Using Pentafluorophenyl as a Lewis Acid To Stabilize a Cis Secondary Amide Conformation
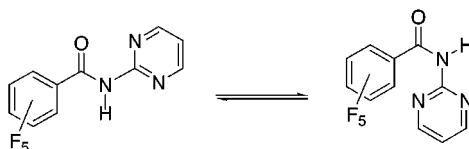
Christopher C. Forbes, Alicia M. Beatty, and Bradley D. Smith*

*Department of Chemistry and Biochemistry, University of Notre Dame,
Notre Dame, Indiana 46556-5670*

smith.115@nd.edu

ABSTRACT

N-(Pyrimidin-2-yl)pentafluorobenzamide adopts a cis amide bond in the solid state with a pyrimidyl nitrogen pointing toward the center of the perfluorophenyl ring. In solution, the compound is a mixture of cis and trans rotamers. The conformational equilibrium is strongly solvent dependent, and the cis rotamer is entropically favored. It is proposed that the entropic driving force is decreased solvation of the two aryl groups when in the cis conformation.

The noncovalent interaction of fluorinated compounds with other organic molecules continues to be an active area of investigation, with potential applications in pharmaceutical science,[1] separations,[2] reaction catalysis,[3] and materials science.[4] One of the better known examples is hexafluorobenzene which has an electric quadrupole moment similar in magnitude but opposite in sign to the quadrupole moment of benzene.[5] The co-facial interaction of benzene with perfluorobenzene is well-documented[4] and is a good example of the polar nature of aromatic rings. In this Letter we address experimentally the question of whether the center of a perfluorophenyl ring can act as a Lewis acid. There is scattered literature evidence in support of this hypothesis. A previous theoretical study of the interaction between hexafluorobenzene and small electron-donor molecules uncovered stable complexes with the donors pointing lone pair electrons toward the center of the pentafluorophenyl ring.[6] Similarly, there is theoretical and experimental evidence of a favorable interaction between the oxygen lone pairs in water and hexafluorobenzene.[7] Moreover, this effect is thought to play a role in the photosplitting of water in the presence of perfluorophenylenes.[8] Finally, a recent X-ray crystal structure of the enzyme carbonic anhydrase II, bound by 2 molar equiv of an inhibitor containing a perfluorophenyl ring, shows a close contact (2.9 Å) between a carbonyl oxygen and the center of a perfluorophenyl.[9]

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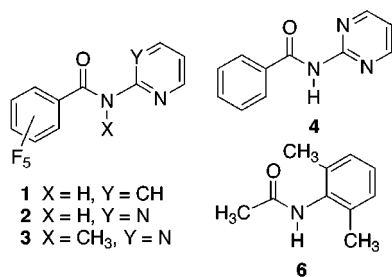(5) Williams, J. H. *Acc. Chem. Res.* **1993**, *26*, 593−598.

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Acyclic secondary amides typically prefer a trans (or Z)[10] conformation about the amide C−N bond;[11] however, there is literature evidence that the conformational equilibrium can be affected by noncovalent interactions. For example, cis (or E)[10] amides can be stabilized by hydrogen bonding templates,[12] electrostatic attraction,[13] and hydrophobic effects.[14] In addition, protein structures show a preference for one of the amino acid residues involved in a cis amide bond to be an aromatic group, suggesting that aromatic residues are able to stabilize the cis conformation via C−H...π interactions.[15] Here we present a study of acyclic amides **1**−**3** and highlight a case were a cis amide is apparently stabilized by a nitrogen lone pair−pentafluorophenyl interaction.

1 X = H, Y = CH
2 X = H, Y = N
3 X = CH₃, Y = N

6

Amides **1**−**3** were prepared in straightforward fashion[16] and crystallized, and their solid-state structures were determined by X-ray crystallography.[17] As shown in Figure 1, the amide bond conformation is trans in compound **1** whereas it is cis in compounds **2** and **3**. In the cases of **2** and **3**, the plane of the pyrimidyl ring is rotated relative to the perfluorophenyl ring by 68° and 64°, respectively, and a pyrimidyl nitrogen is 3.39 and 3.42 Å, respectively, from the center of the perfluorophenyl ring. It is relevant to note that *N*-(pyrimidin-2-yl)benzamide **4** has a trans amide bond in the solid state.[18]
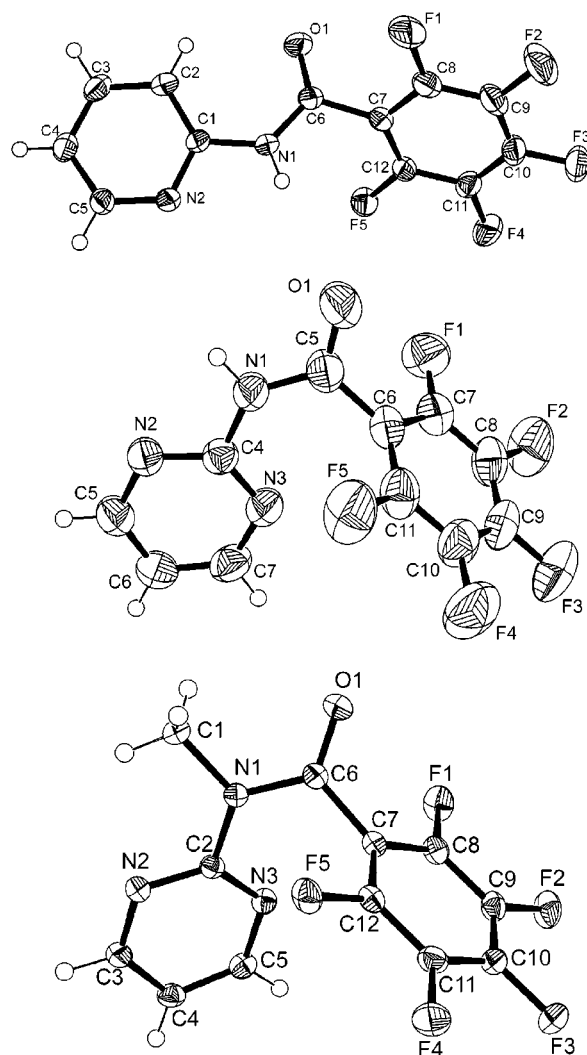
Figure 1. X-ray crystal structures of compounds **1** (top), **2** (middle), and **3** (bottom). All crystal structures show 50% ellipsoid probability. Compounds **1** and **3** were analyzed at low temperature while compound **2** was analyzed at room temperature.

The solution-state structures of secondary amides **1**−**3** were characterized by variable temperature, multinuclear NMR spectroscopy. A solution of **1** in CDCl₃ exhibits a single set of ¹⁹F and ¹H resonances down to −60 °C. Thus, it appears that this compound remains as the trans conformation at all temperatures. Compound **3** also maintains a single set of ¹⁹F and ¹H resonances down to −60 °C although the chemical shifts differ from those of **1**. It appears that this compound remains as the cis conformation at all temperatures which is expected for an *N*-acyl-*N*-methylarene derivative.[19] Compound **2** is a equilibrating mixture of cis and trans isomers in solution. The ¹⁹F NMR spectrum in CDCl₃ is broad at room temperature and resolves into two sets of peaks

(10) Even though cis/trans is ambiguous nomenclature, we have chosen to employ it so as to remain consistent with the majority of papers on amide bond structure.

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(16) Select spectroscopic data: **1**, ¹H NMR (CDCl₃) δ 9.20 (s, 1H), 8.32 (d, 1H, *J* = 8.4 Hz), 8.14 (m, 1H), 7.80 (m, 1H), 7.11 (ddd, 1H, *J* = 7.2, 5.0, 1.1 Hz); ¹⁹F NMR (CDCl₃/CFCl₃, 25 °C) δ −140.3 (d, 2F, *J* = 19.5 Hz), −149.8 (t, 1F, *J* = 22.1 Hz), −159.8 (m, 2F); MS, *m/z* 289 (M⁺); mp = 116 °C (dec). **2**, ¹H NMR (CDCl₃) δ 7.11 (t, 1H, *J* = 5.0 Hz), 8.62 (d, 2H, *J* = 5.0), 10.67 (s, 1H); ¹⁹F NMR (CDCl₃/CFCl₃, 25 °C) δ −141.4 (s, 2F), −152.0 (s, 1F), −161.4 (s, 2F); MS *m/z* 290 (M⁺); mp = 140 °C (dec). **3**, ¹H NMR (CDCl₃) δ 7.04 (t, 1H, *J* = 5.0 Hz), 8.46 (d, 2H, *J* = 5.0), 3.70 (s, 3H); ¹⁹F NMR (CDCl₃/CFCl₃, 25 °C) δ −142.6 (d, 2F, *J* = 15.3 Hz), −153.9 (t, 1F, *J* = 22.1 Hz), −162.2 (m, 2F); MS *m/z* 304 (M⁺); mp = 88 °C (dec).

(17) X-ray data for **1**−**3** can be retrieved from the Cambridge Crystallographic Data Center using deposition numbers CCDC 170474 (**1**), CCDC 170475 (**2**), and CCDC 170476 (**3**).

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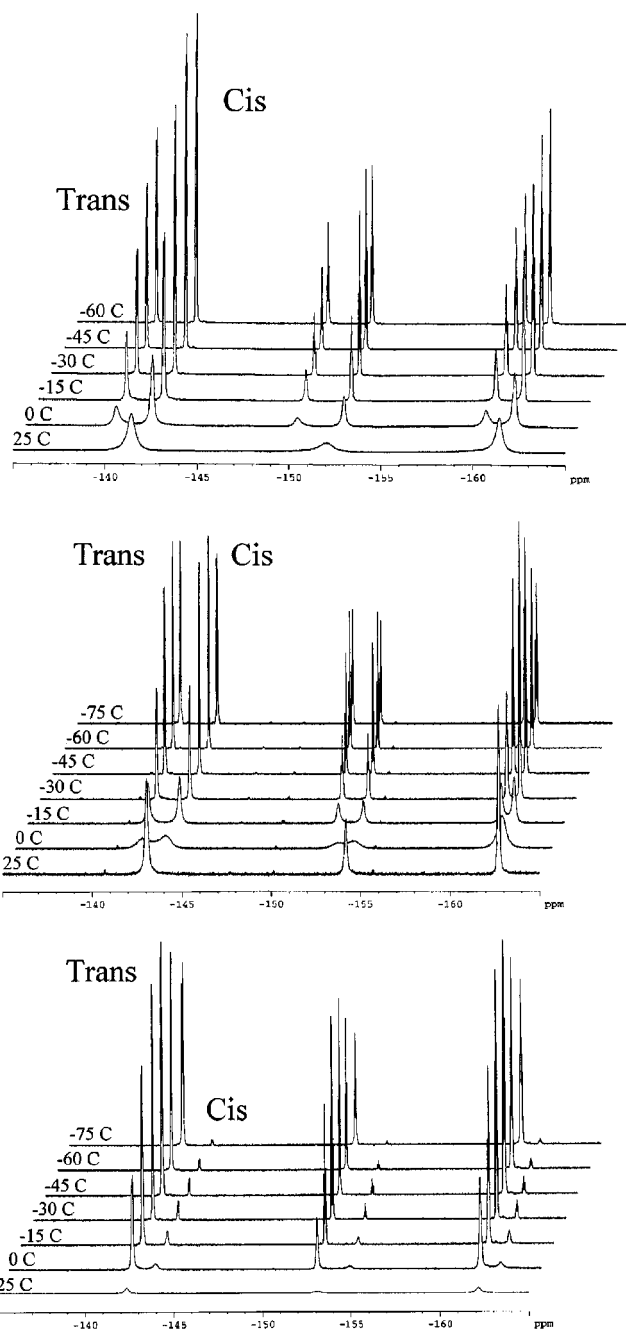
Figure 2. ^{19}F NMR spectra of **2** (34 mM) at different temperatures in CDCl$_3$ (top), acteone-d_6 (middle), and methanol-d_4 (bottom). Referenced to CFCl$_3$ at 0 ppm.

at lower temperatures (Figure 2). For each pair of resolved peaks, the upfield signal is assigned as the cis conformer for the following reasons: (i) The ^{19}F chemical shifts for compounds **1−3** are listed in Table 1 and are highly consistent with the upfield peaks corresponding to the cis conformation. (ii) An ^{19}F spectrum acquired in CDCl$_3$ at −30 °C in the presence and absence of 5 molar equiv of the

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Table 1. [19]F Chemicals Shifts in CDCl$_3$ at −30 °C[a]

compound	F_{ortho}	F_{para}	F_{meta}
trans-**1**	−139.9	−149.4	−159.4
trans-N-phenyl pentafluorobenzamide	−139.9	−149.1	−159.1
trans-**2**	−139.6	−149.0	−159.5
cis-**2**	−141.7	−151.7	−161.1
cis-**3**	−142.3	−152.6	−161.2

[a] Referenced to CFCl$_3$ at 0 ppm.

hydrogen bonding donor−acceptor-donor triad, **5** (which is expected to stabilize the cis conformation of **2**, by forming the supramolecular complex in Figure 3[20]), shows that the
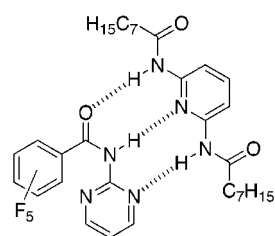

Figure 3. Likely supramolecular complex between *cis*-**2** and template **5**.

upfield peaks increase substantially in intensity in the presence of template **5**. (iii) The upfield NMR peaks increase slightly in intensity when the concentration of the sample is increased 5-fold; this is attributed to stabilization of the cis rotamer due to weak homodimerization.[21]

The cis/trans ratio for **2** (34 mM) at −30 °C is 1.54 in CDCl$_3$, 1.01 in acetone-d_6, and 0.08 in methanol-d_4. This strong solvent dependence is in contrast to the situation with N-methylformamide and N-methylacetamide whose cis/trans equilibria are essentially insensitive to solvent polarity,[22] but it is in line with a recent report that the cis rotamer of a secondary amide with large hydrophobic groups attached to the nitrogen and carbonyl is stabilized in water.[14] It appears that in the case of **2** there is a significant difference in the solvation of the cis and trans conformers. The variable temperature spectra displayed in Figure 2 show that the fraction of cis conformation decreases as the temperature is lowered (in general agreement with previous reports[14,23]). Van't Hoff plots of the trans to cis isomerization data provides ΔH = +0.7 kcal/mol, ΔS = +3.9 cal/mol·K for CDCl$_3$; ΔH = +0.6 kcal/mol, ΔS = +2.4 cal/mol·K for acetone-d_6; ΔH = +3.7 kcal/mol, ΔS = +10.2 cal/mol·K for methanol-d_4. Thus, in all three solvents the isomerization

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of trans to cis conformation is entropically favored. Since cis and trans amide bonds are thought to have similar degrees of solvation,[24] it is likely that the entropic driving force for compound **2** is decreased solvation of the two aryl groups when in the cis conformation.

To learn more about the isomerization thermodynamics for secondary *N*-aryl amides, we examined 2,6-dimethyl-*N*-acetanilide, **6**, as a control compound that is known to have a measurable fraction of cis conformer in $CDCl_3$.[12a] The conformational equilibrium for **6** (34 mM) is also solvent dependent. For example, at -30 °C the cis/trans ratio is 0.26 in $CDCl_3$ and 0.03 in acetone-d_6. Van't Hoff plots of the trans to cis isomerization for **6** provides $\Delta H = +0.6$ kcal/mol, $\Delta S = +0.2$ cal/mol·K for $CDCl_3$; $\Delta H = +1.7$ kcal/mol, $\Delta S = +0.1$ cal/mol·K for acetone-d_6. Thus, in the case of **6** there is negligible entropic effect on cis/trans isomerization.

In summary, we report experimental evidence for an intramolecular perfluorophenyl−lone pair interaction that is sufficiently strong to bias the cis/trans conformational equilibrium for a secondary amide. We find that the cis/trans ratio is strongly solvent dependent and that the cis rotamer is entropically favored. This result is contrary to the literature knowledge on secondary amides with very small groups attached to the nitrogen and carbonyl,[21] but it is in line with a study of amides with larger substituents.[14] Our results support the hypothesis that a perfluorophenyl group can act as a Lewis acid.

Supporting Information Available: Van't Hoff plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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