polyquinane framework and (b) electronic weakening by perfectly coplanar alignment with the empty C2 p-orbital. More detailed information is expected from single-crystal X-ray studies on **6**.

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Thermochemistry of a Structurally Defined Aldol Reaction

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Recent X-ray crystal studies by Williard[1,2] and Seebach[3] provide the basis for the present determination of the heat of reaction, ΔH_{rxn}, for a uniquely well-determined aldol reaction (Scheme I). The lithium enolate of pinacolone (**1**) precipitated from a hydrocarbon solvent is hexameric.[1] Reaction of this enolate with pivalaldehyde (**2**) in pentane at 0 °C yields a clear colorless solution of the lithium aldolate product **3**, whose crystal structure upon precipitation at −30 °C is tetrameric.[2] Additionally, Seebach et al. have reported the crystal structure of the lithiopinacolonate·THF tetramer.[3] We have determined by vapor pressure osmometry and 2D heteronuclear Overhauser NMR spectroscopy (^{6}Li–^{1}H HOESY) that these solid-state structures are maintained in hydrocarbon solution and have repeated these reactions at 25 °C in a Tronac 1250 solution calorimeter operated in the 450 isoperibol mode.[4]

Ampules containing 0.25 mL of a 0.50 M solution of pivalaldehyde in hexane were broken into a 50-mL dewar-calorimeter vessel containing a 0.10 M solution of lithiopinacolonate in hexane and those containing 1 equiv of the various basic ligands, tetrahydrofuran (THF), tetramethylenediamine (TMEDA), and dimethoxyethane (DME). Clean, linear thermograms demonstrated that the exothermic reactions were complete and instantaneous.

Results presented in Table I are the first known to us for the thermodynamics of a clearly defined aldol reaction in nonhydroxylic media. Many complexities (e.g., reversibility, elimination, polymerization) have precluded all save a few previous studies of rates or equilibrium constants under classical conditions with alkali bases in hydroxylic solvents.[5]

The system was modeled to insure that the measured heat changes were actually for aldol addition reactions. One-half an equivalent of pivalaldehyde was added to each of the enolate solutions in hexane and silylated as described by House.[6] Proton NMR spectra for each crude product showed only residual amide base (from the formation of lithiopinacolonate) and silylated aldol product.

Attempts to measure directly the enthalpies of reaction between the various basic ligands and lithiopinacolonate hexamer were unsuccessful. The thermograms that resulted were long sloping curves which made precise ΔH_{rxn} determinations difficult. Our colligative property measurements below provide further evidence of an equilibrium between aggregation states of lithiopinacolonate in the presence of TMEDA and DME.

Scheme I

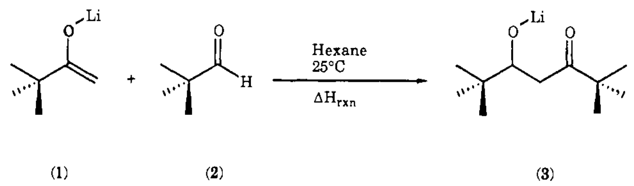

Table I. Heats of Reaction for the Aldol Addition of Lithiopinacolonate (**1**) to Pivalaldehyde (**2**) in Hexane at 25 °C[a]

ligand added	ΔH_{rxn} (kcal/mol)	ligand added	ΔH_{rxn} (kcal/mol)
none	−30.19 ± 0.76	TMEDA (1 equiv)	−20.85 ± 0.72
THF (1 equiv)	−17.94 ± 0.36	DME (1 equiv)	−19.05 ± 0.44

[a] Errors are reported at the 95% confidence limit.

Table II. Aggregation Numbers (*n*) for Lithiopinacolonate (**1**) and the Lithium Aldolate Product **3** in Cyclohexane at 37 °C

ligand added	n^b **1**[c]	n^b **3**[c]	ligand added	n^b **1**[c]	n^b **3**[c]
none	6.4	4.1	TMEDA	5.2	4.3
THF	4.5	4.3	DME	5.5	3.9
THF[e]	4.1				

[a] One equivalent of ligand added prior to measurement. [b] Aggregation numbers carry a nominal 10% uncertainty. [c] Concentrations are 0.1–0.5 M unless noted. [d] Concentration 0.1–0.7 M. [e] Prepared as crystalline **1**·THF.[3]

Recent studies have shown that X-ray crystallographic structures of molecules are not always preserved in solution.[7] However, we have confirmed that in the present case, the solid-state structures of the reactants and products are maintained in a hydrocarbon solution and have determined aggregation numbers for those reactants for which no X-ray crystallographic data exist to date.

Aggregation numbers for **1** and **3** in cyclohexane are presented in Table II. VPO data were obtained at 37 °C with a Wescor 5500-XR vapor pressure osmometer operated totally under argon in a Vacuum Atmospheres HE-43-2 drybox with a HE-493 purification system. Several literature results[8] were duplicated with this technique.

Solution structure studies of the key lithium enolates and aldolate product also employed Schleyer's ^{6}Li–^{1}H HOESY NMR technique for the determination of short Li–H distances in organolithium aggregates in hydrocarbon and other nonpolar solvents.[7,9] NMR spectra were recorded on a General Electric GN-500 spectrometer. HOESY parameters used were based upon those of Schleyer,[9] and the phase cycling was that of Yu and Levy.[10] Figure 1 shows the ^{6}Li–^{1}H HOESY spectrum for ^{6}Li-labeled lithiopinacolonate·THF in cyclohexane-d_{12} at 12 °C. This was prepared as described[3] using [^{6}Li] lithium hexamethyldisilylizane·2THF.[11,12] The only cross-peaks detected were those predicted from the crystal structure. We have also obtained[9] a HOESY spectrum for **3** which provides further evidence that this solid-state structure is preserved in hydrocarbon solution.

At the urging of one referee, we wish to emphasize that our data say nothing about the nature of the reactive intermediate(s)

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[1] Williard, P. G.; Carpenter., G. B. *J. Am. Chem. Soc.* **1985**, *107*, 3345–3346.

[2] Williard, P. G.; Salvino, J. M. *Tetrahedron Lett.* **1985**, *26*, 3931–3934.

[3] Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617–2621.

[4] (a) Arnett, E. M.; Petro, C. *J. Am. Chem. Soc.* **1978**, *100*, 5402–5407. (b) Eatough, D. J.; Christensen, J. J.; Izatt, R. M. In *Experiments in Thermometric and Titration Calorimetry*; Brigham Young University Press: Provo, Utah, 1974.

[5] For leading references, see: (a) Guthrie, J. P. *Can. J. Chem.* **1974**, *52*, 2037–2040. (b) Guthrie, J. P.; Cossar, J.; Taylor, K. F. *Can. J. Chem.* **1984**, *62*, 1958–1964. (c) Guthrie, J. P.; Cooper, K. J.; Cossar, J.; Dawson, B. A.; Taylor, K. F. *Ibid.* **1984**, *62*, 1441–1445.

[6] House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310–3324.

[7] (a) Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371–2379. (b) Schleyer, P. v. R.; Brandsma, L.; Duisenberg, A. J. M.; Keinters, J. A.; Harder, S.; Klusener, P. A. A.; Bauer, W. *Ibid.* **1988**, *7*, 552–555.

[8] (a) Brown, T. L.; Kimura, B. Y. *J. Organomet. Chem.* **1971**, *26*, 57–67. (b) Jackman, L. M.; Smith, B. D. *J. Am. Chem. Soc.* **1988**, *110*, 3829–3835.

[9] (a) Bauer, W.; Clark, T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 970–977. (b) Bauer, W.; Feigel, M.; Müller, G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1988**, *110*, 6033–6046.

[10] Yu, C.; Levy, G. C. *J. Am. Chem. Soc.* **1984**, *106*, 6533–6537.

[11] ^{6}Li metal (95.5%) was obtained from Oak Ridge National Laboratory, Oak Ridge, TN.

[12] Einhorn, J.; Luche, J. L. *J. Org. Chem.* **1987**, 4124–4126.

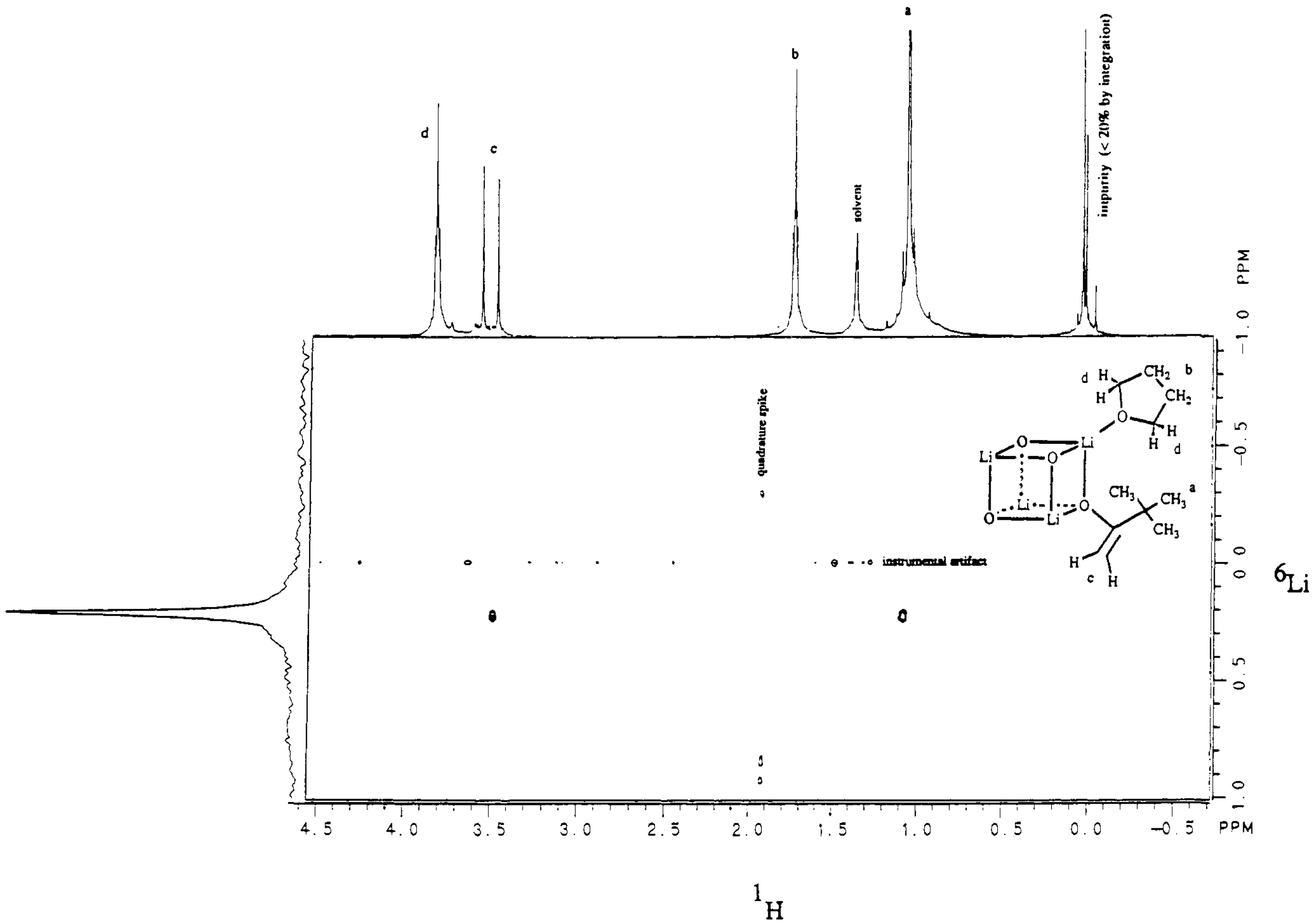

Figure 1. ^{6}Li–^{1}H HOESY spectrum of [^{6}Li] (**1**)·THF (^{6}Li = 95%) (~0.25 M) in cyclohexane-d_{12} at 12 °C: References; ^{1}H, residual C_6H_{12} = 1.38 ppm; ^{6}Li, 2 M LiOH/D_2O (external) = 0.00 ppm. Total measuring time was 11 h.

that lie closest to the product-forming transition state(s). It is clear that the many mechanisms[13] which assume a free monomeric enolate ion or chelate as the true reaction intermediate are at hazard until the necessary kinetic studies to elucidate the mechanism are complete. Although the reaction of lithiopinacolonate·THF tetramer to yield the aldolate product **3** tetramer lends credibility to Seebach's postulated chelated transition state,[14] the nature of the hexamer **1** to tetramer **3** transformation has not yet been demonstrated. The present report deals only with initial and final states, and so is moot about mechanistic details.

The large exothermicity reported here is consistent (in Hammond postulate terms) with the nearly instantaneous rates of aldol addition reactions at low temperatures in nonpolar solvents. However, it contrasts with the near thermoneutrality inferred by Noyori[15] from the failure of the putative "naked" enolate anion to react with benzaldehyde in THF at −78 °C unless excess trimethylsilyl fluoride was added to capture the aldol product. Guthrie[5a] found an enthalpy change of −9.84 kcal/mol for the formation of aldol from acetaldehyde by an indirect thermochemical estimate from tabulated data. His subsequent studies[5b,c] confirm that several hydroxide-catalyzed reactions in hydroxylic media are reversible with only modest driving force.

A crude estimate of the energetics of Scheme I can be made from standard tabulated bond energies.[16] Ignoring all of the special aggregation or chelation effects known to exist in the reactants and products, one may estimate the overall change to be $\Delta H_{rxn} = -20$ kcal/mol from the formation of two C–C bonds (2 × 84 kcal/mol) and the loss of one C=C bond (148 kcal/mol), which is very close to the observed value in the presence of THF. The difference between this value and the 30 kcal/mol observed in hexane may be the result of replacing a weak bond from lithium to the Π system of the enol in the hexameric reactant with a strong bond to the aldolate oxygen in the tetrameric product.[17] The hexamer to tetramer reorganization energy is presently unknown for enolates.[18] Clearly, large contributions from energies of aggregation and chelation play an important part in the overall driving force for the modern aldol reaction.

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(13) Transition states are discussed in the following: (a) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Durst, T., Buncel, E., Eds.; Elsevier: Amsterdam, 1983; Vol. II, Part B. (b) Masamune, S.; Choy, W. *Aldrich. 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.; John Wiley and Sons: 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. *Aldrich. Acta* **1982**, *15*, 23–32. (g) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923. (h) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828–5835. (i) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367–1371. (j) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199–2204. (k) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61–70. (l) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162–7173. (m) Li, Y.; Paddon-Row, M. N.; Houk, K. M. *J. Am. Chem. Soc.* **1988**, *110*, 3684–3686.

(14) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622.

(15) (a) Noyori, R.; Nishida, I.; Sakata, S. *J. Am. Chem. Soc.* **1981**, *103*, 2106–2108. (b) Noyori, R.; Nishida, I.; Sakata, S.; Nishizawa, M. *Ibid.* **1980**, *102*, 1223–1224.

(16) March, J. In *Advanced Organic Chemistry, Reactions, Mechanisms, and Structure*, 3rd ed.; Wiley: New York, 1985.

(17) We appreciate this suggestion by Professor Seebach.

(18) See however ref 145 of Klummp, G. W. *Recl. Trav. Chem. Pays-Bas* **1986**, *105*, 1–21 for hexamer–tetramer interconversions.