mixture of 1.2 g (2.5 mmol) of **13**, 0.4 g (3 mmol) of allyl bromide, and 0.5 g of potassium *tert*-butoxide in 50 mL of *tert*-butyl alcohol was stirred at 40–50 °C for 3 h. The mixture was evaporated under reduced pressure, and the residue was chromatographed on neutral alumina (toluene/ethanol, 50/1) to give 1 g (81%) of **14** as an oil: NMR δ 1.00 (t, 6 H), 2.60 (q, 4 H), 2.75 (m, 14 H), 3.55 (m, 22 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H); MS *m/z* 490. Anal. Calcd for $C_{25}H_{51}N_3O_6$: C, 61.32; H, 10.51. Found: C, 61.27; H, 10.43.

14-[(Allyloxy)methyl]-10,19-diethyl-4-[2-(2-hydroxyethoxy)ethyl]-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (15) (Scheme III). Macrocycle **15** was prepared as above for **2** from 3.35 g (10 mmol) of **46**, 4.24 g (10 mmol) of **54**, 10 g of potassium carbonate, and 0.4 g of sodium iodide in 400 mL of acetonitrile to give 2.9 g (56%) of the product as an oil: NMR δ 1.05 (t, 6 H), 2.70 (m, 18 H), 3.60 (m, 23 H), 3.90 (b, 1 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H); MS *m/z* 519. Anal. Calcd for $C_{26}H_{53}N_3O_7$: C, 60.09; H, 10.28. Found: C, 59.88; H, 10.09.

11-(or 12)-[(Allyloxy)methyl]-16-ethyl-4,7-dimethyl-4,7,16-triaza-1,10,13-trioxacyclooctadecane (16) (Scheme III). Macrocycle **16** was prepared as above for **2** from 1.95 g (4.7 mmol) of **41**, 2.15 g (4.7 mmol) of **54**, 6 g of sodium carbonate, and 0.2 g of sodium iodide in 200 mL of acetonitrile to give 1.2 g (66%) of the product as an oil: NMR δ 1.00 (t, 3 H), 2.30 (2 s, 6 H), 2.65 (m, 14 H), 3.60 (m, 13 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H); MS *m/z* 387. Anal. Calcd for $C_{20}H_{41}N_3O_4$: C, 61.98; H, 10.66. Found: C, 61.92; H, 10.70.

14-(or 15)-[(Allyloxy)methyl]-4,7,10,19-tetraethyl-4,7,10,19-tetraaza-1,13,16-trioxacycloheneicosane (17) (Scheme III). Macrocycle **17** was prepared as above for **2** from 0.72 g (2.4 mmol) of **43**, 1.1 g (2.6 mmol) of **54**, 10 g of potassium carbonate, and 1 g of potassium iodide in 250 mL of acetonitrile to give 0.65 g (56%) of the product as an oil: NMR δ 1.00 (t, 12 H), 2.60 (m, 24 H), 3.60 (m, 13 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H); MS *m/z* 486. Anal. Calcd for $C_{26}H_{54}N_4O_4$: C, 64.16; H, 11.18. Found: C, 64.10; H, 10.96.

17-(or 18)-[(Allyloxy)methyl]-4,7,10,13,22-pentaethyl-4,7,10,13,22-pentaaza-1,16,19-trioxacyclotetracosane (18) (Scheme III). Macrocycle **18** was prepared as above for **2** from 0.4 g (1.1 mmol) of **44**, 0.50 g (1.2 mmol) of **54**, 4 g of potassium carbonate, and 0.1 g of potassium iodide in 150 mL of acetonitrile to give 0.3 g (37%) of the product as an oil: NMR δ 1.00 (t, 15 H), 2.60 (m, 30 H), 3.60 (m, 13 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (s, 1 H); MS *m/z* 558. Anal. Calcd for $C_{30}H_{63}N_5O_4$: C, 64.59; H, 11.38. Found: C, 64.72; H, 11.19.

14-(or 15)-[(Allyloxy)methyl]-4,10-dibenzyl-19-ethyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (19) (Scheme III). Compound **19** was prepared as above for **2** from 1.9 g (4.8 mmol) of **42**, 2.12 g (5 mmol) of **54**, 6 g of sodium carbonate, 4 g of potassium carbonate, and 0.3 g of sodium iodide in 300 mL of acetonitrile to give 1.4 g (51%) of the product as an oil: NMR δ 1.00 (t, 3 H), 2.70 (m, 14 H), 3.60 (m, 21 H), 4.00 (d, 2 H), 5.20 (m, 2 H), 5.90 (m, 1 H), 7.3 (m, 10 H); MS *m/z* 583. Anal. Calcd for $C_{34}H_{53}N_3O_5$: C, 69.94; H, 9.15. Found: C, 70.05; H, 9.05.

4,10,19-Tribenzyl-4,10,19-triaza-1,7,13,16-tetraoxacycloheneicosane (20) (Scheme IV). Macrocycle **20** was prepared as above for **2** from 1.15 g (2.5 mmol) of **48**, 0.93 g (2.5 mmol) of **56**, 10 g of potassium carbonate, and 0.1 g of sodium iodide in 150 mL of acetonitrile to give 0.7 g (49%) of the product as an oil: NMR δ 2.75 (m, 12 H), 3.60 (m, 22 H), 7.25 (m, 15 H); MS *m/z* 575. Anal. Calcd for $C_{35}H_{49}N_3O_4$: C, 73.01; H, 8.57. Found: C, 72.88; H, 8.43.

4,10,14-Tribenzyl-12-methylene-4,10,14-triaza-1,7-dioxacyclohexadecane (21) (Scheme II). Macrocycle **21** was prepared as above for **2** from 1.15 g (2.5 mmol) of **48**, 0.32 g (2.5 mmol) of **50**, 10 g of sodium carbonate, and 0.5 g of sodium iodide in 150 mL of acetonitrile to give 0.8 g (63%) of the product as an oil: NMR δ 2.55 (t, 4 H), 2.80 (t, 4 H), 3.20 (s, 4 H), 3.55 (m, 14 H), 5.10 (s, 2 H), 7.30 (m, 15 H); MS *m/z* 513. Anal. Calcd for $C_{33}H_{43}N_3O_2$: C, 77.15; H, 8.43. Found: C, 77.32; H, 8.35.

4,10,13,19,25,29-Hexaethyl-27-methylene-4,10,13,19,25,29-hexaaza-1,7,16,22-tetraoxacyclohentriacontane (22) (Scheme II). Macrocycle **22** was prepared as above for **2** from 0.46 g (0.8 mmol) of **49**, 0.1 g (0.8 mmol) of **50**, 3 g of potassium carbonate, and 0.5 g of cesium carbonate in 100 mL of acetonitrile to give 0.04 g (8%) of the product as an oil: NMR δ 1.00 (m, 18 H), 2.60 (m, 32 H), 3.00 (s, 4 H), 3.50 (m, 16 H), 5.00 (s, 2 H); MS *m/z* 628. Anal. Calcd for $C_{34}H_{72}N_6O_4$: C, 64.92; H, 11.53. Found: C, 64.72; H, 11.71.

7,13,19,22,28,34-Hexaethyl-7,13,19,22,28,34-hexaaza-1,4,10,16,25,31-hexaoxacyclohexatriacontane (23) (Scheme IV). Macrocycle **23** was prepared as above for **2** from 0.4 g (0.8 mmol) of **49**, 0.33 g (0.9 mmol) of **56**, 3 g of sodium carbonate, 3 g of potassium carbonate, and 2 g of cesium carbonate in 200 mL of acetonitrile to give 0.06 g (11%) of the product as an oil: NMR δ 1.00 (t, 18 H), 2.65 (m, 36 H), 3.50 (m, 24 H); MS *m/z* 691. Anal. Calcd for $C_{36}H_{78}N_6O_6$: C, 62.57; H, 11.38. Found: C, 62.44; H, 11.22.

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Conformations of *N*,*N*-Bis(2-fluorophenyl)carbamoyl Chloride

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The structure of the title compound has been examined by X-ray crystallographic and fluorine NMR methods. In the solid state the planes of the fluorophenyl rings are oriented at angles of 98° and 64° relative to the plane through the atoms of the carbamoyl chloride group. Fluorine NMR studies indicate that the conformational properties of the molecule in solution are similar to this. Fluorine NMR lineshape data were used to estimate the rates of rotation of the fluorophenyl rings and the rate of rotation about the carbamoyl nitrogen–carbon bond. Observation of a large fluorine–fluorine coupling constant, likely the result of a through-space interaction, supports the conclusions regarding the conformations of this compound in solution.

Erlanger and co-workers have shown that diphenylcarbamoyl chloride (I) efficiently inactivates serine proteases.[2] For example, this compound reacts rapidly with α-chymotrypsin, even at a solution pH far from the op-

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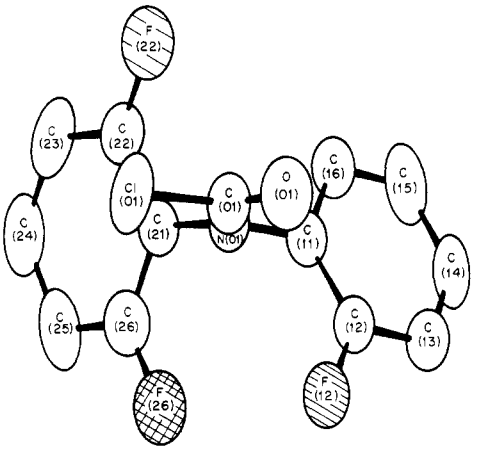
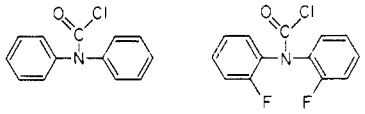


Figure 1. Drawing of the structure of *N,N*-bis(2-fluorophenyl)carbamoyl chloride found in the solid state. One phenyl ring (fluorine positions shaded) is disordered with the structure having the fluorine atoms on the same side of the carbamoyl plane having a 56% occupancy.

timum for catalysis by this enzyme, to form a stable diphenylcarbamoylated protein. In previous work we examined 4-fluorinated derivatives of I and found that these materials also effectively acylate this enzyme.[3] The stability of the fluorinated enzymes toward deacylation and denaturation made it possible to apply fluorine NMR over a broad temperature range to an examination of conformational dynamics of the diphenylcarbamoyl moiety in these proteins.

In the course of extending our previous studies we have obtained fluorine NMR evidence that *N,N*-bis(2-fluorophenyl)carbamoyl chloride (II), another fluorinated analogue of Erlanger's reagent, exists in several conformations. As described below, X-ray diffraction studies show that (1) in the crystalline state the fluorophenyl rings are not co-planar with the carbamoyl group and (2) there are two conformations of II present in the crystal. In one of these conformations the fluorine atoms of the two rings are essentially within van der Waals contact of each other. That these conformations are present in solution is strongly supported by fluorine NMR observations to be described. Conclusions drawn in this study are expected to be germane to interpretation of fluorine NMR studies of enzymes acylated with II.



I II

Results

Crystal Structure. The structure of *N,N*-bis(2-fluorophenyl)carbamoyl chloride, II, in the solid state was determined by X-ray diffraction (Table I, supplementary material). A drawing of the molecule appears in Figure 1 and is based on the fractional coordinates for the atoms of II given in Table II, supplementary material. In the structure, the carbamoyl chloride group is planar, with the sum of the angles around the carbonyl carbon and around N (C(01) and N(01) in Figure 1, respectively) being 360.0°. The overall conformation of the molecule can be characterized by three planes, two through the atoms of the two *o*-fluorophenyl rings and a third through the atoms of the carbamoyl chloride function. In the solid state one of the phenyl ring is turned 98.0° relative to the plane of the carbamoyl group while the other forms an angle of 64.4° with that same plane. The angle between the two phenyl rings is 72.5°.

The observed C–O bond distasnce in the carbamoyl group is 1.194 (4) Å, a little shorter than the corresponding bonds found in *N*-methyl-2,4,6-trinitroacetanilide,[4] *N*-methyl acetanilide,[5] and formamide.[6] The carbonyl carbon–nitrogen bond, at 1.350 (4) Å, is slightly longer than the value (1.34 Å) found in formamide and *N*-methylacetanilide but a little shorter than that found in *N*-methyl-2,4,6-trinitroacetanilide (1.374 Å). Camerman[7] has proposed 1.475 Å for the length of a C_{aryl}–N_{sp^2} bond. The C_{aryl}–N distances in the carbamoyl group of II are 1.443 and 1.435 Å, shorter than Camerman's suggested length, but still considerably longer than the corresponding bond lengths observed in acetanilide or *N*-methyl-2,4,6-trinitroacetanilide (1.417 Å in both). In considering all of these systems there is no correlation of the observed angle between amide or carbamoyl planes and the plane of the aromatic ring with the length of the C–N bond that connects them.

A striking feature of the structure of II is disordering of the 2-fluorophenyl ring that is cis to the chloride atom of the carbamoyl chloride group. The fluorine atom of this ring may be found on either side of the carbamoyl plane, with 44% of the molecules comprising the crystal having this fluorine oriented away from the fluorine atom of the second 2-fluorophenyl ring while in the remaining 56% the aromatic fluorine atoms are on the same side of the carbamoyl chloride plane. The fluorine atom of the disordered ring is indicated in Figure 1 by means of shading. In either conformation, the aromatic carbon–fluorine bond distance of the disordered 2-fluorophenyl ring appears to be unusually short (1.235 (5) and 1.265 (7) Å, respectively, for the major and minor forms) while this bond distance in the other 2-fluorophenyl ring (1.355 (4) nm) is well within the normal range.[8,9] The fluorine–fluorine distance in the major conformer is 3.106 (6) Å. Taking the van der Waals radius of covalent fluorine to be 1.4 Å,[10] it is seen that these two atoms are just outside van der Waals contact in this structure. Tilting of the aromatic ring with the disordered fluorine appears to help these atoms avoid unfavorable interactions with each other and the relatively bulky chlorine. Possibly both electrostatic and other nonbonded interactions between these fluorine atoms and the others of carbamoyl group are the cause of the shortening of the disordered C–F bond length, although this observation could also be an artifact related to thermal motions in the lattice or of the refinement.

Solution Studies. The proton-decoupled fluorine NMR spectrum of *N,N*-bis(2-fluorophenyl)carbamoyl chloride in acetone-d_6 exhibited two doublets of equal intensity, separated by 0.925 ppm (Figure 2A). The

(1) (a) University of Ioannina, on sabbatical leave to UCSB. (b) University of California. (c) University of California, to whom correspondence should be addressed.
(2) (a) Erlanger, B. F.; Cohen, W. *J. Am. Chem. Soc.* **1963**, *85*, 348. (b) Erlanger, B. F.; Castleman, H.; Cooper, A. G. *J. Am. Chem. Soc.* **1963**, *85*, 1872. (c) Erlanger, B. F.; Edel, F. *Biochemistry* **1964**, *3*, 346. (d) Erlanger, B. F.; Cooper, A. G.; Cohen, W. *Biochemistry* **1966**, *5*, 190.
(3) (a) Cairi, M.; Gerig, J. T. *J. Am. Chem. Soc.* **1983**, *105*, 4793. (b) Cairi, M.; Gerig, J. T. *J. Am. Chem. Soc.* **1984**, *106*, 3640.
(4) Christoph, G. C.; Fleischer, E. B. *Acta Crystallogr.* **1973**, *B29*, 121.
(5) Pederson, B. F. *Acta Chem. Scand.* **1967**, *21*, 1415–1424.
(6) Kurland, R. J.; Wilson, E. B. *J. Chem. Phys.* **1957**, *27*, 585.
(7) Camerman, A. *Can. J. Chem.* **1970**, *48*, 179.
(8) Hiyama, Y.; Silverton, J. V.; Torchia, D. A.; Gerig, J. T.; Hammond, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 2715–2723.
(9) Nygaard, L.; Bojeson, I.; Pederson, T.; Rastrup-Andersen, J. *J. Mol. Struct.* **1968**, *2*, 209–214.
(10) Nyberg, S. C.; Faerman, C. H. *Acta Crystallogr.* **1985**, *B41*, 274–279.

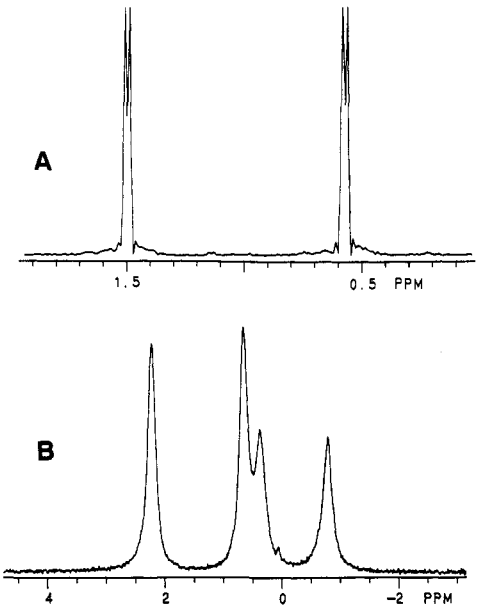


Figure 2. (A) Fluorine NMR spectrum of II at 25 °C, recorded at 470.5 MHz. (B) Fluorine NMR spectrum at 470.5 MHz of II at −91 °C. The relative integrated intensities of the signals are discussed in the text.

separation between the components of the doublets was 10 Hz and was independent of applied magnetic field. It, thus, represents a fluorine–fluorine scalar coupling constant.

The fluorine spectrum of II is strongly temperature-dependent. As the temperature of the sample is decreased to −40 °C small shifts of the two spectral components in opposite directions increases the chemical shift difference to 1.12 ppm while a small amount of viscosity broadening takes place. Below this temperature significant exchange broadening is seen, and, at the lowest temperature accessible (−91 °C) the spectrum consisted of four components, best seen at 470 MHz (Figure 2B), with shifts 2.247 0.694, 0.373, and −0.787 ppm and relative intensities of 0.31:0.31:0.19:0.19, respectively. The lines were still quite broad (ca. 75 Hz) at this temperature, and the appearance of the spectrum was not altered by proton decoupling. Some exchange broadening is likely still present in the spectrum at −91 °C, but solubility considerations did not permit examination of the sample at lower temperatures. There was no direct evidence of fluorine–fluorine coupling in this low-temperature spectrum. However, a COSY experiment performed at this temperature showed cross-peaks between the two major components of the spectrum (Figure 3), indicating the presence of a fluorine–fluorine coupling interaction between these.

The changes in the fluorine spectrum of II with temperature were examined in detail at 282 MHz. The evolution of the low-temperature spectrum was analyzed in terms of two-site exchanges (Figure 4); the line shapes from −91 to −40 °C were produced very well by assuming interconversion of the species represented by lines A and C (Figure 2B or Figure 4) and interconversion of structures represented by lines B and D in the spectra. Several other pairings of the lines as exchange partners were considered, but only the one indicated led to calculated line shapes that were in agreement with experiment over the entire temperature range examined. This analysis suggested that the A-to-C and B-to-D interconversions occur at the same rate.

In making the line-shape analysis the shifts observed at −91 °C were assumed to be the slow-exchange shifts needed

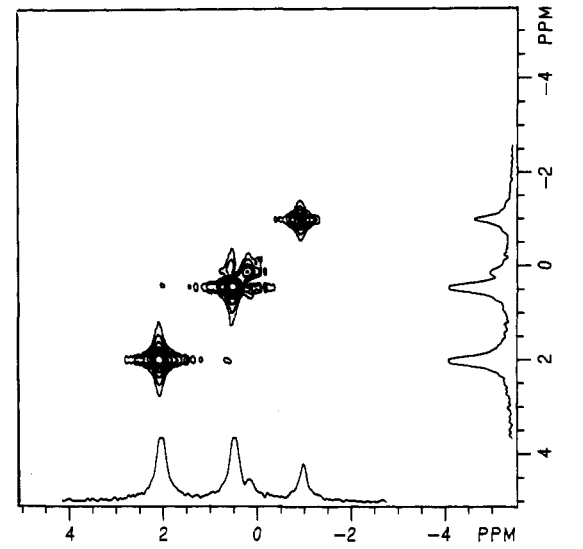


Figure 3. Fluorine homonuclear COSY spectrum of II recorded at −91 °C and 470.5 MHz. The map is presented in absolute value mode. The spectrum was not symmetrized.

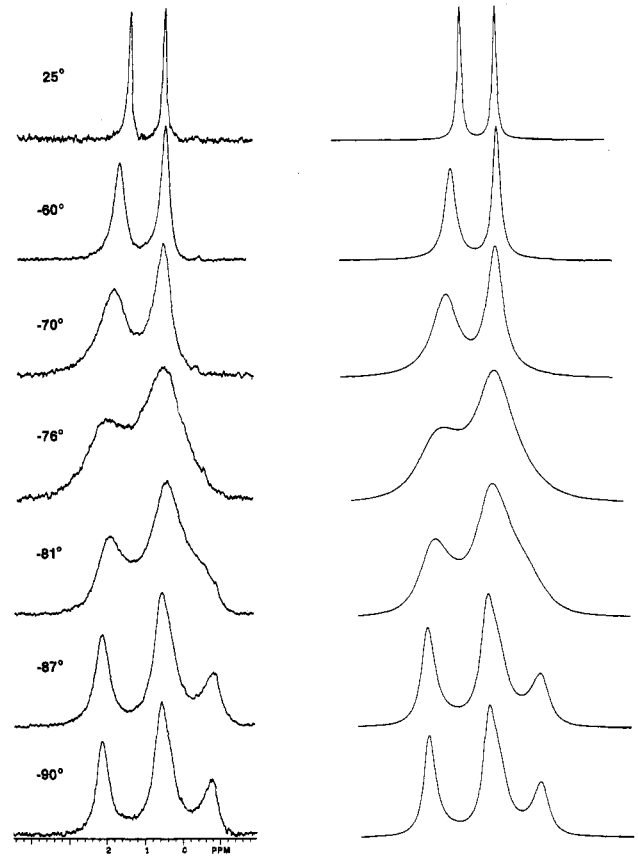


Figure 4. Fluorine NMR spectra of II at various temperatures. Data were obtained at 282.3 MHz. The computed curves (right) were obtained by assuming the presence of two two-site exchange processes that interconvert the signal pairs A and C, and B and D.

for generation of the theoretical line shapes, the (small) temperature variation of the various shift differences was taken into consideration by assuming that the variations of shifts with temperature were linear with temperature and defined by the temperature dependencies observed at temperatures higher and lower than those at which exchange effects are apparent in the spectrum. The temperature variation of the amounts of each species represented in the spectrum was neglected in the analysis. A

Table I. Activation Parameters

	$\Delta G_{25}^{\ddagger}$, kJ/mol	$\Delta H^{\ddagger}$, kJ/mol	$\Delta S^{\ddagger}$, J mol^{-1} K^{-1}
high-temperature process	72.8	92.5	57
low-temperature process (major to minor barrier)	30.8	44.8	47

slow-exchange line width of 35 Hz was used in these analyses; the spectra were not proton decoupled, and proton–fluorine and fluorine–fluorine coupling was neglected. The accuracy of the rate data is likely somewhat limited by these considerations and is probably subject to some systematic errors, but, because the chemical shift differences are large (ca. 800 Hz) relative to the various scalar coupling constants, we believe that the activation parameters for the low-temperature process detected in II and given in Table I are reasonably reliable. Extrapolation of the rate constants obtained at lower temperatures indicated that the rate of the low-temperature process takes place at a rate of about 10^8 s^{-1} at 25 °C.

At temperatures above 25 °C another kinetic process becomes evident in the fluorine spectrum of II (Figure 5). The two doublets present gradually broadened with increasing temperature, eventually merging to a single resonance that sharpened with increasing temperatures after coalescence at 93 °C (Figure 5). The line shapes observed were again analyzed, as an approximation, in terms of a two-site exchange process, neglecting coupling. The rate data available for the high-temperature exchange process afforded the activation parameters listed in Table I. Extrapolation indicates that the rate of the high-temperature process at 25 °C is about 1.5 s^{-1}.

Discussion

We previously determined the barrier to rotation about the carbamoyl carbon–nitrogen bond in *N*,*N*-bis(4-fluorophenyl)carbamoyl chloride and *N*-phenyl-*N*-(4-fluorophenyl)carbamoyl chloride.[11] The solvent used for those experiments was 94:6 cyclohexanone–acetone-d_6 and for both systems $\Delta G_{25}^{\ddagger}$ was 61–62 kJ/mol, $\Delta H^{\ddagger}$ was 68–69 kJ/mol, and $\Delta S^{\ddagger}$ was 21–25 J mol^{-1} deg^{-1}. It seems reasonable to designate this same rotational process as the high-temperature process detected by fluorine NMR of II, although the free energy barriers with the 4-fluorosubstituted compounds are about 10 kJ/mol lower than found with II. (Larger, compensating differences in the enthalpy and entropy parameters between the previous studies and the results presented here are found, but it is not clear that these are not the result of systematic errors, possibly in both sets of experiments.) The solvent composition was somewhat different for the 4-fluoro systems, but this does not seem to be sufficient to account for the changes observed. However, covalent fluorine is slightly larger than covalent hydrogen,[12] and it is possible that altered steric interactions in transition state for rotation are responsible for the increase in rotation barrier observed.

Presuming that the structure of *N*,*N*-bis(2-fluorophenyl)carbamoyl chloride found in the crystal is similar to the one found in solution, it is clear that the 2-fluorophenyl rings cannot achieve coplanarity with the carbamoyl function. It is likely that in solution both phenyl groups will oscillate about their respective C_{phenyl}–N bonds between the steric "stops" provided by the atoms of the carbamoyl group and, thus, have an orientation that on average is approximately normal to the plane through the atoms of this group.[12] With this assumption we can view the molecule in terms of the drawings below. In agreement with the observed spectrum at −91 °C there are four magnetically unique sites available to the aromatic fluorine atoms, with a pair of equally intense resonances expected for each form indicated. The structure shown are interconverted by rotation of the 2-fluorophenyl rings; it may be noted that rotation about the carbamoyl C–N bond interconverts the environments of the fluorines with a given structure but does not provide a means to convert one of the structures shown into the other. The intensity of one pair of lines relative to the intensity of the other pair will depend on the free energies of these syn and anti forms.

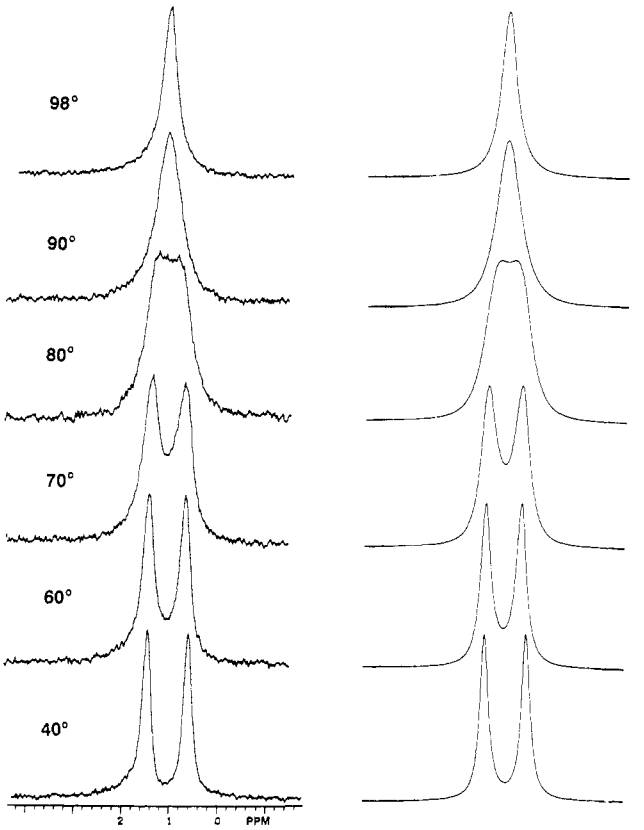
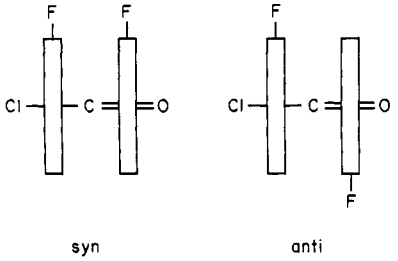


Figure 5. Fluorine NMR spectra of II at various temperatures above room temperature. Data were obtained at 282.3 MHz. The solvent for the high temperature spectra was a mixture of cyclohexanone and acetone-d_6 (60/40). The theoretical curves (right) were obtained assuming a two-site exchange process that interconverts the (apparent) singlets observed at 25 °C.

We propose that the conformational process in II that becomes slow at low temperatures is rotation about C_{phenyl}–N bonds. The energy barrier to aryl group rotation that is observed could presumably be the result of two factors, conjugation between the aromatic rings and the carbamoyl group and steric interactions between atoms in the vicinity of this group. The part due to conjugation must be very small in the present case, given the likely orthogonal orientation of the phenyl rings relative to the carbamoyl plane. Examination of barriers to C_{phenyl}–N rotation in various anilides suggests that interactions between ortho substituents and other nitrogen substituents can produce barriers as high as 120 kJ/mol,[13,14] so that the

(11) M. Cairi, Ph.D. Thesis, University of California, Santa Barbara, 1982; p 81; manuscript in preparation.
(12) Weil, J. A.; Blum, A.; Heiss, A. H.; Kinnaird, J. K. *J. Chem. Phys.* **1967**, *46*, 3132.
(13) Pettersson, I.; Sandström, J. *Acta Chem. Scand.* **1984**, *B38*, 397–405 and references therein.
(14) Siddall, T. H. III; Stewart, W. E. *J. Org. Chem.* **1969**, *34*, 2927.

barrier observed here is not unreasonable.



Fluorine chemical shifts are very sensitive to van der Waals interactions.[15] In one conformation of II the two ortho fluorine atoms are separated by a distance that is barely more than the sum of their van der Waals radii. Significant downfield shifts would be expected because of these interactions. The pair of fluorine signals found at lowest field in the fluorine spectrum of II can thereby reasonably be assigned to the conformation in which the F–F distance is smallest.[16] In solution at −91 °C this conformation represents 62% of the molecules present. Formation of crystals at room temperature produced a material in which 56% of the molecules are of this type, but, given the differences in environment, it is unlikely that the relative amounts of these conformations present in solution and in the crystal will be exactly the same.

Support for the assignment of the low-field pair of signals to the conformation in which both fluorines of II are juxtaposed comes from the observation of a significant fluorine–fluorine spin-coupling constant between the two fluorines. The fluorine nuclei in II are formally separated by six covalent bonds, and, on these grounds, the spin coupling between them would be expected to be small. However, pairs of fluorines that are crowded against one another often experience unusually large coupling constants.[17] Perhaps the most dramatic example of this phenomenon has been observed in a variant of the enzyme dihydrofolate reductase in which 5-fluorotryptophan replaces the normal amino acid. A 17-Hz fluorine–fluorine coupling constant is observed between two fluorines that are within van der Waals contact but separated by dozens of covalent bonds.[18] The coupling constant observed at room temperature with II represents the weighted average of the value for this coupling in each of the conformations that become manifest at low temperature. The COSY experiment suggests that significant fluorine–fluorine coupling is present only is the major conformation, although the sensitivity of the experiment was such that a cross-peak between the peaks of the minor conformer could have been missed. If this coupling constant is assumed to be zero in the minor conformation then a value of J_{FF} of about 16 Hz is indicated for the major conformation. While this coupling constant breaks no records, it is large enough to significantly bolster the assignment of the dominant structure in solution to the form of II having the fluorines abutting each other.

We have shown that carbamoyl chloride II inactivates chymotrypsin and it will be interesting to see what conformations this structure will present when bound to the enzyme.

(15) Rummens, F. H. A. *NMR: Basic Princ. Prog.* **1975**, *10*, 1.

(16) Attempts to observe the fluorine NMR spectrum of II in the solid state were thwarted by fluorine background signals from the solid-state probe available to us. We thank Prof. H. Eckert for his assistance in this regard.

(17) (a) Mallory, F. B.; Mallory, C. W.; Ricker, W. M. *J. Org. Chem.* **1985**, *50*, 457–461. (b) Mallory, F. B.; Mallory, C. W. *J. Am. Chem. Soc.* **1985**, *107*, 4816–9 and references therein.

(18) Kimber, B. J.; Feeney, J.; Roberts, G. C. K.; Birdsall, B.; Griffiths, D. V.; Burgen, A. S. V.; Sykes, B. D. *Nature* **1978**, *271*, 184–5.

Experimental Section

Instrumentation. Melting points were determined on a Thomas-Hoover apparatus and were uncorrected. Routine proton spectra were recorded with Varian EM-390 or Nicolet NT300 spectrometers. Mass spectra were obtained with a VG Micromass ZAB-2F instrument.

Materials. Common salts and organic reagents were the highest grade available commercially. 2-Fluoroacetanilide was prepared by treating 2-fluoroaniline (Fluka) with an excess of acetic anhydride at room temperature. The solid obtained was washed with water and then dried in vacuo over P_2O_5 for at least 24 h.

***N,N*-Bis(2-fluorophenyl)amine** was prepared by placing 3 g (19 mmol) of 2-fluoroacetanilide, 0.4 g (2 mmol) of copper(I) iodide (Fluka), 0.4 g (24 mmol) of K_2CO_3 (Fluka), 5 mL (45 mmol) of *o*-fluorobromobenzene (Fluka), 4 mL (3.9 mmol) of nitrobenzene (Fluka), and a few grains of iodine into a 50-mL round-bottom flask equipped with a reflux condenser and a magnetic stirrer. The mixture was heated to vigorous reflux for 24 h at which time about 70% of the starting 2-fluoroacetanilide had reacted, as determined by proton NMR spectroscopy. Excess *o*-fluorobromobenzene and nitrobenzene were steam distilled from the reaction vessel, and the remaining material was extracted with ether (4 × 150 mL). The combined ether extracts were washed with water, dried over $MgSO_4$, and evaporated in vacuo to leave a brown oil. This residue was taken up in 30 mL of 95% ethanol containing 5.3 g (94 mmol) of KOH, and the solution was heated to reflux for 2 h, whereupon the mixture was poured into 250 mL of water. Extraction with dichloromethane (3 × 150 mL) followed. The combined extracts were washed with water and dried over $MgSO_4$. After removal of the solvent in vacuo a dark brown oil was obtained which was distilled at 0.5 mmHg. The first fraction (40–45 °C) was identified as *o*-fluoroaniline. The next fraction (bp 100–110 °C, 1.9 g, 37%) was the desired aniline as judged by its proton NMR spectrum.

***N,N*-Bis(2-fluorophenyl)carbamoyl chloride** was obtained by treating *N,N*-bis(2-fluorophenyl)amine (0.5 mL, 6 mmol) with phosgene following the procedure used previously.[2] The white, solid product was recrystallized twice from ethanol to afford white needles (0.84 g, 53%, mp 102–104 °C). The proton NMR spectrum of this material showed a complex pattern centered at 7.30 ppm from TMS. The mass spectrum showed parent ions at *m/e* 267 and 269 in the ratio 100:33, a major fragment at *m/e* 232 (M − Cl) and other fragments consistent with the desired structure. The fluorine NMR spectrum of this compound, considered in detail above, was consistent with the expected structure, as were the crystallographic results.

Crystallography. Crystals of II were grown by slow evaporation of an ethanol solution at 4 °C. A fragment of dimensions 0.83 × 0.60 × 0.30 mm, cut from a roughly hexagonal plate, was used in the X-ray diffraction analysis. Data were collected on a Huber four-circle diffractometer automated by Crystal Logic, Inc. The cell constants and other diffraction data are summarized in Tables I and II of the supplementary material.

Three reflections monitored as standards throughout the course of the data collection showed no appreciable decay. No absorption correction was applied due to the small size of the absorption coefficient (3.3 cm^{-1}).

Inspection of the intensity data revealed the systematic absences $hk0$, $h = 2n + 1$; $h0l$, $l = 2n + 1$; $0kl$, $k = 2n + 1$; $h00$, $h = 2n + 1$; $0k0$, $k = 2n + 1$; $00l$, $l = 2n + 1$, consistent with the space group *Pbca*. The carbamoyl chloride moiety and portions of both phenyl rings were located by direct methods using the program MULTAN80.[19] The remaining nonhydrogen atoms were located by successive cycles of full-matrix least-square refinement and difference-Fourier syntheses. A difference map revealed substantial electron density near both ortho carbons of one phenyl ring, suggesting that the fluorine of this ring is disordered.

In the final refinement the positions and anisotropic thermal parameters of all non-hydrogen, non-fluorine atoms were refined. There was no evidence of disorder in the fluorine F(12), and its position and isotropic thermal parameters were refined. The

(19) The UCLA Crystallographic Computing Package was utilized in solution and refinement of the structure.

fluorine atom of the other phenyl ring is disordered between the two ortho positions; the occupancy factor of F(26) is 0.563 and that of F(22) 0.437. Positions for the two partial fluorine atoms were refined with their isotropic thermal parameters constrained to be the same and with the sum of their occupancies, as well as the sum of the occupancies of the disordered ortho hydrogens, each constrained to be 1.0. The positions of the phenyl hydrogen atoms were calculated, and they were included as fixed contributors with isotropic thermal parameters fixed at 5.6 Å^2.

NMR Spectroscopy. Fluorine spectra at 282 MHz were collected with either a Nicolet NT300 or a General Electric GN300 spectrometer, while fluorine spectroscopy at 470 MHz employed a General Electric GN500spectrometer. In all cases 10-mm samples were used with acetone-d_6 (Aldrich) as the solvent for low-temperature (−90 to 25 °C) spectra and a mixture of cyclohexanone and acetone-d_6 (60/40) as the solvent at higher temperatures (25–100 °C). The deuterium of the solvent provided a lock signal. Samples were approximately 0.01 M in solute for the low temperature studies and 0.05 M at temperatures above ambient. Sample temperatures were regulated with the controllers supplied with each instrument and are believed to be accurate to at least ±1 °C. Fluorine COSY spectra were obtained with the phase cycle of Bax[20] to give quadrature detection in both dimensions and are displayed in absolute value mode.

Theoretical line shapes for a system undergoing two-site exchange were generated by using a program based on the derivation of Johnson[21] and run on an IBM-PC. Computed spectra were compared visually to experimental spectra and the input parameters for the calculations adjusted until good agreement between observed and calculated line shapes was obtained.

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Supplementary Material Available: X-ray crystallographic data for compound II (5 pages). Ordering information is given on any current masthead page.

(20) Bax, A. *Bull. Magn. Reson.* **1985**, *7*, 167–183.
(21) Johnson, C. S., Jr. *Adv. Magn. Reson.* **1965**, *1*, 33.

Synthesis and Biological Activity of 9,11-Dehydrovitamin D_3 Analogues: Stereoselective Preparation of 6β-Vitamin D Vinylallenes and a Concise Enynol Synthesis for Preparing the A-Ring[1a-c]

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The $\Delta^{9(11)}$-unsaturated vitamin D analogues **5a** and **5b** are of biochemical interest because they are incapable of tautomerizing via a [1,7]-sigmatropic hydrogen shift to a previtamin structure related to **3** and also because they possess a perturbed π-system. Vitamin **5a** was prepared in eight steps from ketone **18**, with the key steps being the stannylcuprate S_N2' displacement reaction of propargyl benzoate **22** followed by the mild and highly selective fluorodestannylation of allene **23** to afford primarily the 6β-vinylallenes **24a,b**. The enantiomerically pure vitamin D A-ring enyne **38** was prepared in seven steps from (*S*)-(+)-carvone (**29**), with the novel step in this sequence being the SmI_2–Pd^0-mediated transformation of epoxy propargyl acetate **35** to enynol **37**. These two methods were then used to synthesize the trihydroxylated analogue **5b** in 13 steps from (*S*)-(+)-carvone. The analogue **5b** differs from the biologically active hormonal form of vitamin D, 1α,25-dihydroxyvitamin D_3 (**1c**, calcitriol), only by the presence of the double bond at the $\Delta^{9(11)}$-position. Initial in vitro biological screening of vitamins **5a** and **5b** indicate that the 9,11-double bond has only a modest effect on chick intestinal receptor binding, and it therefore seems likely that the vitamin D–previtamin D interconversion is not necessary for the expression of the calcitropic effects of vitamin D.

Introduction

The biosynthesis of vitamin D_3 (**1a**, Scheme I) involves two of the very few known biologically occurring pericyclic reactions.[2] First, 7-dehydrocholesterol (**2**) undergoes (in the skin) a photochemically induced six-electron electrocyclic ring opening to afford previtamin D_3 (**3a**).[3] Second, previtamin D_3 rearranges via a thermal [1,7]-sigmatropic hydrogen shift to afford vitamin D_3 (**1a**). Vitamin D_3 then undergoes hydroxylation in the liver to afford 25-hydroxyvitamin D_3 (**1b**) followed by hydroxylation in the kidney to produce 1α,25-dihydroxyvitamin D_3 [1α,25-$(OH)_2$-D_3, **1c**]. It is the latter compound that acts as a classical steroid hormone to induce the biological effects associated with vitamin D_3 via binding to a receptor protein, which then regulates the expression of certain genes.[4]

(1) (a) This is Paper 35 in the series, Studies of Vitamin D (Calciferol) and Its Analogues. For Paper 34, see: Barrack, S. A.; Gibbs, R. A.; Okamura, W. H. *J. Org. Chem.* **1988**, *53*, 1790. (b) This article was taken in part from the Ph.D. thesis submitted to the University of California, Riverside, by R. A. Gibbs, August, 1988. (c) For preliminary communications of this work, see: Aurrecoechea, J. M.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 4947. Gibbs, R. A.; Okamura, W. H. *Tetrahedron Lett.* **1987**, *28*, 6021. (d) Department of Chemistry. (e) Current address: Dept. of Chemistry, Univ. del Pais Vasco, Bilbao, Spain. (f) Department of Biochemistry.

(2) For general reviews of vitamin D chemistry and biochemistry, see: (a) Norman, A. W. *Vitamin D, the Calcium Homeostatic Steroid Hormones*; Academic Press: New York, 1979. (b) De Luca, H. F.; Paaren, H. E.; Schnoes, H. K. *Top. Curr. Chem.* **1979**, *83*, 1. (c) Georghiou, P. E. *Chem. Soc. Rev.* **1977**, *6*, 83. (d) Fieser, L. F.; Fieser, M. *Steroids*; Reinhold: New York, 1959. (e) Norman, A. W.; Roth, J.; Orci, L. *Endocrine Rev.* **1982**, *3*, 331. (f) De Luca, H. F.; Schnoes, H. K. *Ann. Rev. Biochem.* **1983**, *52*, 411.

(3) (a) MacLaughlin, J. A.; Anderson, R. R.; Holick, M. F. *Science* **1982**, *216*, 1001. (b) Holick, M. F.; MacLaughlin, J. A.; Doppelt, S. H. *Science* **1981**, *211*, 590. (c) Holick, M. F.; MacLaughlin, J. A.; Clark, M. B.; Holick, S. A.; Potts, J. T., Jr.; Anderson, R. R.; Blank, I. H.; Parrish, J. A.; Elias, P. *Science* **1980**, *210*, 203. (d) For another possible example of a biological pericyclic reaction (the rearrangement of chorismate to prephenate) see: Guilford, W. J.; Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5013 and references cited therein.

0022-3263/89/1954-4072$01.50/0