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Enantiomeric Perturbation of Equilibria. Differential Solvation of a Chiral Lithium Amide by the Enantiomers of 2-Methyltetrahydrofuran Measured by NMR Spectroscopy

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We wish to report the first direct observation of diastereoselective solvation of a chiral organolithium compound by the enantiomers of a chiral ether, i.e. solvation by (*R*)- and (*S*)-2-methyltetrahydrofuran (2-MTHF) of the dimer of lithium (2-methoxy-(*R*)-1-phenylethyl)((*S*)-1-phenylethyl)amine ($(LiA)_2$) (Scheme 1). A novel method for determination of accurate equilibrium constants (K) and their temperature dependence (ΔH and ΔS) using NMR chemical shifts is also presented. It has been used to measure the differential solvation of $(LiA)_2$ by the *R*- and *S*-isomers of 2-MTHF.

The ^{13}C NMR spectrum of $(LiA)_2$ in toluene with 2-MTHF added ($[(LiA)_2]_{tot} = 0.25$ M and $[\text{2-MTHF}]_{tot} = 0.1$ M) shows separate signals of equal intensity for (*R*)-2-MTHF and (*S*)-2-MTHF in the diastereomeric complexes $(LiA)_2{\cdot}(R)$-2-MTHF and $(LiA)_2{\cdot}(S)$-2MTHF at all temperatures (−80 to +25 °C). All 2-MTHF molecules are complexed, and $(LiA)_2$ has been shown by integration to form 1:1 complexes with 2-MTHF. With excess of 2-MTHF at −80 °C separate signals are observed for the complexes as well as for uncomplexed 2-MTHF (Figure 1). Some signals (C_2 and C_5) from noncoordinated 2-MTHF and 2-MTHF in the diastereomeric complexes are shown.

The signals from 5-carbons (C_5) in the (*R*)- and (*S*)-isomers, respectively, of 2-MTHF appear with different intensities, indicating that the solvation of $(LiA)_2$ shows stereoselection and that diastereomeric complexes are formed, i.e., K in Scheme 1 differs from unity. The assignment of each set of peaks to the stereoisomers of 2-MTHF has not yet been made. The signals from the 2-carbons (C_2) appear at about the same chemical shift (δ 76.24 and 76.31 at −80 °C). In Figure 1 these signals are not resolved. Obviously, the exchange between coordinated and noncoordinated 2-MTHF is slow at −80 °C, since separate sharp signals are observed for the coordinated and noncoordinated (*R*)- and (*S*)-2-MTHF molecules. Since no ^{13}C signals from uncomplexed $(LiA)_2$ are observed, it is concluded that all $(LiA)_2$ molecules are complexed by 2-MTHF.

When the temperature is raised, the rate of exchange between coordinated and noncoordinated ether molecules increases and coalescence is observed. At even higher temperature (−40 °C) pairs of sharp signals are observed for each of the two types of carbon (C_2 and C_5). At 25 °C it is obvious that the intensities of the signals in each pair is equal.

Thus, it is concluded that one of the signals in a pair originates from (*R*)-2-MTHF molecules in $(LiA)_2{\cdot}(R)$-2-MTHF and noncoordinated (*R*)-2-MTHF molecules, which are rapidly exchanging. Similarly, the other one originates from exchanging (*S*)-2-MTHF molecules.

The chemical shift difference between the signals in the pair originating from C_2 is mainly due to the fact that the (*R*)- and (*S*)-2-MTHF molecules have different complexation constants since the shift difference between C_2 of 2-MTHF in $(LiA)_2{\cdot}(R)$-2-MTHF and $(LiA)_2{\cdot}(S)$-2-MTHF is only ca. 0.07 ppm.

To our knowledge this is the first example of chiral "discrimination" by a chiral organolithium compound between the enantiomers of an ethereal solvent. Previously slow ethereal ligand exchange on the NMR time scale between ethers coordinated to achiral lithium amides and noncoordinated ethers has been reported.[1,2] Slow exchange between $(LiA)_2$ coordinated to achiral ethers and noncoordinated achiral ethers has also been recently reported.[3,4]

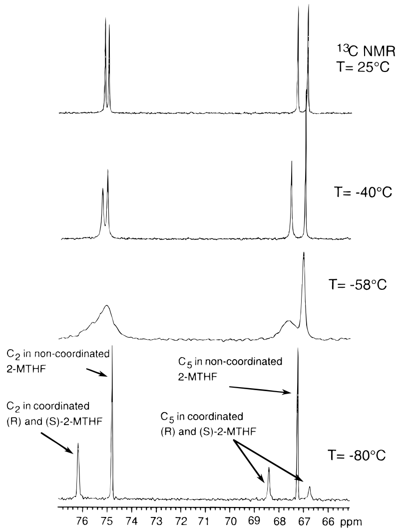
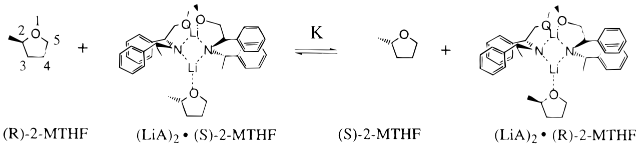


Figure 1. Partial ^{13}C NMR spectra at 125 MHz of 0.25 M $[^6Li](LiA)_2$− 0.5 M 2-MTHF in toluene-d_8 at different temperatures.

Scheme 1



The ^{13}C NMR and the ^{6}Li NMR spectra of the solutions used in the above experiments also showed the exclusive presence of the lithium amide dimer $(LiA)_2$. However, addition of large amounts of 2-MTHF to the toluene solution of $(LiA)_2$ at −80 °C results in the appearance of separate signals of the solvated monomer (LiA) in addition to the signals from the dimer. Increase of temperature strongly disfavors the monomers. Figure 1 shows that the shift difference between the signals from the diastereomeric solvates shows temperature dependence.

The results presented above indicate that accurate equilibrium constants (K) and their temperature dependence (ΔH and ΔS) may be determined as shown below for the equilibrium in Scheme 1. Thus the differential solvation of $(LiA)_2$ by the enantiomers of 2-MTHF could be accurately measured.

The equilibrium constant is defined as in eq 1.

$$K = \frac{[(LiA)_2{\cdot}(R)\text{-2-MTHF}][(S)\text{-2-MTHF}]}{[(LiA)_2{\cdot}(S)\text{-2-MTHF}][(R)\text{-2-MTHF}]} \qquad (1)$$

At fast ligand exchange the average chemical shift (δ_R) for (*R*)-2-MTHF is given by eq 2.

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(1) (a) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6009. (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863.

(2) Slow ligand exchange rates have also been reported with HMPA and diamines, see: (a) Reich, H. J.; Green, D. P. *J. Am. Chem. Soc.* **1989**, *111*, 8729. (b) Barr, D.; Doyle, M. J.; Mulvey, R. E.; Raithby, P. R.; Reed, D.; Snaith, R.; Wright, D. S. *J. Chem. Soc., Chem. Commun.* **1989**, 318. (c) Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, *112*, 1282. (d) Boche, G.; Fraenkel, G.; Cabral, J.; Harms, K.; van Eikema Hommes, N. J. R.; Lohrenz, J.; Marsch, M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1992**, *114*, 1562. (e) Hoffman, R. W.; Klute, W.; Dress, R. K.; Wenzel, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1721.

(3) Hilmersson, G.; Davidsson, Ö. *J. Organomet. Chem.* **1995**, *489*, 175.; *J. Org. Chem.* **1995**, *60*, 7660.

(4) The structure of THF monosolvated $(LiA)_2$ has been determined by X-ray crystallography. Hilmersson, G.; Davidsson, Ö; Håkansson, M. *Manuscript in preparation.*

0002-7863/96/1518-3539$12.00/0

Table 1. Equilibrium Constants (K) at Different Temperatures for the Equilibrium in Equation 1 Measured in Toluene-d_8 Using Different Total Concentrations of 2-MTHF. The Initial Concentration of $(LiA)_2$ Was 0.25 M

	K at different temperatures (K)								
$[2\text{-MTHF}]_{tot}$ (M)	231.4	242.7	254.1	264.7	275.8	286.6	297.5	ΔH (kJ mol^{-1})	ΔS (J mol^{-1})
0.44	1.752[a]	1.709	1.650	1.595	1.543	1.511	1.476	−1.63	−2.3
0.66	1.776[a]	1.719	1.690	1.612	1.557	1.514	1.471	−1.71	−2.5
0.95	1.758[a]	1.751	1.690	1.627	1.568	1.526	1.475	−1.89	−3.1

[a] These equilibrium constants have not been used in the calculation of ΔH and ΔS since the signals for C_2 are broad at this temperature.

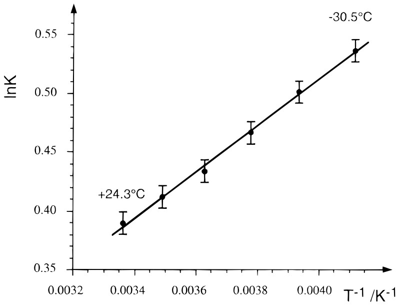

Figure 2. Plot of ln K vs $1/T$ for the equilibrium between the two diastereomeric solvation complexes (R)-2-MTHF·$(LiA)_2$ and (S)-2-MTHF·$(LiA)_2$. Errors have been calculated assuming chemical shift errors of 0.001 ppm (0.12 Hz).[5]

$$\delta_R = \frac{\delta_{FR}[(R)\text{-2-MTHF}] + \delta_{LiR}[(LiA)_2\cdot(R)\text{-2-MTHF}]}{[(R)\text{-2-MTHF}] + [(LiA)_2\cdot(R)\text{-2-MTHF}]} = \frac{\delta_{FR} + \delta_{LiR}\dfrac{[(LiA)_2\cdot(R)\text{-2-MTHF}]}{[(R)\text{-2-MTHF}]}}{1 + \dfrac{[(LiA)_2\cdot(R)\text{-2-MTHF}]}{[(R)\text{-2-MTHF}]}} \quad (2)$$

δ_{FR} and δ_{LiR} are the chemical shifts for free 2-MTHF (the noncoordinated enantiomers have the same chemical shifts) and (R)-2-MTHF coordinated to $(LiA)_2$, respectively. Analogously a similar expression for the (S)-isomer of 2-MTHF is obtained by changing R for S in eq 2.

Substitution with a_r and a_s defined below allow us to express the concentration ratios as ratios between chemical shift differences (eqs 3 and 4).

$$a_r = \frac{[(LiA)_2\cdot(R)\text{-2-MTHF}]}{[(R)\text{-2-MTHF}]} \text{ and } a_s = \frac{[(LiA)_2\cdot(S)\text{-2-MTHF}]}{[(S)\text{-2-MTHF}]}$$

$$\delta_R + \delta_R a_r = \delta_{FR} + \delta_{LiR} a_r$$

$$\delta_R - \delta_{FR} = a_r(\delta_{LiR} - \delta_R) \Rightarrow a_r = \frac{\delta_R - \delta_{FR}}{\delta_{LiR} - \delta_R} \quad (3)$$

$$\delta_S - \delta_{FS} = a_s(\delta_{LiS} - \delta_S) \Rightarrow a_s = \frac{\delta_S - \delta_{FS}}{\delta_{LiS} - \delta_S} \quad (4)$$

Thus substitution in eq 1 results in eq 5.

$$K = \frac{a_r}{a_s} = \frac{\delta_R - \delta_{FR}}{\delta_{LiR} - \delta_R}\,\frac{\delta_{LiS} - \delta_S}{\delta_S - \delta_{FS}} \quad (5)$$

The assignment of absolute configurations to the signals is tentative. Molecular modeling shows that $(LiA)_2\cdot(R)$-2-MTHF is slightly more stable than $(LiA)_2\cdot(S)$-2-MTHF.

The ^{13}C chemical shifts δ_S, δ_R, δ_{FS}, δ_{FR}, δ_{LiR}, and δ_{LiS} were determined at each temperature using the chemical shift of the Me group of toluene-d_8 as reference. The shift δ_{FR} which equals δ_{FS} was measured in absence of $(LiA)_2$. δ_{LiR} and δ_{LiS} were approximated by the δ_R and δ_S values, respectively, obtained using a solution containing $[(LiA)_2]_{tot} = 0.25$ M and $[2\text{-MTHF}]_{tot} = 0.1$ M. In such a mixture only a tiny fraction of the 2-MTHF molecules are uncomplexed. This was shown at 25 °C using mixtures with $[2\text{-MTHF}]_{tot}$ equal to 0.15, 0.10, and 0.05 M, respectively. Since the extrapolated values of δ_R and δ_S to $[2\text{-MTHF}]_{tot} = 0$ differ only slightly from these measured with $[2\text{-MTHF}]_{tot} = 0.10$ M, it is concluded that the latter values well approximate δ_{LiR} and δ_{LiS}, respectively. Obviously the equilibrium constants for the equilibria in Scheme 2 are large.

Scheme 2

$$(R)\text{-2-MTHF} + (LiA)_2 \rightleftharpoons (LiA)_2\cdot(R)\text{-2-MTHF}$$

$$(S)\text{-2-MTHF} + (LiA)_2 \rightleftharpoons (LiA)_2\cdot(S)\text{-2-MTHF}$$

K for the differential solvation equilibrium in Scheme 1 has been measured at three different concentrations of 2-MTHF (0.4, 0.7, and 1.0 M). The results are shown in Table 1.

At 25 °C, $K = 1.470 \pm 0.015$ which corresponds to a $\Delta G_{298K} = -0.955 \pm 0.024$ kJ mol^{-1}. The estimated maximal errors are based on the assumption that each of the chemical shifts in eq 5 has a maximal error of 0.001 ppm (0.12 Hz).[5]

In Figure 2, ln K has been plotted vs $1/T$. The error limits shown are calculated based on the above chemical shift errors. From the plot in Figure 2 the differential solvation enthalpy (ΔH) and entropy (ΔS) are calculated to be -1.63 ± 0.20 kJ mol^{-1} and -2.3 ± 0.7 J K^{-1}mol^{-1}, respectively. In view of the good fit of the line to the measured values the errors in ΔH and ΔS seem to be overestimated.

Thus the solvation of $(LiA)_2$ by one of the enantiomers of 2-MTHF is favored by 1.63 kJ mol^{-1} compared with that of the other one. However, this enthalpy gain is only partially compensated by an entropy loss of 2.3 J K^{-1} mol^{-1} ($-T\Delta S = 0.67$ kJ mol^{-1} at 298 K). One of the enantiomers of 2-MTHF fits better to $(LiA)_2$ than the other one which results in an enthalpy gain, but at the same time the mobility of the former becomes somewhat restricted compared with that of the latter.

The lithium organic reagent $(LiA)_2$ functions as a chiral shift reagent but with slower ligand exchange.[6] The presented method shows resemblance with that of isotopic perturbation[7,8] and may have wide applicability for accurate determination of equilibrium constants as well as thermodynamic parameters for equilibria.

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(5) The ^{13}C NMR spectral width was 25 000 Hz, and 2000 transients were collected with 128 000 data points for each spectra. Zero-filling to 512 000 data points gave a digital resolution of less than 0.1 Hz. The probe temperature was calibrated (±0.5 °C) with a standard methanol thermometer after more than 1 h of temperature equilibration.

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