Solvent Effects on the Barrier to Rotation in Carbamates

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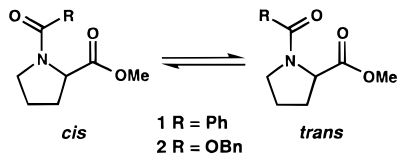
In the 40 years since the inception of dynamic NMR methods, much effort has been invested to quantify and understand the barrier to rotation about the C−N bond in amides.[1] Carbamates, which also exhibit the approximately planar N−C═O framework responsible for hindered rotation in amides, have received considerably less attention, although they are important biologically as anticonvulsants, local anesthetics, sedatives, muscle relaxants,[2] enzyme inhibitors,[3] and surrogates for amides in enzyme mimetics.[4] Although amides and carbamates share common features, the additional oxygen of the carbamate functionality exerts unique steric and electronic perturbations. One consequence of this difference is that the barriers to rotation in carbamates are usually 3−4 kcal/mol (about 15−20%) lower than those in the corresponding amides.

During a study on the catalysis of cis−trans amide and carbamate isomerization, we observed that the barriers to rotation ($\Delta G^{\ddagger}$) in prolyl carbamates were surprisingly insensitive to solvent effects. This behavior contrasts that of amides, where it is common for $\Delta G^{\ddagger}$ to increase by as much as 3 kcal/mol (>100-fold rate decrease) upon a change in environment from a nonpolar, non-hydrogen bonding solvent to water.[5] In this paper, we report the first systematic investigation of solvent effects on $\Delta G^{\ddagger}$ for hindered C−N bond rotation in carbamates and that this process occurs with a negative $\Delta S^{\ddagger}$ for acyclic tertiary carbamates in aqueous solution.

We began our investigation by studying the effect of solvent on $\Delta G^{\ddagger}$ for the interconversion of the cis and trans forms of the related proline derivatives **1** and **2** (eq 1). The



(1)

barrier to isomerization was measured by ^{1}H saturation transfer (ST) NMR[6] in a number of solvents, and the results are summarized in Table 1. As expected,[5] the rotational barrier of amide **1** increases from 17.4 to 20.2 kcal/mol as the dielectric constant and hydrogen-bond-donating ability of the solvent increase. With carbamate **2**, the barrier exhibits almost complete insensitivity to solvent.

Table 1. Solvent Effects on the Barrier to Rotation of Amide 1 and Carbamate 2[a]

entry	solvent	$\Delta G^{\ddagger}_{\text{amide}}$ [b,c]	$\Delta G^{\ddagger}_{\text{carbamate}}$ [b−d]
a	CCl_4	17.4[e]	17.1
b	$CDCl_3$	18.7[f]	17.2
c	CD_3OD	19.1[f]	17.3
d	25% D_2O/CD_3OD	19.6[g]	17.4
e	50% D_2O/CD_3OD	19.9[g]	17.4
f	75% D_2O/CD_3OD	20.2[g]	17.3

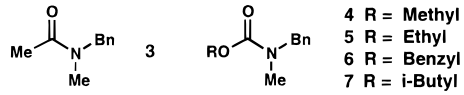
[a] Measured by ^{1}H ST NMR at 10 mg/mL. [b] Trans-to-cis, kcal/mol. [c] ±0.2 kcal/mol. [d] 25 °C. [e] 15 °C. [f] 35 °C. [g] 50 °C.

Table 2. Solvent Effects on the Barrier to Rotation of Amide 3 and Carbamate 4[a]

entry	solvent	$\Delta G^{\ddagger}_{\text{amide}}$ [b,c]	$\Delta G^{\ddagger}_{\text{carbamate}}$ [b−d]
a	CCl_4	16.7[d]	15.5
b	CD_3CN	17.7[e]	15.3
c	CD_3OD	18.5[e]	15.5
d	25% D_2O/CD_3OD	18.8[f]	15.6
e	50% D_2O/CD_3OD	19.1[f]	15.6
f	75% D_2O/CD_3OD	19.3[f]	15.5

[a] Measured by ^{1}H ST NMR at 10 mg/mL. [b] Trans-to-cis, kcal/mol. [c] ±0.2 kcal/mol. [d] 0 °C. [e] 25 °C. [f] 40 °C.

The reported barriers for prolyl amide bond rotation are often smaller than those in the analogous acyclic tertiary amides due to increased pyramidalization of the prolyl nitrogen.[5b] We therefore chose amide **3** and carbamate **4** so we could investigate a "normal" (nonprolyl) amide/carbamate pair to see if the insensitivity of $\Delta G^{\ddagger}$ to solvent occurs in acyclic tertiary carbamates as well. The data in Table 2 indicate that this pair mimics the behavior of the prolyl derivatives: the amide shows a large dependence of $\Delta G^{\ddagger}$ on solvent, whereas $\Delta G^{\ddagger}$ of the carbamate is independent of solvent. Consequently, insensitivity of $\Delta G^{\ddagger}$ to solvent effects appears to be a general characteristic of simple carbamates.[7]



We performed Eyring analyses of **4** in various solvents, as depicted in Table 3.[8] Entries a and b indicate that the barrier to isomerization of carbamate **4** in organic solvents is almost totally enthalpic, with no significant $\Delta S^{\ddagger}$; this observation is in accord with previously reported data for carbamates in non-hydrogen-bonding solvents[9] and for amides in all solvents.[5b] It is generally accepted that unimolecular isomerization processes of this type occur with no solvent participation or reorganization and, therefore,

(1) For leading reviews, see: (a) Stewart, W. E.; Siddall, T. H., III. *Chem. Rev.* **1970**, *70*, 517. (b) Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: Deerfield Beach, 1985; Chapter 2.

(2) Souza, W. F.; Kambe, N.; Sonoda, N. *J. Phys. Org. Chem.* **1996**, *9*, 179 and references therein.

(3) Takayama, H.; Shirakawa, S.; Kitajima, M.; Aimi, N.; Yamaguchi, K.; Hanasaki, Y.; Ide, T.; Katsuura, K.; Fujiwara, M.; Ijichi, K.; Konno, K.; Sigeta, S.; Yokota, T.; Baba, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1993.

(4) Shi, Z.; Griffin, J. H. *J. Am. Chem. Soc.* **1993**, *115*, 6482.

(5) (a) Drakenberg, T.; Dahlqvist, K.-I.; Forsen, S. *J. Phys. Chem.* **1972**, *76*, 2178. (b) Eberhardt, E. S.; Loh, S. N.; Hinck, A. P.; Raines, R. T. *J. Am. Chem. Soc.* **1992**, *114*, 5437.

(6) For applications of saturation transfer to amide isomerization, see: (a) Perrin, C. L.; Thouburn, J. D.; Kresge, J. *J. Am. Chem. Soc.* **1992**, *114*, 8800. We have used this technique in previous related studies; see: (b) Cox, C.; Ferraris, D.; Murthy, N. N.; Lectka, T. *J. Am. Chem. Soc.* **1996**, *118*, 5332. (c) Cox, C.; Young, V. G., Jr.; Lectka, T. *J. Am. Chem. Soc.* **1997**, *119*, 2307.

(7) To our knowledge, only two cursory reports on the isomerization of simple carbamates in a hydrogen-bond-donating solvent (both in MeOH) have appeared. See: (a) De Leer, E. W. B.; Toorn, J. M. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 119. (b) Yamagami, C.; Takao, N.; Takeuchi, Y. *Aust. J. Chem.* **1986**, *39*, 457.

(8) Because the relatively hydrophobic carbamates **6** and **7** have limited solubility in aqueous solutions, we chose to perform the experiments in Table 3 at 1 mg/mL so all substrates could be analyzed under identical conditions.

(9) Early reports on carbamates in organic solvents claimed relatively large, negative entropies of activation but have subsequently been proven unreliable owing to systematic errors in the methods of kinetic analysis; see: Martin, M. L.; Mabon, F.; Trierweiler, M. *J. Phys. Chem.* **1981**, *85*, 76 and references therein.

(10) (a) Lemire, A. E.; Thompson, J. C. *Can. J. Chem.* **1970**, *48*, 824. (b) Hobson, R. F.; Reeves, L. W.; Shaw, K. N. *J. Phys. Chem.* **1973**, *77*, 1228. (c) Reference 1a.

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Table 3. Solvent Effects on the Activation Parameters of Carbamates[a]

entry	carbamate[b]	solvent	$\Delta G^{\ddagger}$ [c]	$\Delta H^{\ddagger}$ [d]	$\Delta S^{\ddagger}$ [e]
a	**4**	CCl_4	15.1	15.1	−1
b	**4**	CD_3CN	15.3	14.9	−1
c	**4**	CD_3OD	15.5	14.4	−4
d	**4**	12.5% D_2O/CD_3OD	15.7	11.4	−16
e	**4**	25% D_2O/CD_3OD	15.6	10.0	−21
f	**4**	50% D_2O/CD_3OD	15.6	10.3	−20
g	**4**	75% D_2O/CD_3OD	15.5	7.9	−27
h	**5**	25% D_2O/CD_3OD	15.4	13.7	−6
i	**6**	25% D_2O/CD_3OD	15.6	12.9	−10
j	**7**	25% D_2O/CD_3OD	15.5	13.8	−6

[a] Eyring plots were constructed from ^{1}H ST NMR data. See Supporting Information for details. [b] 1 mg/mL. [c] 0 °C, ±0.2 kcal/mol. [d] ±0.4 kcal/mol. [e] ± 4 cal/mol·K (see ref 12).

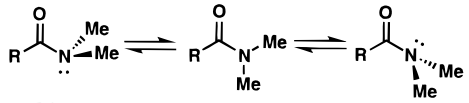

Figure 1. Ground and rotational transition states for amide and carbamate isomerization. [a] Dipole moment in D for R = Me, ref 14c. [b] Dipole moment in D for R = OMe, this study.

should have little or no $\Delta S^{\ddagger}$.[10] However, when **4** was examined in aqueous solvents (entries d−g),[11] we found a large negative $\Delta S^{\ddagger}$ in each case.[12,13] The related carbamates **5**−**7** were also examined in aqueous solution, and entries h−j in Table 3 indicate that they too display a negative $\Delta S^{\ddagger}$, although the absolute values are smaller for **5**−**7** than for **4**. This is the first well-documented example of a simple unimolecular carbamate isomerization to display a significant negative $\Delta S^{\ddagger}$.

Theoretical studies have been published to explain the amide isomerization process both in the gas phase and in solution.[14] The two possible transition states for rotation are TS1 and TS2, where the lone pair on the pyramidalized nitrogen is anti or syn to the carbonyl oxygen, as shown in Figure 1. It has been shown for dimethylacetamide (DMA) that TS1 is more stable than TS2 by 4.1 kcal/mol at 6-31G* and that both transition states have a lower dipole moment than the ground state (Figure 1, R = Me).[14c] For amides, the increase in $\Delta G^{\ddagger}$ with solvent polarity has been attributed to differential solvation, where polar solvents preferentially stabilize the more polar ground state relative to the less polar rotational transition state.[14a]

Related theoretical studies of carbamates in the gas phase are scarce, and no studies exist that include solvation effects.[15] At the 6-311G**//6-31G* level, we found that TS1 of methyl *N*,*N*-dimethylcarbamate (Figure 1, R = OMe) is favored over TS2 by 0.6 kcal/mol.[16,17] The carbamate and amide are therefore both predicted to go through TS1 in the gas phase, although the energy gap between the two carbamate transition states is much smaller than that between the corresponding transition states of DMA (4.1 kcal/mol) at the same level of theory. We also calculated the dipole moments of the ground state and rotational transition states at this level, as shown in Figure 1. Jorgensen has found a general correlation between dipole and solvation for amide transition states, suggesting that TS2 is more strongly solvated in water than TS1.[14c] For DMA, Jorgensen determined that this differential solvation favors TS2 by almost 4 kcal/mol over TS1, leaving TS1 only slightly favored in water (0.2 kcal/mol).

For carbamates, this differential solvation, if of the same magnitude, should leave TS2 the most stable in water by several kcal/mol. Thus, the negative $\Delta S^{\ddagger}$ found for acyclic carbamates may be associated with stronger solvation of the more polar TS2 relative to the less polar ground state. Additionally, recent theoretical studies suggest that the carbonyl oxygen of carbamates is a weaker hydrogen bond acceptor than the amide carbonyl.[18] These interactions in the ground state may be replaced in the transition state by stronger hydrogen bonds to an ether-like oxygen, to an ester-like carbonyl, and to a pyramidalized amine nitrogen, leading to the observed negative $\Delta S^{\ddagger}$. The data also indicate that the charge separation present in the amide ground state is decreased in the carbamate by the presence of the ester-type resonance. The stabilization of this charge separation in the amide ground state is important for explaining the increased $\Delta H^{\ddagger}$ in more polar solvents. The opposite trend in carbamates (more charge separation in the transition state) can explain in part the lack of solvent effects on $\Delta G^{\ddagger}$ by contributing to the decrease in $\Delta H^{\ddagger}$ that offsets the change in $\Delta S^{\ddagger}$.

The large variation in $\Delta S^{\ddagger}$ for **4** upon change from methanol to 12.5% D_2O/MeOD (Table 3, entries c and d) is likely due to specific solvation by water. It is known that for binary solvent mixtures the ratio of solvents in the solvation shell can differ from that in bulk solution,[19] and there is precedent for large variations in $\Delta S^{\ddagger}$ upon change from polar protic solvents to water, most notably in solvolysis reactions.[20] Future studies will be aimed at determining the precise interactions of water with the carbamate transition states.

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Supporting Information Available: Experimental procedures, including details of saturation transfer experiments and Eyring analyses (6 pages).

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(11) These simple carbamates are not amenable to analysis in pure water due to lack of solubility.

(12) Questions have been raised about the reliability of $\Delta S^{\ddagger}$ values from data obtained over a limited temperature range; see ref 9. We conservatively report our error as ±4 cal/mol·K, even though least-squares analysis of the Eyring data indicated ±2 cal/mol·K. We have performed in excess of 25 Eyring analyses on amides and carbamates and in no case other than the carbamates discussed here have we found $\Delta S^{\ddagger}$ to deviate from zero by more than 3.3 cal/mol·K.

(13) There is precedent for cases such as this where the $\Delta G^{\ddagger}$ of a process does not vary as expected with changes in solvent, most notably in decompositions involving radicals; see: (a) Leffler, J. E. *J. Org. Chem.* **1955**, *20*, 1202. In those cases and in our present ones, the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ do change with solvent, but vary in such a way as to cancel and cause no net effect on $\Delta G^{\ddagger}$. This compensating effect has also been observed in enzymes; see: (b) Stein, R. *Adv. Protein Chem.* **1993**, *44*, 1 and references therein.

(14) For leading references on solution-phase calculations, see: (a) Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *J. Am. Chem. Soc.* **1995**, *117*, 4261. (b) Gao, J. *J. Am. Chem. Soc.* **1993**, *115*, 2930. (c) Duffy, E. M.; Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 7535.

(15) The authors cited in ref 2 found that in contrast to amides, TS2 is favored for simple carbamates in the gas phase at the MP2//3-21G* level. We believe 3-21G* is an inadequate basis set for this case, and correlation makes little difference in energy orderings. At all higher levels of theory, we found that TS1 is favored.

(16) We used the Spartan 5.0.3 program (Wavefunction, Inc.) and Gaussian 94 for molecular orbital calculations.

(17) Energies of the calculated states at 6-311G**//6-31G* are as follows: ground state (−360.9959379 H, ΔE_{rel} = 0.0 kcal/mol); TS1 (−360.9724752 H, ΔE_{rel} = 14.7 kcal/mol); TS2 (−360.9714638 H, ΔE_{rel} = 15.3 kcal/mol).

(18) Bandekar, J.; Okuzumi, Y. *THEOCHEM* **1993**, *281*, 113.

(19) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry;* VCH: New York, 1988; Chapter 2.

(20) Winstein, S.; Fainberg, A. H. *J. Am. Chem. Soc.* **1957**, *79*, 5937.