good agreement between experimental observations and these preliminary calculations suggests that thermodynamic simulation methods may provide a quantitative approach to determining the thermodynamic properties of protein hydration, although much work must be done to make these methods efficient and simple to use. A complete account of the methods used here, and the thermodynamic and structural changes observed, will be given elsewhere.

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Structural and Energetic Evidence for O–Li–N Chelation in a Model for Asymmetric Induction

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Although controlled synthesis of optically active isomers has been a well-recognized goal of organic chemistry for nearly a century it has only begun to be attained in the last 25 years, primarily through the use of lithium reagents adding to suitably substituted multiple bonds in solvents of low polarity, usually at low temperatures.[3] In view of the high charge density of lithium and its resulting tendency to form contact ion pairs, it is very reasonable that the transition structures for stereoselective addition reactions should be controlled by lithium chelation between two adjacent electronegative atoms. Appropriate structures have been proposed for many such cases.[4]

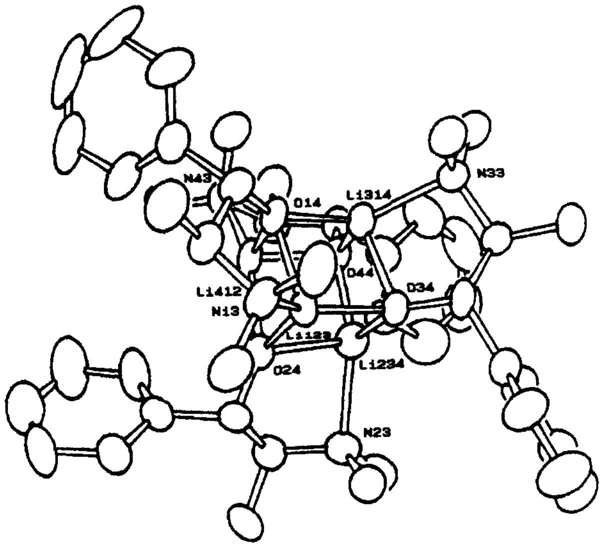

Figure 1. ORTEP diagram of the lithium *N*-methylpseudoephedrate (I) solid-state tetramer. Hydrogen atoms have been omitted for clarity. The Li–O and Li–N bond distances range from 1.870 (13) to 1.985 (13) Å (mean 1.929 Å) and 2.047 (13) to 2.197 (13) Å (mean 2.122 Å), respectively.

Table I. VPO and Cryoscopic Aggregation Numbers (n) for Lithium *N*-Methylpseudoephedrate (I) and *N*-Methylephedrate (II) in Benzene and Dioxane[a]

compd	n (benzene)[b]	n (dioxane)[b]
I	4.05 ± 0.94 (3.11 ± 1.07)	insoluble
II	4.45 ± 1.02 (3.74 ± 1.67)	5.02 ± 1.31[c] (5.5 ± 2.5)[c]

[a] Cryoscopic results are given in parentheses. [b] Concentrations are 0.150–0.200 m. [c] These results indicate that the aggregate is either a tetramer or hexamer.

Table II. Heats of Deprotonation (ΔH_{dep}) for the Alcohols of *N*-Methylpseudoephedrate (I), *N*-Methylephedrate (II), and 2-Methyl-1-phenyl-1-butoxide (III), 2-Methyl-1-phenyl-1-butoxide (IV), and 3-Methyl-1-phenyl-1-butoxide (V) by Lithium Bis(trimethylsilyl)amide (LHMDS) in Benzene and Dioxane at 6 and 13 °C, Respectively[a]

	ΔH_{dep}, kcal/mol	
alcohol	benzene[b]	dioxane[b]
I	-33.59 ± 1.38	c
II	-35.53 ± 0.74	-20.50 ± 1.15
III	-27.15 ± 0.45	-13.58 ± 0.34
IV	-26.22 ± 0.26	-13.21 ± 0.33
V	-27.64 ± 0.80	-14.11 ± 0.76

[a] Errors are given at the 95% confidence limit. [b] Corrected for the $\Delta H_{dilution}$ of HMDS into benzene and dioxane, +1.30 and +0.97 kcal/mol, respectively. [c] The insolubility of the alkoxide prevented this measurement.

Lithium enolates, amides, and related compounds are highly aggregated in solution[5] as dimers, tetramers, or even hexamers and X-ray crystal structures have been reported in which lithium is chelated between appropriately positioned oxygen, nitrogen, and carbon atoms.[6] To our knowledge, only one series of extensive studies has addressed the actual structures and determined the corresponding energy terms of chelated systems that are directly analogous to the transition structures for asymmetric syntheses employing lithium-controlled chelation.[4j,7]

We have chosen the lithium alkoxides of (–)-ephedrine and (+)-pseudoephedrine, their *N*-methyl derivatives,[8] and a number

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[1] From the projected Ph.D. dissertation of Michael A. Nichols, Duke University, 1990.

[2] Duke University Structure Center.

[3] (a) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice-Hall: Englewood Cliffs, NJ, 1971. (b) *Asymmetric Syntheses*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vols. 2, 3. (c) Eliel, E.; Otsuka, S. *Asymmetric Reactions and Processes in Chemistry*; ACS Symposium Series 185; American Chemical Society: Washington, DC, 1982. (d) Mosher, H. S.; Morrison, J. D. *Science* **1983**, *221*, 1013–1019.

[4] (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275–316. (b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Ibid.* **1984**, *84*, 471–523. (c) Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59–68. (d) Meyers, A. I. *Lect. Heterocycl. Chem.* **1984**, *7*, 75–81. (e) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095–5108. (f) Meyers, A. I.; Knaus, G.; Karnata, K. *J. Am. Chem. Soc.* **1974**, *96*. 268. (g) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356–363. (h) Lutomski, K. A.; Meyers, A. I. Asymmetric Synthesis via Chiral Oxazolines. In *Asymmetric Syntheses*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, pp 213–274. (i) Enders, D. Alkylation of Chiral Hydrazones. In *Asymmetric Syntheses*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, pp 275–339. (j) Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1–21, and references therein. (k) See, however: Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1990**, *112*, 4350–4362.

[5] (a) For an excellent review, see: Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624–1654. (b) Jackman, L. M.; Smith, B. D. *J. Am. Chem. Soc.* **1988**, *110*, 3829–3835, and references therein. (c) DePue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5518–5524, and references therein. (d) Arnett, E. M.; Fisher, F. J.; Nichols, M. A.; Ribeiro, A. A. *J. Am. Chem. Soc.* **1990**, *112*, 801–808.

[6] (a) For a review of X-ray structures of organolithium compounds, see: Setzer, W.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353–450. (b) Footnotes 11–14, 126, 127, 132, and 133 of ref 4g. (c) Jastrzebski, J. T. B. H.; van Koten, G.; van de Meiroop, W. F. *Inorg. Chim. Acta* **1988**, 169–171. (d) Moene, W.; Schakel, M.; Hoogland, J. M.; de Kanter, F. J. J.; Klumpp, G. W. *Tetrahedron Lett.* **1990**, *31*, 2641–2642, and refs 6 and 7 therein.

[7] For a pioneering study, see: Beak, P.; Seigel, B. *J. Am. Chem. Soc.* **1974**, *96*, 6803–6805.

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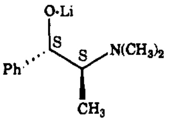
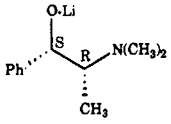
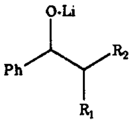
of related compounds as a testing ground for the chelation hypothesis.[9] Figure 1 presents an ORTEP diagram of the structure of lithium (+)-*N*-methylpseudoephedrate (I) determined from



I



II



III: R_1 = Me; R_2 = Et
IV: R_1 = Me; R_2 = Me
V: R_1 = H; R_2 = *i*-Pr

crystals obtained by precipitation from a 95:5 *p*-dioxane–THF solution.[10,11] In the solid state, the lithium atoms are chelated between oxygen and nitrogen and the alkoxide is tetrameric.[12] That the solution structure (which is more relevant to synthetic processes) is tetrameric in benzene was demonstrated by vapor pressure osmometry (VPO, 37 °C) and cryoscopy (5.5 °C)[5d,13-17] (Table I). A strong argument for chelation in solution can be made upon examination of the vicinal coupling constant (8.62 ± 0.60 Hz) between protons b and c, which is consistent with the conformation of an intramolecularly chelated alkoxide.[18,19] A ^{6}Li–^{1}H NOE NMR spectrum of [^{6}Li]I in benzene-d_6 at 25 °C was obtained and is also consistent with intramolecular chelation. We have submitted this spectrum as supplementary material.

The foregoing structural information supports the proposal[4] that intramolecular lithium chelation occurs in some asymmetric syntheses and also provides permissive evidence for transition structures where attack occurs on an edge of an aggregated species.[20] However, the more familiar monomeric transition structures cannot be ruled out entirely.[4]

We have estimated the chelation energy by comparing the heats of deprotonation (ΔH_{dep}, determined calorimetrically[5d]) for chelatable 2-substituted-1-phenyl-1-propanols with appropriate analogues that are incapable of chelation. Data for the present case are provided in Table II, where the ΔH_{dep} of *N*-methylpseudoephedrine and *N*-methylephedrine by lithium bis(trimethylsilyl)amide (LHMDS) are compared to the corresponding values for deprotonation of 2-methyl-1-phenyl-1-butanol (III),[21] 2-methyl-1-phenyl-1-butanol (IV), and 3-methyl-1-phenyl-1-butanol (V).[22] The enthalpies of stabilization due to chelation (ΔH_{stab}) can be calculated from these ΔH_{dep} data by using eq 1.

$$\Delta H_{stab} = \Delta H_{dep}(\text{chelatable}) - \Delta H_{dep}(\text{nonchelatable}) \quad (1)$$

These values were found to range from 6.4 to 8.4 kcal/mol, which are in agreement with previous thermodynamic measurements of Klumpp (3.59-9.80 kcal/mol)[4j] and Beak (8.3 kcal/mol),[7] and the calculated values of Schleyer (10.2–13.1 kcal/mol).[23]

Further explorations of the chelation question using the above techniques for a variety of other compounds have been completed and will be reported in a future publication.

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Supplementary Material Available: Atomic numbering scheme and tables of crystallographic data, atomic positional and thermal parameters, bond lengths and angles, and selected torsion angles for the solid-state tetramer $(I)_4$ and a ^{6}Li–^{1}H NOE NMR spectrum of [^{6}Li]I (16 pages); a listing of observed and calculated structure amplitudes for $(I)_4$ (13 pages). Ordering information is given on any current masthead.

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(8) The optically active alcohols were obtained from Aldrich Chemical Co.

(9) These studies will be submitted as a full paper in the future.

(10) The lithium alkoxides were prepared by addition of equimolar amounts of the alcohol and solid LHMDS (purified as described in ref 5d) in the solvent of interest.

(11) The tetramer $[C_{11}H_{16}LiNO]_4$, depicted in Figure 1, crystallizes in the monoclinic system, space group $P2_1$ (C_2^2), with a = 15.758 (5) Å, b = 12.617 (4) Å, c = 11.579 (4) Å, β = 90.78 (2)° (from 25 orientation reflections, 40° < θ < 47°), V = 2302 (2) Å^3, Z = 2, d_{calcd} = 1.069 g cm^{-3}, μ(Cu Kα) = 4.9 cm^{-1}. Intensity data ($+h,+k,\pm l$; 4323 nonequivalent reflections; θ_{max} = 67°) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu Kα radiation, λ = 1.5418 Å; graphite monochromator; ω–2θ scans). The crystal structure was solved by direct methods (MULTAN11/82). Full-matrix least-squares refinement of atomic parameters (anisotropic C, Li, N, O; fixed H contributions) converged (maximum shift 0.02σ) at R = 0.057 (R_w = 0.070, GOF = 1.45) over 1894 reflections with $I > 2.0\sigma(I)$. Further details are provided as supplementary material.

(12) A similar tetrameric structure was obtained for the benzene solvate of lithium (+)-*N*-methylephedrate (II) when crystallized from benzene. This structure will be reported in the future.

(13) HMDS did not interact with the alkoxide aggregate in either solvent (see ref 5d).

(14) We suspect II to be tetrameric in dioxane, although our colligative measurements failed to differentiate between the tetramer and hexamer.

(15) Variable-temperature ^{6}Li NMR of [^{6}Li]I and -II showed only one resonance, which was invariant to temperature.

(16) Bauer, W.; Schleyer, P. v. R. *Magn. Reson. Chem.* **1988**, *26*, 827–833, and references therein.

(17) ^{6}Li metal (95.5%) was obtained from ORNL, Oak Ridge, TN. The [^{6}Li]alkoxides were prepared as described in refs 10 and 5d.

(18) Using the Karplus equation: Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11; *J. Am. Chem. Soc.* **1963**, *85*, 2870. Bothner-By, A. A. *Adv. Magn. Reson.* **1965**, *1*, 195.

(19) The validity of using the vicinal coupling constant to determine the conformation of the alcohols has been shown: (a) Kanzawa, T. *Bull. Chem. Soc. Jpn.* **1956**, *29*, 398. (b) Portoghese, P. S. *J. Med. Chem.* **1967**, *10*, 1057.

(20) Aggregated transition states have been proposed for the aldol reaction: (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.

(21) A 59:41 (±)-*RR*/*RS* mixture of diastereomers was used: Gonzalez, F.; Perez-Ossorio, R.; Plumet, J. *An. Quim.* **1975**, *71*, 208–212.

(22) While the aggregation states of III–V were not determined, lithium *sec*-phenethanolate was found to be hexameric and tetrameric in benzene and dioxane, respectively.

(23) See: Reference 4j, p 19.

The Remarkable Cobalt- and Phase-Transfer-Catalyzed Carbonylation of Epoxy Alcohols: A Formal Triple Carbonylation Reaction

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Carbonylation reactions are one of the most important classes of metal-catalyzed processes.[1,2] An attractive method for effecting a variety of carbon monoxide insertion reactions, under mild conditions, is by the use of phase-transfer catalysis. A rich chemistry has developed using cobalt carbonyl as the metal catalyst under such conditions.[3-5] Of particular note are single and double carbonylation reactions, which occur by the reaction of in situ generated acylcobalt tetracarbonyl (from cobalt carbonyl, methyl iodide, and carbon monoxide) with unsaturated and strained ring compounds. Concerning the latter, vinyl epoxides undergo monocarbonylation to unsaturated hydroxy acids,[6] while styrene oxides experience double carbonylation, affording the enol tautomer of an α-keto lactone.[7] It was reasoned that, by the use

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(1) Sheldon, R. A. *Chemicals from Synthesis Gas*; Reidel: Dordrecht, Holland, 1983.

(2) Tkatchenko, I. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Elmsford, NY, 1982; Vol. 8, pp 101–223.

(3) Petrignani, J. F. *The Chemistry of the Metal–Carbon Bond*; Hartley, F. R., Ed.; J. Wiley and Sons, Ltd.: New York, 1989, Vol. 5; pp 63–106.

(4) des Abbayes, H. *New J. Chem.* **1987**, *11*, 535.

(5) Alper, H. *Fundam. Res. Homogeneous Catal.* **1984**, *4*, 79.

(6) Alper, H.; Calet, S. *Tetrahedron Lett.* **1988**, *29*, 1763.

(7) Alper, H.; Arzoumanian, H.; Petrignani, J. F.; Saldana-Maldonado, M., *J. Chem. Soc., Chem. Commun.* **1985**, 340.

0002-7863/90/1512-7060$02.50/0