Using Hydrogen Bonding to Control Carbamate C−N Rotamer Equilibria

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Received April 7, 1998

In chloroform solution, the *syn*/*anti* rotamer ratios for *N*-(2-pyridyl)carbamates, **3**, and *N*-phenylcarbamates, **4**, are close to 0.05. Addition of the double hydrogen bonding acetic acid moderately stabilizes the *syn* rotamer of **4**, but has no measurable effect on the *syn*/*anti* ratio for **3**. Conversely, the hydrogen bond donor−acceptor-donor triad in 2,6-bis(octylamido)pyridine, **1**, strongly stabilizes the *syn* rotamer of **3**, but has no effect on the *syn*/*anti* ratio for **4**. The K_a for *syn*-**3**:**1** is 10^3−10^4 times higher than the K_a for *anti*-**3**:**1**. This implies that the alkoxy oxygen in *anti*-**3** is a much poorer hydrogen bond acceptor than the carbonyl oxygen in *syn*-**3**, most likely because of a combination of steric and electrostatic factors.

Introduction

Rotational changes about individual bonds in a protein backbone can sometimes induce large changes in protein tertiary structure and consequently protein function.[1] In general, the secondary amide linkages in proteins have a strong preference for the *anti* C−N rotamer. A recent survey of 399 protein structures found only 0.03% of the peptide bonds had adopted a *syn* C−N conformation.[2] With tertiary amides, the *syn*/*anti* rotamer equilibrium constant is closer to unity, and proline derivatives in particular readily undergo amide bond rotation at physiological temperatures.[3] In fact, peptidyl-prolyl isomerases (rotamases) are enzymes that specifically catalyze proline amide rotation.[4,5]

The carbamate group also exists as *syn* and *anti* rotamers, with the *anti* rotamer favored by 1.0−1.5 kcal/mol for steric and electrostatic reasons (Figure 1).[6] As with tertiary amides, the more-balanced rotamer equilibria and low activation energies mean that carbamates can act as conformational switches in molecular devices. A relevant example is the recent ion channel work of Woolley and co-workers.[7] They used a carbamate linker to connect different ammonium groups to the entrance of the channel-forming peptide, gramicidin. Cation flux through the channel was found to be controlled by the thermal *syn*/*anti* isomerization of the carbamate linker. The ion channel model proposed by Woolley suggests that a compound with the ability to change the carbamate *syn*/*anti* ratio may be a chemical regulator of ion channel flux.

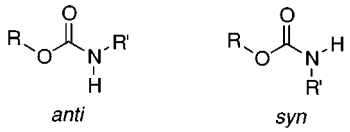


Figure 1. Carbamate rotamers.

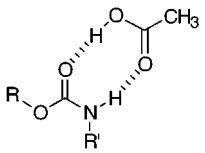
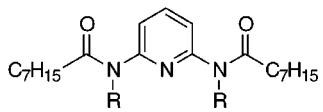


Figure 2. Stabilization of *syn*-carbamate by hydrogen bonding with acetic acid.

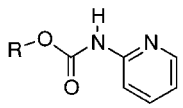
But what sort of molecule could be used to alter the carbamate C−N rotamer equilibrium?

In 1996, Nudelman and co-workers reported that the *syn* rotamer of a carbamate group can be stabilized by hydrogen bonding with a carboxylic acid (Figure 2).[6] In particular, they showed that the *syn*/*anti* rotamer ratios for *N*-alkyl carbamates (*i.e.*, R′ = alkyl in Figure 1) in $CDCl_3$ solution could be increased from their normal values of around 0.1 to 0.5 by the addition of large amounts of acetic acid. We were intrigued by this discovery, as it coincides with our interest in conformational switches.[8] Consequently, we set out to design a more effective hydrogen bonding system that selectively perturbs the *syn*/*anti* rotamer equilibrium of a target carbamate group.

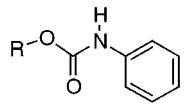
We chose to evaluate the abilities of acetic acid and 2,6-bis(octylamido)pyridine, **1**, to perturb the *syn*/*anti*



1 R = H
2 R = CH_3



3 **a** R = *tert*-butyl
b R = cholesteryl



4 **a** R = *tert*-butyl
b R = cholesteryl

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S0022-3263(98)00644-6 CCC: $15.00
Published on Web 09/29/1998

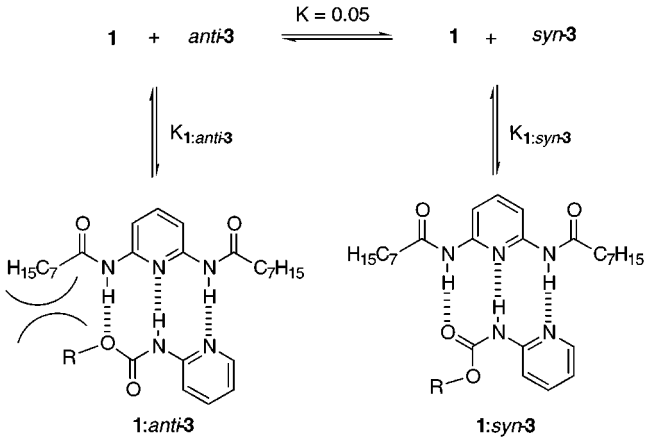

Figure 3. Association of **1** with the *syn* rotamer of **3** is favored over association with the *anti* rotamer.

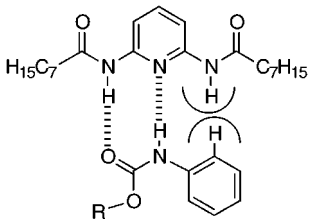

Figure 4. Disfavored association of **1** with the *syn* rotamer of **4**.

ratio of carbamates **3** and **4**. We hypothesized that the *syn* rotamer of an *N*-(2-pyridyl)carbamate, **3**, with its acceptor−donor-acceptor (ADA) triad, would be preferentially stabilized by forming three hydrogen bonds with the DAD array in **1** (Figure 3). Moreover, triad **1** should stabilize the *syn* rotamer of **3** much better than the *syn* rotamer of *tert*-butyl *N*-phenylcarbamate, **4** (Figure 4).

Results

Compounds **1**−**4** were prepared in straightforward fashion using standard procedures.[9] The carbamate *syn*/*anti* rotamer ratios were determined by ^{1}H and ^{13}C NMR spectroscopy. In general, the most diagnostic peak was the carbamate NH signal.[6] In a preliminary study, solutions of *tert*-butyl carbamates **3a** and **4a** in $CDCl_3$ were titrated with **1** and acetic acid at 25 °C. In all cases, *syn* NH peaks were not observed so the titrations were repeated at lower temperatures. In the absence of acetic acid, the *syn* rotamers of **3a** and **4a** were not observed until the temperature was lowered to −20 °C. The *anti* to *syn* equilibrium constants, $K_{s/a}$, at this temperature were both 0.05.[10] In the case of phenyl carbamate **4a**, the signals corresponding to the *syn* rotamer increased in intensity upon addition of acetic acid at low temperature. The ^{1}H spectrum of a mixture of **4a** (6 mM) and acetic acid (120 mM) in $CDCl_3$ at −20 °C showed the *anti* NH at δ 6.58 ppm and the *syn* NH at δ 8.43 ppm, with a *syn*/*anti* rotamer ratio of 0.12. Addition of much larger amounts of acetic acid increased the *syn*/*anti* ratio to 0.4. The ^{1}H spectrum of 2-pyridyl carbamate **3a** (6 mM) and acetic acid (120 mM) in $CDCl_3$ at −20 °C showed only one set of peaks corresponding to the *anti* rotamer, but the *anti* NH signal had moved substantially from its chemical shift of δ 8.63 ppm in the absence of acetic acid to δ 10.00 ppm.

A low temperature ^{1}H NMR study of a mixture of **4a** (10 mM) and bis(amido)pyridine **1** (100 mM) showed no evidence for the presence of *syn* rotamer. The *anti* NH signal moved from δ 6.5 to 6.7 ppm upon cooling but no peak was observed for the *syn* NH. On the other hand, **1** was found to significantly stabilize the *syn* rotamer of **3a**. A sample of **3a** (6 mM) and **1** (60 mM) in $CDCl_3$ was examined by ^{1}H NMR at −10, −20, −30, and −40 °C. In addition, mixtures of **3a**/**1** at ratios of 1:1, 1:5, 1:10, and 1:20 were examined at −20 °C. The chemical shifts of both the *anti* and *syn* NH signals for **3a** are listed in Tables 1 and 2, along with the apparent *anti* to *syn* equilibrium constants, $K_{s/a}$. The chemical shift data from Table 2 is also presented as a graph in Figure 5. The *anti* NH signal chemical shift is more sensitive to changes in temperature and relative amount of **1** than is the *syn* NH signal. $K_{s/a}$ for a sample containing [**3a**] = 6 mM

Table 1. Temperature Dependence of NH Chemical Shifts and $K_{s/a}$ for 3a in the Presence of 1[a]

T, °C	δ *anti* NH, ppm	δ *syn* NH, ppm	$K_{s/a}$
−10	8.64	10.51	0.82
−20	8.96	10.58	0.96
−30	9.32	10.64	1.38
−40	9.68	10.70	1.78

[a] [**3a**] = 6.0 mM and [**1**] = 60 mM in $CDCl_3$; $K_{s/a}$ is the *anti* to *syn* equilibrium constant.

Table 2. NH Chemical Shifts and $K_{s/a}$ for Different Ratios of 3a:1[a]

3a:**1**	δ *anti* NH, ppm	δ *syn* NH, ppm	$K_{s/a}$	ΔG, kcal/mol
1:0	8.64	8.64[b]	0.05	+1.52
1:1	8.71	10.36	0.18	+0.87
1:5	8.83	10.56	0.59	+0.27
1:10	8.96	10.58	0.96	+0.02
1:20	9.26	10.60	1.50	−0.21

[a] In $CDCl_3$ at −20 °C; [**3a**] ranged from 9.80 mM to 7.14 mM over the course of the titration; $K_{s/a}$ is the *anti* to *syn* equilibrium constant. [b] See ref 10.

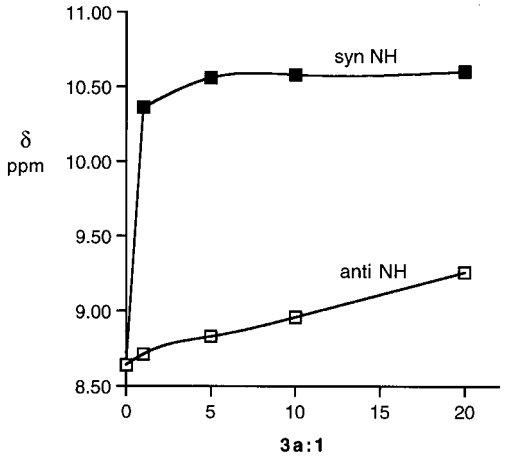

Figure 5. NH chemical shifts as a function of **3a**:**1**, in $CDCl_3$ at −20 °C.

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(10) The values of $K_{s/a}$ = 0.05 for **3a** and **4a** at −20 °C were determined by integrating the *tert*-butyl resonances for the *anti* rotamer at 1.49 ppm and the *syn* rotamer at 1.55 ppm. The *syn* NH signal was too weak to be observed; however, Nudelman and coworkers found that in the absence of hydrogen bonding the *syn* NH and *anti* NH chemical shifts differ by less than 0.1 ppm.[6] Therefore, a reasonable estimate of the *syn* NH chemical shift for **3a** in the absence of **1** is 8.64 ppm at −20 °C in $CDCl_3$.

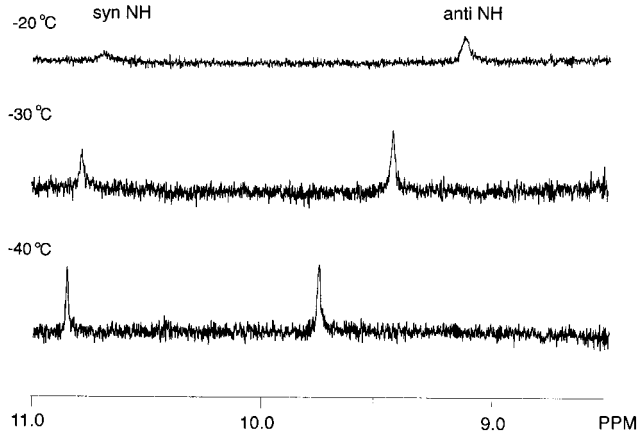

Figure 6. Downfield ^{1}H NMR spectra of **3b**:**1** (1:10) in $CDCl_3$ at −20, −30, and −40 °C.

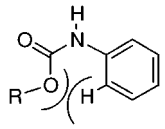

Figure 7. Steric destabilization of the *syn* rotamer of **4**.

and [**1**] = 60 mM increases with decreasing temperature and is unity at around −22 °C. A plot of $-RT\ln K_{s/a}$ versus $1/T$ for this system provides values of $\Delta H° = -3.2$ kcal/mol and $\Delta S° = -12.8$ cal/mol K. The ^{13}C NMR spectrum of a mixture of **3a** (100 mM) and **1** (1.0 M) in $CDCl_3$ at −20 °C shows two sets of signals for **3a**. The best resolved pair correspond to the quaternary carbon of the *tert*-butoxy group at δ 81.2 (anti) and 84.0 (syn) ppm.

^{1}H and ^{13}C NMR spectra of mixtures of **3a** and *N*-methylated control **2**, at a ratio of 1:10 in $CDCl_3$ at −20 °C exhibit only one set of signals for **3a**. The chemical shifts closely match those for **3a** on its own (the peak for the quaternary carbon of the *tert*-butoxy group is at δ 81.0 ppm). In other words, **2** does not stabilize the *syn* rotamer of **3a**.

The rotamer equilibria for cholesteryl derivatives **3b** and **4b** are very similar to the *tert*-butyl analogues described above. The ^{1}H NMR spectrum of a mixture of phenyl carbamate **4b** (10 mM) and **1** (100 mM) at −20 °C shows no evidence for the *syn* rotamer, whereas spectra of a mixture of 2-pyridyl carbamate **3b** (10 mM) and bis(amido)pyridine **1** (100 mM) at −20, −30, and −40 °C closely match those for the **3a**/**1** system. The *anti* NH signal moves significantly downfield, and $K_{s/a}$ increases as the temperature is decreased from −20 to −40 °C (Figure 6).

Discussion

At low temperatures, the *syn*/*anti* rotamer ratio, $K_{s/a}$, for *N*-alkyl carbamates (*i.e.*, R′ = alkyl in Figure 1) in $CDCl_3$ solution is ∼0.1.[6] For the N-aromatic carbamates **3** and **4**, $K_{s/a} \sim 0.05$, indicating that their *syn* rotamers are particularly unfavored. A likely explanation is the steric hindrance shown in Figure 7. Addition of acetic acid to a solution of phenyl carbamate **4a** in $CDCl_3$ at −20 °C stabilizes the *syn* rotamer of **4a** and raises the *syn*/*anti* rotamer ratio from 0.05 to 0.4. This observation is consistent with the work of Nudelman and co-workers[6] and is attributed to the acetic acid stabilizing the *syn* rotamer by hydrogen bonding (Figure 2). Acetic acid has no observable effect on the *syn*/*anti* rotamer ratio for 2-pyridyl carbamate **3a**. In this case, the carboxylic acid prefers to donate a hydrogen bond to the more basic pyridyl nitrogen and form the complex shown in Figure 8. The association constant for this complex must be reasonably high because the carbamate NH signal moves substantially from its chemical shift of δ 8.63 ppm in the absence of acetic acid to δ 10.00 ppm.

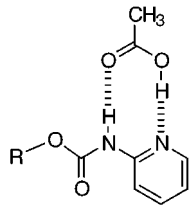

Figure 8. Association of acetic acid with the *anti* rotamer of **3**.

In $CDCl_3$ solution the triad **1** strongly stabilizes the *syn* rotamer of **3a** and raises the *syn*/*anti* rotamer ratio from 0.05 to 1.5 (Table 2). The failure of the *N*-methylated control **2** to affect the *syn*/*anti* ratio is strong evidence that the stabilization provided by **1** is due to its hydrogen bonding properties. This stabilization increases as the temperature is lowered (Table 1). A van't Hoff plot of the temperature dependence of the apparent *anti* to *syn* equilibrium constant, $K_{s/a}$, for **3a** in the presence of **1** provides $\Delta H° = -3.2$ kcal/mol and $\Delta S° = -12.8$ cal/mol K. Assuming $\Delta H° = +1.5$ kcal/mol for the *anti* to *syn* isomerization in the absence of **1** means that under these conditions the *syn*-**3a**:**1** complex is 4.7 kcal/mol (3.2 + 1.5) more stable than the anti-**3a**:**1** complex.

This difference in stabilities is confirmed by the different sensitivities of the *anti* and *syn* NH chemical shifts to temperature and concentration changes. The chemical shift of the *syn* NH signal for **3a** (or **3b**) (6 mM) in the presence of **1** (60 mM) hardly moves as the temperature is lowered (Table 1 and Figure 6), indicating that *syn*-**3** is saturated with **1** at these concentrations. This is confirmed by the titration curve shown in Figure 5 which shows that less than 5 mol equiv of **1** is needed to saturate *syn*-**3a**. The *anti* NH chemical shift, however, moves significantly downfield as the temperature is decreased (Table 1), or as the relative amount of **1** is increased (Figure 5), indicating that anti-**3** (or anti-**3b**) is far from saturation. The titration curves in Figure 5 clearly show that the association of **1** with *syn*-**3a** is much stronger than with anti-**3a**. A fully quantitative treatment of the titration data would involve fitting the binding curves to the scheme shown in Figure 3. However, the errors would be very large due to the many independent variables and the small number of data points. Instead, a semiquantitative analysis was conducted. We determined an overall association constant of 4×10^2 M^{-1} by titrating **1** with **3a** in $CDCl_3$ at −20 °C[11] and assumed that it was approximately equal to K_a for the *syn*-**3a**:**1** equilibrium.[12] The anti-**3a**:**1** titration curve was then fitted to a 1:1 binding model using

(11) The chemical shift of the NH signal for bis(amide) **1** (2 mM) was determined as a function of different amounts of **3a** (0.2−10 mM), and the resulting curve fitted to a 1:1 binding model.[13] The homodimerization of acylated 2-aminopyridines such as **3a** is known to be sufficiently weak ($K_d \sim 2$ M^{-1}) that it can be ignored for this calculation. Zimmerman, S. C.; Murray, T. J. *Philos. Trans. R. Soc., London A* **1993**, *345*, 49−57.

standard regression methods,[13] which resulted in a K_a of ~0.1 M^{-1}.

While the uncertainties associated with the van't Hoff and titration analyses are probably quite large, they both agree that the K_a for *syn*-**3a**:**1** is 10^3-10^4 times higher than the K_a for anti-**3a**:**1**. This implies that the *tert*-butoxy oxygen in anti-**3a** is a much poorer hydrogen bond acceptor than the carbonyl oxygen in *syn*-**3a**, most likely because of a combination of steric and electrostatic factors (Figure 3).[14]

As expected, the cholesteryl derivative, **3b**, behaves much like the *tert*-butyl analogue except the values for $K_{s/a}$ are slightly lower (compare Figure 6 with Table 1). Cholesterol carbamates are used as building blocks for a range of supramolecular assemblies such as DNA-containing lipoplexes, liquid crystals, gels, and Langmuir−Blodgett films.[15,16] In each case the macroscopic properties of the assembly are controlled by apparently subtle changes in the shape of the cholesteric component. The next goal of this research is to prepare liquid crystalline films that incorporate cholesterol carbamates such as **3b** and to determine if the films' optical properties change when exposed to compounds such as bis(amide) **1**.[17]

Conclusion

In $CDCl_3$ solution, the double hydrogen bonding acetic acid moderately stabilizes the *syn* rotamer of phenyl carbamate **4** (Figure 2) but has no measurable effect on the *syn*/*anti* ratio for 2-pyridyl carbamate **3** (Figure 8). Conversely, the donor−acceptor-donor triad **1** strongly stabilizes the *syn* rotamer of **3** (Figure 3), but has no effect on the *syn*/*anti* ratio for **4**, presumably because of steric hindrance to the formation a hydrogen bonded complex (Figure 4).

Experimental Section

The low-temperature NMR studies were conducted on a Varian 500 MHz instrument. The probe temperatures were measured with a calibrated, digital thermocouple which is accurate to ±0.5 °C. Fresh bottles of $CDCl_3$ (Aldrich) were used to prepare the NMR samples.

2,6-Bis(octylamido)pyridine, 1. 2,6-Diaminopyridine (0.5 g, 4.58 mmol) was dissolved in ethyl acetate and added to an aqueous solution of NaOH (5.7 M, 2 mL). The reaction flask was cooled to 0 °C, and octanoyl chloride (2 mL, 11.5 mmol) was added dropwise. The reaction mixture was stirred for several hours and then washed five times with 0.2 M NaOH. The organic layer was dried over $MgSO_4$ and the solvent evaporated. The product was recrystallized from chloroform/hexane to give a white solid. Yield: 30%. mp 99−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 6 H, J = 6.0 Hz), 1.31 (m, 16 H), 1.72 (quint, 4 H, J = 7.0 Hz), 2.39 (t, 4 H, J = 7.5 Hz), 7.2 (s, 2 H), 7.70 (t, 1 H, J = 8.0 Hz), 7.90 (d, 2 H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 22.8, 25.6, 29.2, 29.4, 31.9, 38.1, 109.6, 141.1, 149.6, 171.8; FAB MS m/z 362 $(MH)^+$; FAB HRMS (calcd for $C_{21}H_{35}N_3O_2$) 362.2808, found 362.2797. Anal. Calcd for $C_{21}H_{35}N_3O_2$: C, 69.77; H, 9.76; N, 11.62. Found: C, 69.92; H, 9.85; N, 11.70.

***N,N′*-Dimethyl-2,6-bis(octylamido)pyridine, 2.** Compound **1** (500 mg, 1.38 mmol) was dissolved in dry THF (9−10 mL) and placed under N_2 atmosphere. The reaction flask was cooled to −78 °C, and $NaN(Si(CH_3)_3)_2$ (3.04 mL, 2.2 equiv) was added dropwise. Methyl iodide (430 μL, 6.88 mmol, 5 equiv) was added dropwise and the mixture allowed to warm to room temperature. After stirring overnight, the solvent was evaporated to give a yellow precipitate which turned blue-green after sitting for a day. Purification by column chromatography (silica gel, 5:1 chloroform/methanol) yielded a brownish oil. Yield: 84%. R_f (5:1 chloroform/methanol) = 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, 6 H, J = 6.0 Hz), 1.20 (s, 16 H), 1.63 (m, 4 H), 2.39 (t, 4 H, J = 7.5 Hz), 3.38 (s, 6 H), 7.24 (s, 2 H), 7.78 (t, 1 H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 22.8, 25.5, 29.3, 29.4, 31.8, 35.2, 35.6, 118.4, 139.9, 155.0, 173.9; FAB MS m/z 390 $(MH)^+$; FAB HRMS (calcd for $C_{23}H_{39}N_3O_2$) 390.3121, found 390.3112.

***tert*-Butyl *N*-(2-Pyridyl)carbamate, 3a.**[9a] Di-*tert*-butyl dicarbonate (2.4 g, 11 mmol) was added to 2-aminopyridine (940 mg, 10 mmol) in *tert*-butyl alcohol. The mixture was stirred overnight at 30−40 °C. The solvent was evaporated, and the residue was filtered through silica gel with methylene chloride as the eluant. The product was a white solid (with THF as the solvent, the major product was *N*,*N*′-bis(2-pyridyl)-urea, as described in the literature[9a]). Yield: 60%. mp 93−94 °C (lit. 92−93 °C).[9a] R_f (methylene chloride) = 0.59; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 9 H), 6.95 (t, 1 H, J = 6.5 Hz), 7.68 (t, 1 H, J = 8.0 Hz), 7.98 (d, 1 H, J = 5.5 Hz), 8.30 (d, 1 H, J = 7.5 Hz), 8.72 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5, 80.8, 112.6, 118.1, 138.7, 147.7, 152.9, 153.2; FAB MS m/z 195 $(MH)^+$; FAB HRMS (calcd for $C_{10}H_{14}N_2O_2$) 195.1134, found 195.1127. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42. Found: C, 62.05; H, 7.50; N, 14.62.

Cholesteryl *N*-(2-Pyridyl)carbamate, 3b. 2-Aminopyridine (0.50 g, 5.31 mmol) was added to solution of cholesteryl chloroformate (2.38 g, 5.31 mmol) and K_2CO_3 (3.76 g, 26.5 mmol) in dry THF (22 mL). The reaction was allowed to reflux for 3 h before the solvent was evaporated. The residue was recrystalized from 1:1 hexane/methylene chloride. Yield: 32%. mp 212−214 °C. R_f (ethyl acetate) 0.75. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (s, 6 H), 0.86 (d, 6 H, J = 7.8 Hz), 0.92 (d, 3 H, J = 6.6 Hz), 0.93−2.43 (m, 22 H), 1.04 (s, 6 H), 4.64 (m, 1 H, J = 5.6 Hz), 5.41 (d, 1 H, J = 5.4 Hz), 6.97 (t, 1 H, J = 6.2 Hz), 7.49 (s, 1 H), 7.67 (t, 1 H, J = 7.1 Hz), 7.95 (d, 1 H, J = 8.7 Hz), 8.24 (d, 1 H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 18.9, 19.6, 21.3, 22.8, 23.0, 24.1, 24.5, 28.2, 28.3, 28.5, 28.6, 32.2, 36.0, 36.4, 36.8, 37.2, 38.7, 39.7, 40.0, 42.6, 50.3, 56.4, 56.9, 75.3, 81.0, 112.6, 118.4, 188.6, 123.0, 138.4, 138.6, 139.8, 147.9, 152.5, 152.6, 152.9, 153.2; FAB MS m/z 507 (M^+); FAB HRMS (calcd for $C_{33}H_{51}N_2O_2$) 507.3951, found 507.3974. Anal. Calcd for $C_{33}H_{50}N_2O_2$: C, 78.21; H, 9.94; N, 5.53. Found: C, 78.35; H, 10.03; N, 5.41.

***tert*-Butyl *N*-Phenylcarbamate, 4a.**[9b] Di-*tert*-butyl dicarbonate (2.4 g, 11 mmol) was added to aniline (911 μL, 10 mmol) in dry THF (25 mL), and the mixture was stirred at room temperature for 12 h. The solvent was evaporated and the residue taken up in hexane and filtered. The white solid was recrystallized from hexane/methylene chloride. Yield: 90%. mp 136−137 °C (lit. 135−136 °C).[9b] R_f (4:1 hexane/ethyl acetate) = 0.61. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 9 H), 6.55 (s, 1 H), 7.02 (t, 1 H, J = 7.5 Hz), 7.32 (t, 2 H, J = 8.0 Hz), 7.39 (d, 2 H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.6, 80.7, 118.7, 123.3, 129.2, 138.5, 191.2; FAB MS m/z 193 $(M)^+$; FAB HRMS (calcd for $C_{11}H_{15}NO_2$) 193.1103, found 193.1103. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.50; H, 7.81; N, 7.47.

Cholesteryl *N*-Phenylcarbamate, 4b. 2-Aniline (0.50 g, 5.36 mmol) was added to solution of cholesteryl chloroformate (2.40 g, 5.36 mmol) and K_2CO_3 (3.80 g, 26.8 mmol) in dry THF

(12) Association constants for hydrogen bonded DAD−ADA pairs are typically 10^2-10^3 M^{-1}. Beijer, F. H.; Kooijman, H.; Spek, A. L.; Sijbesma, R. P.; Meijer, E. W. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 75−78. Beijer, F. H.; Sijbesma, R. P.; Vekemas, J. A. J. M.; Meijer, E. W.; Kooilman, H.; Spek, A. L. *J. Org. Chem.* **1996**, *61*, 6371−6380.

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(22 mL). The reaction was allowed to reflux for 3 h before the solvent was evaporated. The residue was recrystalized from 1:1 hexane/methylene chloride. Yield: 78%. mp 169−171 °C. R_f (ethyl acetate) 0.80. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68 (s, 6 H), 0.87 (d, 6 H, J = 7.8 Hz), 0.85−2.47 (m, 22 H), 0.92 (d, 3 H, J = 6.6 Hz), 1.03 (s, 6 H), 4.61 (m, 1 H, J = 5.5 Hz), 5.40 (d, 1 H, J = 5.4 Hz), 6.53 (s, 1 H), 7.05 (t, 1 H, J = 7.2 Hz), 7.30 (t, 2 H, J = 8.0 Hz), 7.38 (d, 2 H, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 18.9, 19.6, 21.3, 22.8, 23.0, 24.1, 24.5, 28.2, 28.3, 28.4, 32.1, 36.0, 36.4, 36.8, 37.2, 38.7, 39.7, 40.0, 42.5, 50.2, 56.4, 56.9, 75.1, 118.8, 123.0, 123.4, 129.2, 138.3, 139.8, 153.3; FAB MS m/z 504 $(M - 1)^+$. Anal. Calcd for $C_{34}H_{51}NO_2$: C, 80.74; H, 10.16; N, 2.77. Found: C, 81.00; H, 10.09; N, 2.71.

Acknowledgment. This work was supported by the National Science Foundation (CHE95-01166) and the University of Notre Dame. We are grateful to D. Schifferl for assistance with the variable temperature NMR studies.

JO980644D