexane-d_{12} at 9 °C are shown in Figure 3. Spectra A, B, and C show the resonances for the hexameric, tetrameric, and dimeric aggregates of I, respectively. While only one resonance is seen for I·TMEDA (spectrum C), I·DME (spectrum D) clearly shows the dimer and hexamer coexisting in solution at 9 °C. The observation of this equilibrium in the presence of DME and not with TMEDA at 9 °C is consistent with the VPO data, where TMEDA was seen to reduce the aggregation number more than DME.

Could it be possible that a tetramer may also be part of the dimer–hexamer equilibrium?[49,50] The presence of a third resonance in spectrum D at ~–0.25 ppm is speculative at best. When the temperature of the I·DME sample was increased to 25 °C, the peak broadened and could *not* be successfully deconvoluted with the chemical shifts of the dimer and hexamer. The missing part of the theoretical spectrum was a peak centered at ~–0.25 ppm (tetrameric resonance, spectrum B, –0.28 ppm). While this could be used to support the existence of the tetramer, it could be argued equally as well that the broadening of the line results from increased exchange between the two aggregation states. At this time, we have no answer to this somewhat subtle question. It does serve as an example of the hidden complexities that may exist in even the simplest studies.

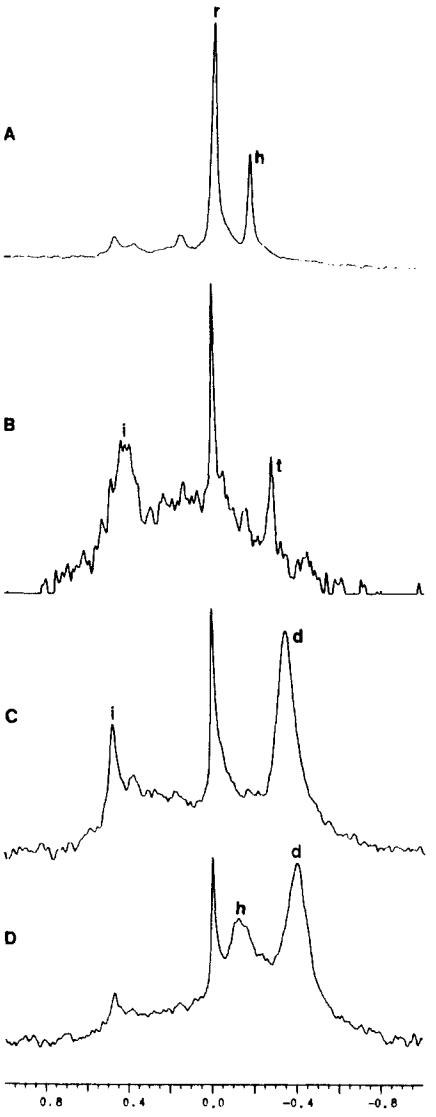


Figure 3. ^{6}Li spectra of [^{6}Li]I (~0.25 M) + 1.2 equiv of ligand in cyclohexane-d_{12} at 9 °C. Spectrum A – [^{6}Li]I; B – [^{6}Li]I + THF; C – [^{6}Li]I + TMEDA; D – [^{6}Li]I + DME. r = reference signal of saturated ^{6}LiO-t-Bu/C_6H_6 (internal); h = hexamer signal (–0.17 ppm); t = tetramer signal (–0.28 ppm); d = dimer signal (–0.35 ppm); i = decomposition product.

Table V. Heats of Interaction of the Ligands with the Lithium Aldolate Product (III) in Cyclohexane at 6.3 and 25 °C

ligand	$\Delta H_{interaction}$ (kcal/mol) 6.3 °C	$\Delta H_{interaction}$ (kcal/mol) 25 °C	$\Delta H_{dilution}$ (kcal/mol)
THF	+0.65	+0.65	+0.74
TMEDA	+0.54	+0.54	+0.87
DME	+1.25	+1.37	+1.66

[a] Errors are less than 0.25 kcal/mol.

2D ^{6}Li–^{1}H HOESY NMR. The 2D ^{6}Li–^{1}H HOESY spectrum for I·THF in cyclohexane-d_{12} at 12 °C was published in our preliminary communication.[19] Unfortunately, I, I·TMEDA, and I·DME are not stable in cyclohexane solution for the 10 h required for our version of the ^{6}Li–^{1}H NOE experiment. Attempts are currently underway to implement an improved experiment which is amenable to samples with limited stabilities. Figure 4 shows the 2D ^{6}Li–^{1}H HOESY spectrum for [^{6}Li]III in cyclohexane-d_{12} at 12 °C. The only NOE cross-peaks observed were those from

(49) However, equilibria between different aggregation states of alkyllithium compounds have been observed: Fraenkel, G.; Hsu, H.; Su, B. M. In *Lithium, Current Applications in Science, Medicine, and Technology*; Bach, R. O., Ed.; Wiley: New York, 1985; Chapter 19.

(50) (a) Jackman, L. M.; Haddon, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 3687–3692. (b) Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954–4962.

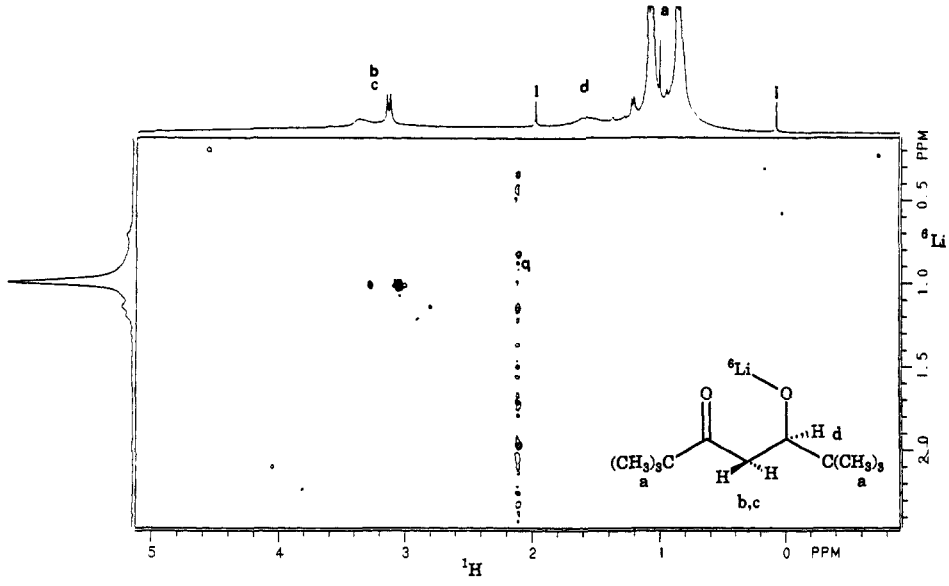


Figure 4. ^{6}Li–^{1}H heteronuclear NOE (HOESY) spectrum of the [^{6}Li]lithium aldolate product (III) in cyclohexane-d_{12} at 12 °C. Mixing time = 1.8 s; relaxation delay = 6 s; 256 increments in t_1; total measuring time = 10.5 h; i = impurity; q = quadrature signal.[53]

the protons α to the carbonyl (b, c). From the crystal structure, these protons were found to lie within 3.5 Å of the lithium ions.[51] However, so were those of the *tert*-butyl groups and the proton attached to the carbon of the alkoxide. The most probable explanation for the absence of these cross-peaks is the low resolution of the experiment.[52]

Calorimetry. In selecting the conditions under which ΔH_{rxn} and $\Delta H_{interaction}$ would be measured (Tables I, II, and V), it was important to have the solution structures of the lithium enolate and aldolate elucidated. Enthalpies of reaction measurements are useless (or worse) unless the initial and final states are defined clearly. The calorimetric and aggregation data are combined in Figure 5. It was fortuitous that the lithium aldolate product assumed the same solution structure regardless of the ligand present. Not only was this demonstrated by the cryoscopic titration data (Figure 2) but it is also consistent with the summarized data in Table V, where the $\Delta H_{interaction}$ values of the ligands with III were seen to equal their heats of dilution into the pure hydrocarbon solution (i.e., the measured heat change actually refers only to dilution, not interaction with the aldolate). Therefore, the enthalpies of the various enolate aggregates can be compared relative to one another, once a correction is made for the dilution of the enolate-complexed ligand into solution after the aldolate is formed. From Figure 5, the enthalpies of formation of the aggregates are seen to vary quite drastically. There is a 5 kcal/mol difference in the ΔH_{rxn}'s of the hexameric and tetrameric species, while the difference in ΔH_{rxn} between the hexameric and dimeric species is approximately 2–3 kcal/mol.

An internal check of these data can be performed if the $\Delta H_{interaction}$ is added to the ΔH_{rxn} for the reactions where ligands were present. If the thermochemical data are accurate, then each sum should be that of the reaction where no ligand was present. This is the case as the sums −22.52 (THF), −22.50 (TMEDA), and −23.01 kcal/mol (DME) all lie within error of −21.59 kcal/mol (no ligand).

Comments. We wish to emphasize that the data in Figure 5 represent only the changes in enthalpy of the aggregated enolate reactant and the aggregated aldolate product. *These data say* ***nothing directly*** *about the nature of the reactive species or possible*

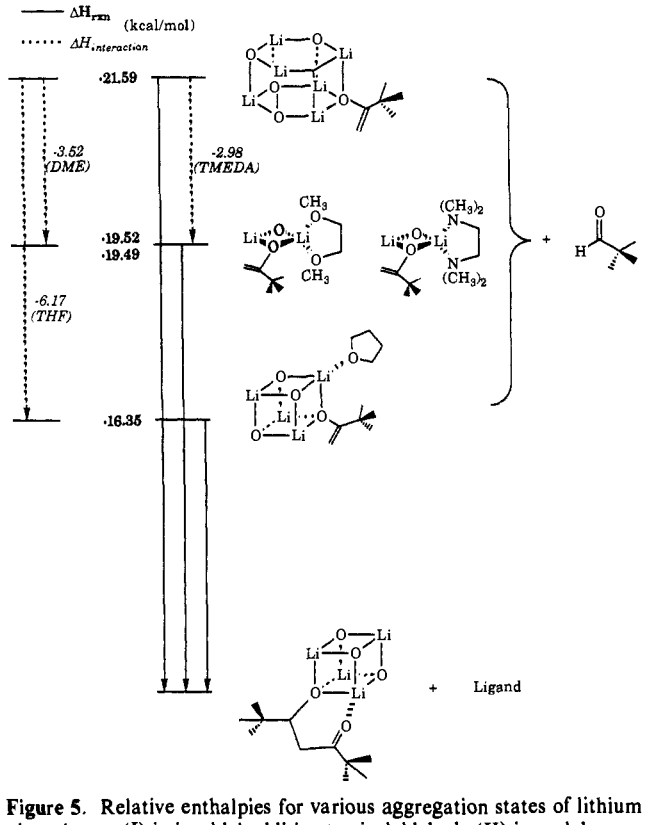


Figure 5. Relative enthalpies for various aggregation states of lithium pinacolonate (I) in its aldol addition to pivalaldehyde (II) in cyclohexane at 6 °C. See Tables I and II for relevant data.

transition states! We hope to obtain the necessary kinetic data for determining the reactive species. However, there are serious obstacles to normal kinetic analysis of this reaction.

An important aspect of this study is the fact that in the presence of THF, the tetrameric enolate is converted to the tetrameric aldolate. While this supports Seebach's proposed aldol mechanism,[11a] the conversion of the dimeric and hexameric enolate aggregates to the tetrameric aldolate imply that this mechanism is probably not a general one, especially in non-ether solvents. Speculation about the details of these dimer/hexamer to tetramer conversions is premature at this time.

It should be stressed that HMDS does not participate in this aldol reaction. In light of the popularity of LiHMDS and LDA as kinetic bases for ketone deprotonation and the studies where

(51) Schleyer and Bauer et al. have estimated that 3.5 Å is the maximum Li–H distance that NOEs can be observed. See ref 45.

(52) From the crystal structure model, protons b and c were seen to lie nearly equidistant from two ^{6}Li ions. The other protons were found to be within 3.5 Å of only one ^{6}Li.

(53) Schleyer et al. have described the origin of these signals. See footnote 62 of Bauer, W.; Feigel, M.; Muller, G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1988**, *110*, 6033–6046.

diisopropylamine has been shown to influence reaction product distributions,[10h,i] to the best of our knowledge, this is the first systematic study proving that HMDS is free in solution *prior to* and *after* completion of an aldol reaction. Previously, it had been *assumed* that the steric bulk of HMDS prevented it from interacting with the enolate.

The influence of counterion effects was probed by the reaction of sodium, potassium, and cryptated-potassium pincolonates with pivalaldehyde. The non-lithium aldolate products were found to undergo elimination after several seconds, making the analogous structural and calorimetric investigations impossible, and emphasizing yet again the important role of lithium in these reactions.

Conclusions

In order to study even the simplest aldol reaction in nonpolar media systematically, it is necessary to apply a methodology that employs a variety of methods to elucidate the structures of the reactants and products, thermochemical measurements, and, ultimately, kinetic studies. Excluding kinetics, we have successfully applied this methodology to yield the first concrete structure–energy analysis of the reactants and products for an aldol reaction. It was found that the enthalpy of reaction for the hexameric enolate was approximately 5–6 kcal/mol more exothermic than for the tetrameric enolate complexed with THF. The reaction of the hexameric enolate was also ~2 kcal/mol more exothermic than were the dimeric enolates (complexed with TMEDA and DME).

Enolates complexed with DME and TMEDA were seen to have nearly identical ΔH_{rxn}s. However, TMEDA was found to complex lithiopinacolonate to a slightly greater degree than DME in cyclohexane by VPO and ^{6}Li NMR. THF was more efficient than either TMEDA or DME in this respect, since no equilibrium effects were observed. It is hoped that these studies will be the first in a series which will ultimately lead to a thoroughly documented mechanism for the modern aldol reaction under synthetic conditions.

Acknowledgment. This work was supported by NSF Grant CHE-8709249 to E.M.A. and by funding from NSF, NIH, the North Carolina Biotechnology Center, and Duke University to the Duke NMR Center, for which we are most appreciative.

Supplementary Material Available: Spectra and experimental conditions including proton assignments made from 1D ^{1}H decoupling, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HETCOR, and ^{1}H–^{6}Li HOESY experiments and descriptions of the error analyses used in the various techniques (9 pages). Ordering information is given on any current masthead page.

Asymmetric, Stereocontrolled Total Synthesis of (−)-Brevianamide B†

Robert M. Williams,*,‡ Tomasz Glinka, Ewa Kwast, Hazel Coffman, and James K. Stille

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received June 16, 1989*

Abstract: The asymmetric, stereocontrolled total synthesis of (−)-brevianamide B (**2**) is described. The synthesis features a stereocontrolled intramolecular S_N2' cyclization to construct the central bicyclo[2.2.2] nucleus. A synthetic route to C-10-epibrevianamide A (**49**) is also described. A synthetic sample of a shunt metabolite (**9**) proposed by Birch in 1972 has been prepared and its oxidation chemistry in the context of the proposed biosynthetic schemes is discussed.

In 1969, the yellow culture extract of *Penicillium brevicompactum* was observed by Birch and Wright[1] to produce in very low yield several neutral, toxic metabolites that were named brevianamides A–E. Based primarily on spectroscopic evidence, chemical degradation, and biogenetic considerations, the structure **1** was proposed[1b] and later shown in 1974[2] to be correct by single-crystal X-ray analysis of a bromination product, 5-bromobrevianamide A. The X-ray structure also established the relative and absolute configuration of **1**. Brevianamide A was subsequently isolated from *Penicillium viridicatum*[3] and *Penicillium ochraceum*.[4] Birch and Russell[1c] also isolated brevianamides C (**3**) and D (**4**) from the same culture filtrates, but these are thought to be artifacts since white light irradiation of **1** in MeOH efficiently produces **3** and **4**. It was also shown that brevianamide F [**6**, *cyclo*(L-tryptophyl-L-proline)] is biosynthetically incorporated into brevianamide A. From these observations, Birch postulated a biosynthetic pathway involving prenylation of **6** to the dioxopiperazine **7** (deoxybrevianamide E)[6]. However, deoxybrevianamide E (**7**) has not been detected in culture filtrates that produce **1** and **2** and thus must still be considered a hypothetical shunt metabolite. Formation of the bicyclo[2.2.2]dioxopiperazine nucleus is then thought to arise via oxidation of the tryptophanyl moiety **8** and a unique intramolecular [4 + 2] cycloaddition reaction[7] to furnish the hexacyclic indole **9**; oxidative spiro re-

† Dedicated to the late Professor John K. Stille.

‡ Fellow of the Alfred P. Sloan Foundation 1986–1990. NIH Research Career Development Awardee 1984–1989. Eli Lilly Grantee 1986–1988.

(1) (a) Birch, A. J.; Wright, J. J. *J. Chem. Soc., Chem. Commun.* **1969**, 644. (b) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329. (c) Birch, A. J.; Russell, R. A. *Ibid.* **1972**, *28*, 2999.

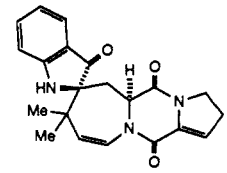
(2) Coetzer, J. *Acta Crystallogr.* **1974**, *B30*, 2254. The absolute configuration of natural brevianamide A is *opposite* to that depicted throughout this manuscript.

(3) Wilson, B. J.; Yang, D. T. C.; Harris, T. M. *Appl. Microbiol.* **1973**, 633.

(4) Robbers, J. E.; Straus, J. W. *Lloydia* **1975**, *38*, 355.

(5) Baldas, J.; Birch, A. J.; Russell, R. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 50.

(6) Compound **8** has subsequently been isolated from *Aspergillus ustus* and serves as the biosynthetic precursor to a product of alternative ring closure, austamide i: Steyn, P. S. *Tetrahedron Lett.* **1971**, 3331.



I, AUSTAMIDE

0002-7863/90/1512-808$02.50/0