Unusually Low Barrier to Carbamate C−N Rotation

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Abstract: The barrier for rotation about an *N*-alkylcarbamate C(carbonyl)−N bond is around 16 kcal/mol. In the case of an *N*-phenylcarbamate, the rotational barrier is lowered to 12.5 kcal/mol, but with *N*-(2-pyrimidyl)carbamates the barriers are so low (<9 kcal/mol) that the syn and anti rotamers cannot be observed as separate signals by 500 MHz NMR spectroscopy at 183 K. X-ray and computational data show that the *N*-(2-pyrimidyl) carbamates have C(carbonyl)−N bonds that are on average 0.03 Å longer than for related *N*-phenylcarbamates. The computational results trace the origin of the effect to increased single bond character for the C(carbonyl)−N bond due to the increased electron-withdrawing ability of the pyrimidyl ring.

Hindered rotation about the amide C−N single bond is one of the most extensively studied phenomena in conformational stereochemistry.[1] Carbamates are also known to exist as syn and anti rotamers (Figure 1) although far fewer systems have been investigated.[2] From the experimental data, it appears that the typical isomerization barrier for carbamates (∼16 kcal/mol) is 1−4 kcal lower than that for structurally related amides. Typically, secondary carbamates and amides strongly prefer an anti conformation; however, hydrogen bonding templates can be used to alter the equilibrium.[3,4] For example, we recently reported that the presence of donor−acceptor−donor (DAD) template **1** increases the syn/anti ratio for *N*-(2-pyridyl)carbamate **2** and *N*-(2-thiazyl)carbamate **3** in $CDCl_3$ by selectively forming hydrogen-bonded complexes with the syn rotamer as shown in Figure 2.[4]

An exception to the normal conformational preference of secondary amides is a report by Beijer and co-workers, who showed that the amide group in a secondary 2-(acylamino)pyrimidine prefers a syn conformation.[5] This unusual result has prompted us to examine some analogous *N*-(2-pyrimidyl)carbamate derivatives. Specifically,

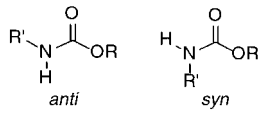


Figure 1. Secondary carbamate rotamers.

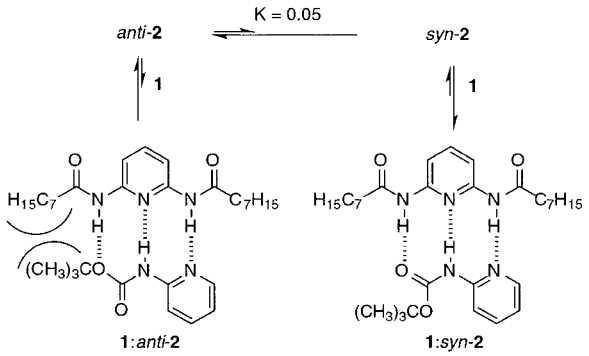
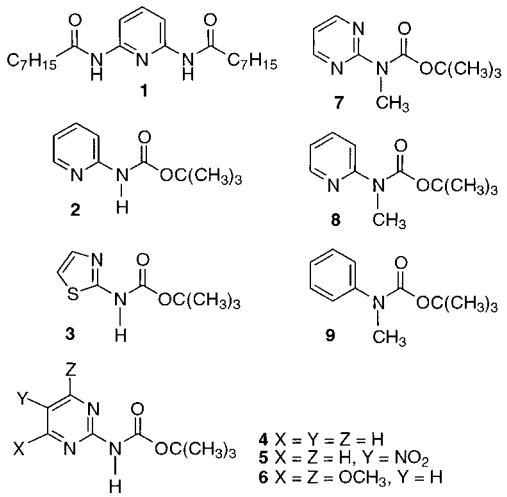


Figure 2. Association of **1** with the syn rotamer of **2** favored over association with the anti rotamer leading to an increased syn:anti ratio.

we have prepared and characterized the secondary carbamates **4**−**6** and the tertiary carbamates **7**−**9**. Unexpectedly, we find that we are unable to measure the syn/anti equilibrium for the pyrimidyl carbamates using low-temperature, high-field NMR spectroscopy because the C−N rotational barriers are very low. We provide structural data and computational analyses to help rationalize our results.



Secondary *N*-(2-Pyrimidyl)carbamates. Separate samples of *N*-(2-pyrimidyl)carbamates **4**−**6** in $CDCl_3$ solution were examined by NMR spectroscopy. Usually, the rate of conformational exchange for carbamate rotamers is sufficiently slow at low temperature that separate signals can be observed by ^{1}H NMR. However, in the cases of **4**−**6**, only one set of signals is observed upon cooling the samples to 213 K. Even the addition of 10 mol equiv of template **1** does not induce the appearance of a second set of signals, which is contrary to the previously studied cases of pyridyl analogue **2** and thiazyl **3**.[4]

In an effort to explain these unexpected results, we considered the following questions: (i) *Do these secondary*

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(1) (a) Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: Deerfield Beach, FL, 1985; Chapter 2. (b) Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517−551. (c) Scherer, G.; Kramer, M. L.; Schutkowski, M.; Reimer, U.; Fischer, G. *J. Am. Chem. Soc.* **1998**, *120*, 5568−5574.

(2) (a) Rablen, P. R. *J. Org. Chem.* **2000**, *65*, 7930−3937. (b) Lectka, T.; Cox, C. *J. Org. Chem.* **1998**, *63*, 2426−2427. (c) Kost, D.; Kornberg, N. *Tetrahedron Lett.* **1978**, *35*, 3275−3276.

(3) Marcovici-Mizrahi, D.; Gottlieb, H. E.; Marks, V.; Nudelman, A. *J. Org. Chem.* **1996**, *61*, 8402−8406. Deetz, M. J.; Fahey, J.; Smith, B. D. *J. Phys. Org Chem.* **2001**, *14*, 463−467.

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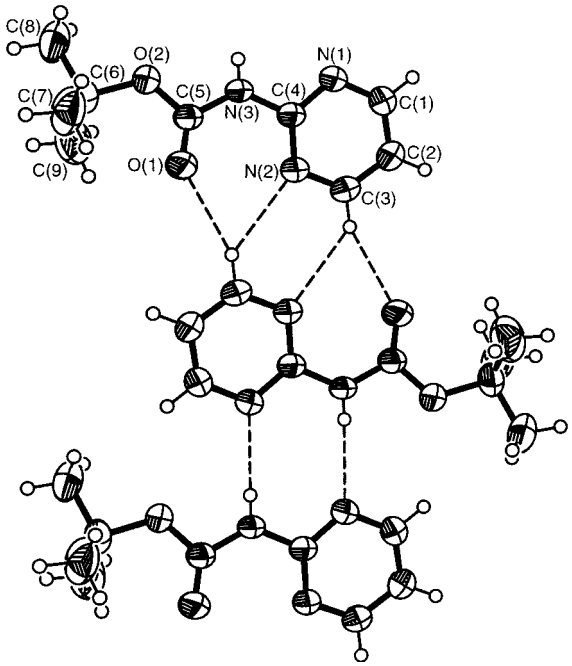

Figure 3. X-ray structure of carbamate **4** showing the atom-numbering scheme and important intermolecular interactions. Each hydrogen-bonded antiparallel dimer is connected via bifurcated CH−X interactions.

pyrimidyl carbamates exist in an unusual tautomeric form? No tautomeric forms were observed by ^{1}H NMR in agreement with the known preference for 2-(acylamino)pyridines to exist solely as their acylamino tautomers.[6] In addition, a low-temperature ^{1}H NMR study of carbamate **4** in the more polar solvent acetone-d_6 showed no additional peaks upon cooling to 183 K. (ii) *Do these pyrimidyl carbamates exist as predominantly one rotamer*? In the solid state, carbamate **4** adopts an anti conformation although the structure is somewhat distorted.[7] It packs as an array of hydrogen bonded antiparallel dimers (Figure 3), but it does not strongly dimerize in solution (K_{dimer} = 8 M^{-1} in $CDCl_3$ at 20 °C).[8] The inability to obtain dynamic NMR data makes it difficult to unambiguously measure the isomerization equilibrium in solution.[9,10] However, theoretical insight was gained by performing a series of hybrid DFT calculations.[11] The syn and anti isomers of **4** were found to be very close in energy. The calculated energy and free energy differences are 0.4 and −0.1 kcal/mol, within the error limits that can reasonably be expected for the calculation of rotamers at this level of theory. (iii) *Can the rotational barrier for* **4** *be so low as to not produce separate rotamer signals in the NMR?* The calculated transition structure for the syn/anti interconversion in **4** is only 8.4 kcal/mol higher in energy than *anti*-**4**. This suggests that the barrier to rotation is unusually low and that the presence of template does not increase it significantly. Experimentally, template **1** has a surprisingly weak affinity for carbamate **4** ($K_{1:4}$ = 8 M^{-1} in $CDCl_3$ at −20 °C, which is significantly lower than the value of 400 M^{-1} previously measured for the association between **1** and **2**[3,12]). Although a thermochemical analysis of the binding energies by computation is not useful because the expected binding energy is smaller than the expected basis set superposition error, the computed structures of the hydrogen-bonded complexes (Figure 4) can be used to rationalize this weak affinity. The computed structures show that the intermolecular hydrogen bonds do not have an optimal alignment. In the case of the **1**·*syn*-**4** complex, the planes of the molecules have a 27.1° angle to each other, whereas for **1**·*anti*-**4**, steric repulsion leads to an increase of this angle to 43.7°.

Experimental evidence that the carbamate C(carbonyl)−N bond in **4** (see Figure 5 for bond-labeling scheme) is unusually long comes from its X-ray crystal structure (Figure 3). Unlike the literature structure of ethyl *N*-phenylcarbamate, where the C(aryl)−N bond (1.405(6) Å) is significantly longer than the C(carbonyl)−N bond (1.352(8) Å),[13] the C(aryl)−N bond (1.381-(4) Å) in **4** is essentially the same length as the C(carbonyl)−N bond (1.377(4) Å). This is also the case for another *N*-(2-pyrimidinyl)carbamate described in the literature.[14]

Tertiary *N*-Aryl-*N*-methylcarbamates. To further test this hypothesis of an unusually low C−N rotational barrier, we prepared and analyzed the tertiary *N*-aryl-*N*-methylcarbamates **7**−**9**. We observed that cooling

(6) Katritzky, A. R.; Ghiviriga, I. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1651−1653.

(7) To minimize electrostatic repulsion between the carbonyl oxygen, O(1), and the ring nitrogen, N(2), the molecule adopts some unusual bond and torsional angles (see Figure 3 for atom numbering). In particular, the bond angle C(5)−N(3)−C(4) is increased to 127.7°. The torsional angles O(1)−C(5)−N(3)−C(4) = 15.16° and C(5)−N(3)−C(4)−N(2) = 10.25° demonstrate how the carbamate group is skewed from planarity.

(8) Association constants were determined using the NMR titration and dilution methods described in the following: Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072−7080.

(9) Even ^{13}C NMR does not give a clear picture. Probably the most diagnostic signal is the chemical shift for the *tert*-butyl quaternary carbon, which in the case of **2** in the presence of 1 mol equiv of template **1** at 253 K is 81.2 ppm for the anti rotamer and 84.0 ppm for the syn rotamer.[4] In the case of **4** under the same conditions, the quaternary *tert*-butyl carbon signal occurs at 81.9 ppm. This could be interpreted as a rapidly equilibrating mixture that is 75% anti rotamer but the uncertainty is high. We also considered if adventitious water in the NMR solvent selectively stabilizes *anti*-**4** by forming a chelated complex. Experimentally, we find that the presence or absence of water in the $CDCl_3$ has no apparent effect on the low-temperature ^{1}H NMR spectrum of **4**. In addition, calculation of some bridged structures did not yield a stable doubly hydrogen bonded species.

(10) We acquired IR spectra of dilute samples of **2**, **4**, and *tert*-butyl *N*-(phenyl)carbamate, **10**, in CH_2Cl_2, and in each case a single NH stretching vibration was observed. Specifically, the NH stretching frequencies for **2**, **4**, and **10** (5 mM in CH_2Cl_2) are 3417, 3422, and 3431 cm^{-1}, respectively. It is known experimentally that the NH stretching vibration for an anti amide is about 40 wavenumbers higher than the syn form,[5] and we have confirmed this large difference with DFT calculations. However, in the case of the syn and anti isomers of secondary carbamates, our calculations indicate that the difference in NH stretching frequencies is so small (∼5 wavenumbers) that the experimentally observed values cannot be unambiguously assigned to a specific structure. Other major IR absorbances not obscured by the solvent are the following: **2**, 1731, 1578, 1514, 1153 cm^{-1}; **4**, 1754, 1576, 1504, 1147 cm^{-1}; **10**, 1728, 1605, 1595, 1522, 1161 cm^{-1}. The carbonyl stretching frequency order of **4** (1754 cm^{-1}) > **2** (1731 cm^{-1}) > **10** (1728 cm^{-1}) agrees with the resonance effect described in Figure 7.

(11) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

(12) Typically, the association constants for hydrogen-bonded ADA·DAD complexes are around 10^2 M^{-1}: Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382−2426.

(13) Ganis, P.; Avitabile, G.; Migdal, S.; Goodman, M. *J. Am. Chem. Soc.* **1971**, *93*, 3328−3331.

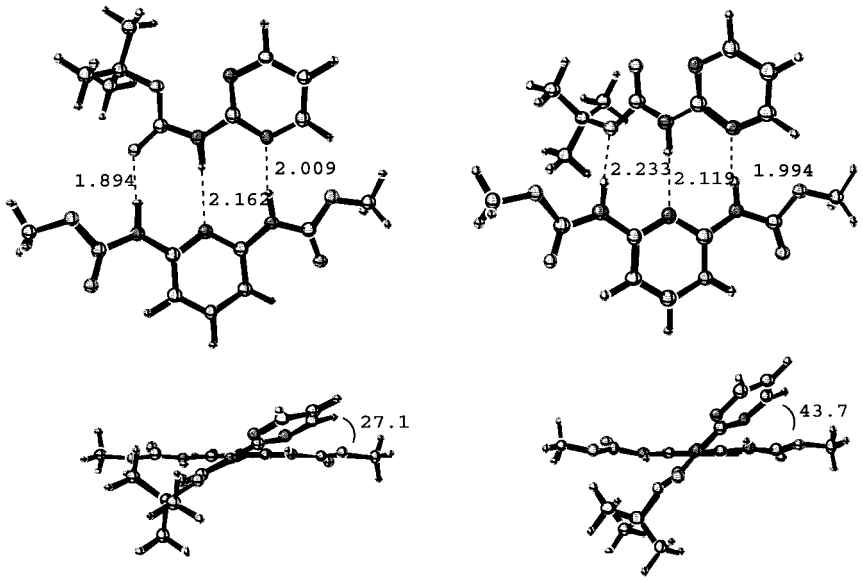

Figure 4. Top and side views of the B3LYP/6-31+G*-calculated structures of the *syn*-**4**·**1** (left) and *anti*-**4**·**1** (right) complexes.

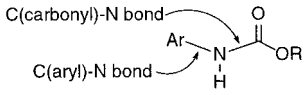

Figure 5.

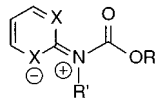

Figure 6.

Table 1. Experimental and Calculated C(carbonyl)−N Rotational Barriers (kcal/mol)

carbamate	$\Delta G^{\ddagger}_{exp}$	$\Delta G^{\ddagger}_{comp}$
7	<9	5.7[c]
8	10.2[a]	10.2[c]
9	12.3[b]	13.4[c]

[a] 203 K. [b] 250 K. [c] 298 K.

samples of pyridyl carbamate **8** and phenyl analogue **9** resulted in splitting of the spectra into two sets of signals (ratio of 29:71 for **8** at 183 K and 41:59 for **9** at 218 K);[15] however, the 500 MHz ^{1}H NMR spectra of the pyrimidyl analogue **7** remained sharp even at 183 K in THF-d_8. Coalescence of the *tert*-butyl signals occurred at 203 K for **8** in THF-d_8 and at 250 K for **9** in $CDCl_3$. These values correspond to $\Delta G^{\ddagger}$ of 10.2 and 12.3 kcal/mol, respectively. In the case of **7** we estimate from the experimental data that the rotational barrier is <9 kcal/mol (see Experimental Section).

We also studied the rotational energetics for **7**−**9** using computational methods. In each case, the syn and anti rotamers were found to be essentially identical in energy. As shown in Table 1, the calculated free energy barriers for rotation around the respective C(carbonyl)−N bonds are very close to the experimentally observed values. Inspection of the calculated rotamer structures provides further insight into the geometric and electronic origin of these very low barriers. As already seen in the X-ray structure of **4**, the calculated C(aryl)−N and C(carbonyl)−N bond lengths in **7** are almost identical (Table 2). However, in case of the *N*-phenyl analogue **9**, the C(aryl)−N and C(carbonyl)−N bond lengths differ by 0.05 Å. This trend is also seen in the partial charges on the carbonyl oxygen, also listed in Table 2. The effect is explained in part by the resonance contributor shown in Figure 6. The *N*-aryl ring withdraws π-electron density which shortens the carbamate C(aryl)−N bond and thus there is less π-electron density available for resonance delocalization with the carbamate carbonyl.[10] Electron-withdrawing ability is enhanced in the case of pyrimidyl analogues **4** and **7** because of the presence of the aryl ring nitrogens. This barrier-lowering effect also occurs with *N*-aryl amide systems, although in this case it is experimentally harder to characterize because *N*-aryl amide rotational equilibria are usually strongly biased toward one isomer.[5,16]

Table 2. Calculated Bond Lengths (Å) and Partial Charges on the Carbonyl Oxygen for *syn*- and *anti*-Carbamate Rotamers

carbamate rotamer	C(aryl)−N	C(carbonyl)−N	charge (carbonyl oxygen)
syn-**7**	1.401	1.402	−0.582
anti-**7**	1.407	1.399	−0.576
syn-**8**	1.421	1.388	−0.595
anti-**8**	1.422	1.388	−0.595
syn-**9**	1.433	1.380	−0.624
anti-**9**	1.430	1.384	−0.611

The barrier for rotation about an *N*-alkylcarbamate C(carbonyl)−N bond is usually around 16 kcal/mol.[2] In the case of an *N*-phenylcarbamate, such as **9**, the rotational barrier is lowered to 12.5 kcal/mol, but in the case of *N*-(2-pyrimidyl)carbamates, such as **4** and **7**, the barrier is around 5−8 kcal/mol. This effect is attributed primarily to increased contribution by the resonance

(14) Muller, J.-C.; Ramuz, H.; Daly, J.; Schonholzer, P. *Helv. Chim. Acta* **1982**, 1454−1466.

(15) Attempts to assign the resolved low-temperature signals to syn or anti rotamers by NOE were unsuccessful. For example, irradiation of the *N*-methyl signals produced no enhancement of either of the *tert*-butyl signals.

(16) For conformational studies of *N*-methyl-*N*-phenyl amide derivatives, which are known to rotate the amide C−N=O plane out of conjugation with the phenyl ring, see: Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron* **1995**, *51*, 5277−5290. Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. *J. Org. Chem.* **1995**, *60*, 4715−4720. Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649−10650.

structure shown in Figure 6. To put these values into perspective, the barriers for rotation around the C2−C3 single bond in 1,3-butadiene and the C1−C2 single bond in acrolein are about 4 and 6 kcal/mol, respectively.[17]

Experimental Section

***tert*-Butyl *N*-(2-Pyrimidyl)carbamate (4).** 2-Aminopyrimidine (0.49 g, 5.0 mmol) was dissolved in *tert*-butyl alcohol (10 mL) containing di-*tert*-butyl carbonate (1.20 g, 5.5 mmol). The reaction was stirred at room temperature for 48 h under an atmosphere of argon. The solvent was removed in vacuo and the residue dissolved in ethyl acetate. The organic layer washed three times with brine and dried with $MgSO_4$, and the solvent was removed leaving a white solid (0.50 g, 51% yield): mp 147−148 °C; ^{1}H NMR (500 MHz, 295 K, 10 mM in $CDCl_3$) δ 8.59 (d, 2H, J = 4.5 Hz), 7.77 (bs, 1H), 6.96 (t, 1H, J = 4.5 Hz), 1.55 (s, 9H) ppm. ^{13}C NMR (125.7 MHz, 295 K, $CDCl_3$) δ 158.4, 158.0, 115.4, 81.5, 28.1 ppm. HRMS (FAB$^+$) calcd for $[M + H]^+$ 196.1086, found 196.1079. Anal. Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71. Found: C, 55.19; H, 6.52.

***tert*-Butyl *N*-(5-Nitro-2-pyrimidyl)carbamate (5).** 2-Amino-5-nitropyrimidine (0.075 g, 0.52 mmol) was dissolved in *tert*-BuOH (3 mL). Di-*tert*-butyl dicarbonate (0.133 g, 0.57 mmol) was added along with 4-(dimethylamino)pyridine (~2 mg, catalytic). The mixture was heated to reflux for 15 h under an atmosphere of argon. The solvent was removed and the residue dissolved in EtOAc and washed twice with water. The combined organic layers were dried over $MgSO_4$. The material was chromatographed on silica (19:1 CH_2Cl_2/MeOH, R_f = 0.2), leaving a white solid (2.2 mg, 2% yield): ^{1}H NMR (300 MHz, 295 K, $CDCl_3$) δ 9.19 (s, 2H), 8.00 (bs, 1H), 1.62 (s, 9H); ^{13}C NMR (75 MHz, 295 K, $CDCl_3$) δ 160.1, 154.9, 149.2, 137.9, 83.4, 28.1; MS (FAB$^+$) *m/e* 241 $[M + H]^+$.

***tert*-Butyl *N*-(4,6-Dimethoxy-2-pyrimidyl)carbamate (6).** 2-Amino-4,6-dimethoxypyrimidine (0.50 g, 3.2 mmol) was dissolved in *tert*-BuOH (10 mL). Di-*tert*-butyl dicarbonate (0.80 g, 3.5 mmol) was added, and the mixture was heated to reflux for 15 h under an atmosphere of argon. The solvent was removed and the residue dissolved in EtOAc and washed three times with water. The combined organic layers were dried over $MgSO_4$. The solvent was removed under vacuum leaving a white solid (0.3 g, 35% yield): ^{1}H NMR (300 MHz, 295 K, $CDCl_3$) δ 5.32 (s, 1H), 5.15 (bs, 1H), 3.70 (s, 6H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, 295 K, $CDCl_3$) δ 172.1, 162.2, 146.4, 84.7, 79.1, 53.2, 27.0; MS (FAB$^+$) *m/e* 256 $[M + H]^+$.

General Synthesis Procedure for Tertiary *N*-Methylcarbamates. The appropriate secondary carbamate[4] in DMF (~50 mg/mL) was treated with 1.5 mol equiv of NaH (60% dispersion in mineral oil) and 5 mol equiv of methyl iodide. The reaction was stirred for 30 min, quenched with water, and extracted with CH_2Cl_2. The organic phase was dried and then evaporated. The residue was purified by chromatography (silica gel) using 80:20 CH_2Cl_2/hexanes as the eluent.

***tert*-Butyl *N*-methyl-N-(2-pyrimidyl)carbamate (7):** 40% yield; ^{1}H NMR (500 MHz, 295 K, $CDCl_3$) δ 1.56 (s, 9H) 3.46 (s, 3H) 7.08 (t, J = 4.5 Hz, 1H) 8.71 (d, J = 4.5 Hz); ^{13}C NMR (125.7 MHz, 295 K, $CDCl_3$) δ 28.2, 35.2, 81.8, 116.4, 153.6, 157.9, 160.9; MS (FAB$^+$) *m/e* 210 $[M + H]^+$.

***tert*-Butyl *N*-methyl-*N*-(2-pyridyl)carbamate (8):** 40% yield; ^{1}H NMR (500 MHz, 295 K, THF-d_6) δ 1.51 (s, 9H) 3.37 (s, 3H) 6.95 (dd, J = 7.5, 4.5 Hz, 1H) 7.60 (td, J = 8.0, 2.0 Hz,) 7.80 (d, J = 8.5 Hz, 1H, py) 8.29 (dd, J = 4.8, 1.8 Hz, 1H); ^{13}C NMR (125.7 MHz, 295 K, $CDCl_3$) δ 28.4, 34.5, 81.3, 119.4, 119.6, 137.1, 147.5, 154.6, 155.2; MS (FAB$^+$) 209 $[M + H]^+$.

***tert*-Butyl *N*-methyl-*N*-(phenyl)carbamate (9):** 90% yield; ^{1}H NMR (500 MHz, 295 K, $CDCl_3$) δ 1.45 (s, 9H) 3.25 (s, 3H) 7.2 (m, 5H); ^{13}C NMR (125.7 MHz, 295 K, $CDCl_3$) δ 28.4, 37.5, 80.4, 125.5, 125.6, 128.7, 143.9, 154.9; MS (FAB$^+$) 208 $[M + H]^+$.

X-ray Crystallography. Single crystals of **4** were obtained by recrystallization from dichloromethane/hexanes. Crystallographic summary:[18] monoclinic, *C*2/*c*; Z = 8 in a cell of dimensions a = 19.109(3) Å, b = 8.888(2) Å, c = 13.961(3) Å, β = 112.572(13)°, V = 2189.5(8) Å^3; ρ_{calc} = 1.184 Mg M^{-3}; F(000) = 832. The structure was refined on F^2 to a R_w = 0.1168, with a conventional R = 0.0423 (1469 reflections with $I > 2\sigma(I)$) and a goodness of fit = 1.016 for 180 refined parameters.

Computational Studies. All computations were performed using the GAUSSIAN98 series of programs.[11] All geometries were fully optimized and subjected to harmonic frequency analysis at the B3LYP/6-31+G* level of theory. Bond distances are given in Å, and energies are zero-point corrected and are given in kcal/mol. Gibbs free energies were calculated from the harmonic frequency analysis from 298 K and 1 atm. Partial charges were calculated using the ChelpG model.

Dynamic NMR Studies. Variable-temperature NMR spectra were acquired using a 500 MHz instrument. Probe temperatures (±0.5 K) were measured with a calibrated, digital thermocouple. The rotational barriers at coalescence were determined by treating the dynamic ^{1}H NMR spectra as an exchange between two unequally populated sites.[19] Values for Δp (the rotamer population difference) and $\Delta\nu$ (the limiting chemical shift difference) were obtained from spectra acquired at temperatures well below coalescence. Coalescence temperatures (T_c) were determined for the *tert*-butyl signals for **8** and **9**. For compound **8** in THF-d_8, T_c = 203 K, Δp = 0.42, and $\Delta\nu$ = 30 Hz, which leads to k_c = 43 s^{-1} and $\Delta G^‡$ of 10.2 kcal/mol. For compound **9** in $CDCl_3$, T_c = 250 K, Δp = 0.18, and $\Delta\nu$ = 53 Hz, which leads to k_c = 90 s^{-1} and $\Delta G^‡$ of 12.3 kcal/mol. Coalescence could not be observed for compound **7** in THF-d_8, at 183 K. This means that k_c > 80 s^{-1} at 183 K or $\Delta G^‡$ < 9 kcal/mol.

NMR Titrations.[8] The chemical shift for the NH signal in **4** (10 mM) was monitored as a function of increasing amounts of **1** and the resulting curve fitted to a 1:1 binding model. The homodimerization of **4** was determined by the dilution method.[8]

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Supporting Information Available: X-ray data in CIF format and the coordinates, energies, zero point energies, and Gibbs free energies of all calculated structures that are discussed. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The X-ray data have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. Fax: (+44)1223-336-033. E-mail: deposit@ccdc.cam.ac.uk.

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