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Martin J. Deetz[a]; Marco Jonas[a]; Jeremiah P. Malerich[a]; Bradley D. Smith[a]
[a] Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN, USA

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Conformational Switches: Controlling the Carbamate C–N Rotamer Equilibrium

MARTIN J. DEETZ, MARCO JONAS, JEREMIAH P. MALERICH and BRADLEY D. SMITH*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46656, USA

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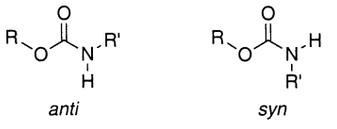
The *syn*/*anti* rotamer ratio for *tert*-butyl *N*-(2-thiazyl)-carbamate 3 was measured by solution-state NMR in the presence and absence of a donor–acceptor–donor hydrogen bonding template. The template is able to switch the conformation of carbamate 3 from >95% *anti* to >70% *syn* making it the most effective carbamate conformational switch yet reported. B3LYP calculations provide insight into the factors that produce this result.

Keywords: Rotamer; *Syn*/*anti* ratio; Carbamate; Hydrogen bonding

As part of an ongoing study of conformational switches [1,2], we are examining the use of hydrogen bonding templates to control amide [3] and carbamate C–N rotamer equilibria [4]. It is generally known that amides and carbamates can exist as *syn* or *anti* rotamers about the C–N bond (Fig. 1). Typically the fraction of *syn* rotamer is less than 1% in the case of secondary amides [5], and around 10% in the case of secondary alkyl carbamates [6]. Recently, we and others have shown how hydrogen bonding strategies can be used to stabilize *syn* carbamate rotamers [4,6]. For example, the addition of 60 mM of donor–acceptor–donor (DAD) template **1** increases the *syn*/*anti* ratio for *N*-(2-pyridyl)carbamate **2** (6 mM) from 0.05 to 0.96 in $CDCl_3$ at −20°C. Template **1** alters the *syn*/*anti* equilibrium by stabilizing the *syn* rotamer as shown in Fig. 2. We envision that eventual applications will require carbamate derivatives with increased sensitivity to conformational switching [3,4], thus, we are examining the switching ability of other carbamates. In this report, we evaluate the ability of template **1** to perturb the *syn*/*anti* ratio of *tert*-butyl *N*-(2-thiazyl)carbamate **3**. We find that **3** is the most sensitive carbamate switching system reported so far.



Mixtures of **3**† (10 mM) and template **1** at ratios of 1:0, 1:1, 1:5, and 1:10 in $CDCl_3$ were examined by NMR spectroscopy at −20°C, a temperature that is sufficiently low to allow direct observation of both sets of rotamer signals. The ^{1}H NMR signals for the two thiazole

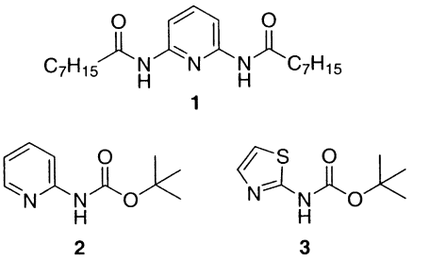


FIGURE 1 Carbamate rotamers.

*Corresponding author. Tel.: +219-631-8632. Fax: +219-631-6652. E-mail: smith.115@nd.edu

†Selected physical and spectroscopic data for carbamate **3**: mp 182–183°C; ^{1}H NMR (300 MHz, +22°C, 10 mM in $CDCl_3$) δ 7.39 (d, 1H, J = 3.5 Hz), 6.91 (d, 1H, J = 3.5 Hz), 1.58 (s, 9H) ppm; ^{13}C NMR (75 MHz, +22°C, 50 mM in $CDCl_3$) δ 162.0, 153.0, 136.7, 112.0, 81.8, 28.3 ppm; HRMS (FAB$^+$) Calcd for $[M + H]^+$ 201.0698, found 201.0716. Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04. Found: C, 48.06; H, 5.89.

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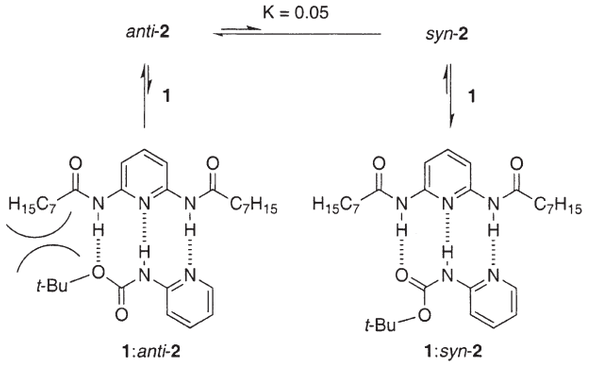

FIGURE 2 Association of **1** with the *syn* rotamer of **2** is favored over association with the *anti* rotamer leading to an increased *syn*/*anti* ratio.

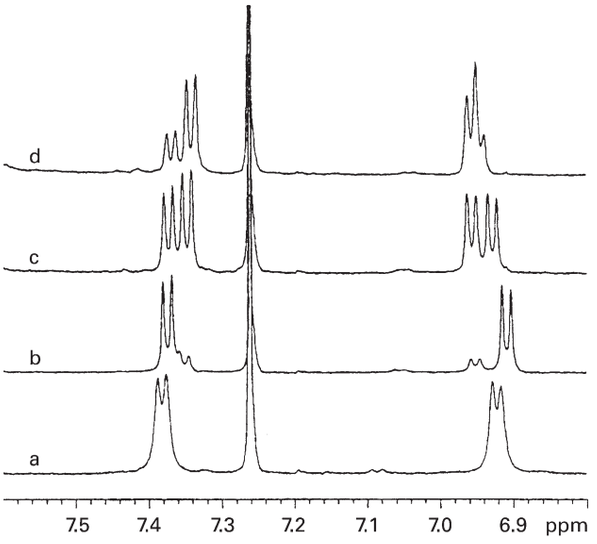

FIGURE 3 ^{1}H NMR signals for the two thiazyl CH residues in **3** (10 mM) in the presence of template **1** at **3**:**1** ratios of (a) 1:0, (b) 1:1, (c) 1:5, and (d) 1:10 at −20°C in $CDCl_3$. The signals for the *syn* rotamer are the upfield doublet in the set at 7.35 ppm and the downfield doublet in the set at 6.95 ppm. The single at 7.26 ppm corresponds to the residual $CHCl_3$.

CH residues are shown in Fig. 3‡. In the absence of template, the *syn*/*anti* ratio for **3** was < 0.05 (see spectrum *a* in Fig. 3). In the presence of template **1**, the carbamate *syn*/*anti* ratio increased significantly (see spectra *b*–*d* in Fig. 3). When the **3**:**1** ratio is 1:10, the *syn*/*anti* ratio is 2.38 which is more than twice the value observed for **2**:**1** under the same conditions. The *syn* and *anti* rotamers for **3** could be also observed by ^{13}C NMR and, as before [4], the peaks that were most diagnostic were the signals for the *tert*-butyl quaternary carbon at 81.9 ppm for the *anti* rotamer and 85.6 ppm for the *syn* rotamer¶.

The overall association constant for **1** and **3** in $CDCl_3$ at −20°C was determined by an NMR titration method [7]. The chemical shift for the equivalent NH signals in **1** (10 mM) was monitored as a function of increasing amounts of **3** and the resulting curve fitted to a 1:1 binding model (the homodimerization of **3** is sufficiently weak [8] that it can be ignored for this calculation) to give an association constant of $60\,M^{-1}$ ($\Delta\delta_{max} = 1.6$ ppm). This is significantly lower than the value of $400\,M^{-1}$ previously measured for the association between **1** and **2** [4]. Thus, while the template **1** overall binds less strongly to carbamate **3**, it is nonetheless more capable of switching *anti* to *syn* conformation. Qualitative experimental evidence that template **1** binds much more strongly to *syn*-**3** than *anti*-**3** is gained by inspecting the set of NMR signals at 6.95 ppm in Fig. 1. The chemical shift for the *syn* rotamer signal hardly changes with increasing amounts of template **1** indicating that the *syn* rotamer is essentially saturated with template **1**, whereas the signal for the *anti* rotamer moves considerably downfield with increasing amounts of template **1** indicating that it is well below saturation.

Further insight into the switching behavior was gained from hybrid DFT calculations for **3** in the presence and the absence of **1** [9]. All geometries were fully optimized and subjected to harmonic frequency analysis at the B3LYP/6-31 + G* level of theory. The computational data corroborates our experimental results that carbamate **3** can be switched to its *syn* form upon addition of the template **1**. Theoretically, the free energy difference of $+2.3\,kcal\,mol^{-1}$, for the transformation of uncomplexed *anti* to *syn*-**3**, is lowered to $-1.0\,kcal\,mol^{-1}$ in the presence of **1**. The computed structures of the two rotamers complexed to **1** (Fig. 4) give an indication why the affinity between **1** and **3** is relatively weak. The hydrogen bonds do not have optimum alignment in the *syn*-**3**:**1** complex because the planes of the two molecules are at an angle of 17.6° to each other. In the case of *anti*-**3**:**1**, steric repulsion leads to an increase of this angle to 39.4°, thus further destabilizing the complex. There appears to be no single structural reason why the thiazole carbamate **3** is switched to *syn* isomer more easily than pyridyl carbamate **2**. Computationally, the free energy for isomerization of uncomplexed *anti* to *syn*-**2** is essentially the same as for uncomplexed **3** but it is only lowered to $0.0\,kcal\,mol^{-1}$ by the presence of **1**. A comparison of the computed structures suggests that the *syn*-**2**:**1** complex has a slightly poorer hydrogen bonding alignment than the *syn*-**3**:**1** complex, whereas the *anti*-**2**:**1** complex has a slightly better alignment than the *anti*-**3**:**1** complex.

‡The carbamate NH signal was less helpful in this case because the *anti* NH was greatly broadened by exchange processes.
¶^{13}C chemical shifts for carbamate **3** (0.5 M) in the presence of **1** (0.5 M) in $CDCl_3$ at −20°C. *anti*-**3**: δ 161.9, 152.5, 136.4, 112.0, 81.9, 28.1 ppm. *syn*-**3**: δ 161.3, 152.5, 137.2, 113.2, 85.6, 28.1 ppm.

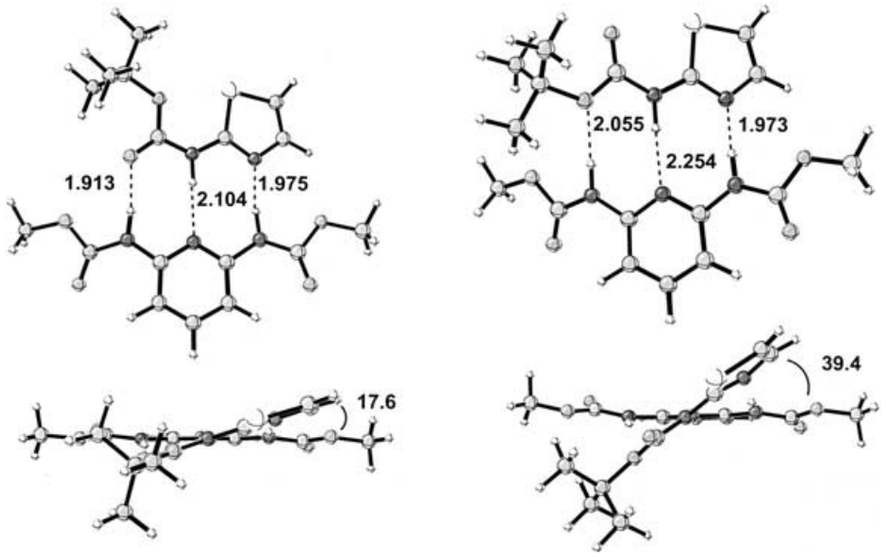

FIGURE 4 Two views of the B3LYP/6-31 + G* calculated structures of the complexes *syn*-**3**:**1** (left) and *anti*-**3**:**1** (right).

In summary, the template **1** is able to switch the conformation of carbamate **3** from >95% *anti* to >70% *syn* making it the most effective carbamate conformational switch yet reported. It is likely that the switching sensitivity can be further improved by using a DAD hydrogen bonding template with higher overall affinity for carbamate **3** [10]. A future goal is to incorporate carbamate derivatives of 2-aminothiazole into polymer backbones and use DAD templates to switch the polymer's shape and supramolecular function.

Acknowledgments

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