Conformational and Configurational Dynamics of a Highly Fluorinated Hydrazone

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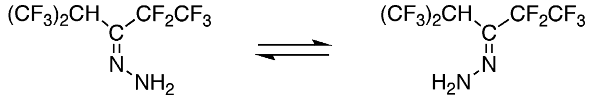
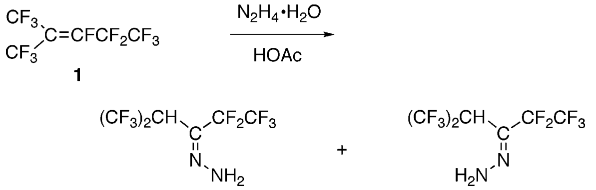


The relative populations of two rotamers in the hydrazone of 2*H*-perfluoro-2-methyl-3-pentanone can be altered from one extreme to the other by increasing the Lewis basicity of the solvent, and the equilibrium *E*/*Z* ratio grows correspondingly. Both trends reflect an increase in the effective size of the amino group as a result of hydrogen bonding. The rate of *E*/*Z* interconversion is insensitive to the choice of solvent, consistent with the conclusion that the isomerization occurs via N-inversion and not C═N bond rotation.

Introduction

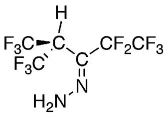
Furin et al. have reported that treatment of perfluoro-2-methyl-2-pentene (**1**) with hydrazine hydrate in acetic acid yields hydrazone **2** as a 2.1:1 mixture of *Z*- and *E*-isomers, respectively, characterized by ^{1}H, ^{13}C, and ^{19}F NMR spectra.[1] We repeated the preparation of **2** to study the interesting transformation it undergoes upon treatment with triethylamine.[2] In the course of that investigation, we observed in the hydrazone striking behavior that became the subject of this report.



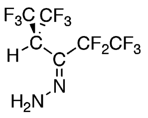
Results and Discussion

The (H, F) NOESY spectrum of the stereoisomeric mixture revealed that the major isomer is the *E* form and not the *Z* form as reported. In the dominant isomer, interaction was found between the *geminal* CF$_3$ fluorines and N−H protons but not between the N−H protons and the CF$_2$ fluorines. Correspondingly, the minor isomer displayed the latter interaction but not the former.

Conformational Structure and Dynamics.[3] The ^{19}F NMR spectrum in CDCl$_3$ of the mixture comprises three signals for each isomer,[1] but we found that in CD$_3$CN each of the signals for the *E*-isomer, but not the *Z*, is doubled. The geminal CF$_3$ groups in the *E* form appear at δ −59.8 and −61.3. The other CF$_3$ group appears at δ −79.4 and −79.5, and the CF$_2$ appears at δ −106.2 and −108.1. The doubling signifies the existence of two rotamers about the C2−C3 bond, present in the ratio 3:2, that do not interconvert on the NMR time scale rapidly enough at room temperature for line broadening to occur. However, the (H, F) NOESY of the CD$_3$CN solution at room temperature failed to distinguish between the two rotamers because their interconversion was fast enough that each rotamer appeared to have interactions characteristic of both. It was nonetheless possible to assign the rotamer conformations as **2E$_1$** and **2E$_2$** for the low- and high-field sets of signals, respectively, as described below. Calculated geometries[4] for the two rotamers are shown in Figure 1. When a CD$_3$CN solution of **2** was heated in the NMR probe, the pairs of ^{19}F NMR signals broadened and coalesced. By extrapolation of the rotamer chemical shifts from the slow exchange regime and line shape simulation, the barrier to rotation (for the major form) was found to be $\Delta G^{\ddagger}$ =



2E$_1$



2E$_2$

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[1] Furin, G. G.; Chi, K.-W.; Protsuk, N. I.; Lopyrev, V. A. *Zh. Org. Khim.* **2001**, *37*, 1693.

[2] Ramanathan, S.; Lemal, D. M. *J. Org. Chem.* **2007**, *72*, 1570.

[3] For a general discussion of conformational and configurational isomerism in hydrazones, see: Karabatsos, G. J.; Taller, R. A. *Tetrahedron* **1968**, *24*, 3923.

10.1021/jo061945n CCC: $37.00

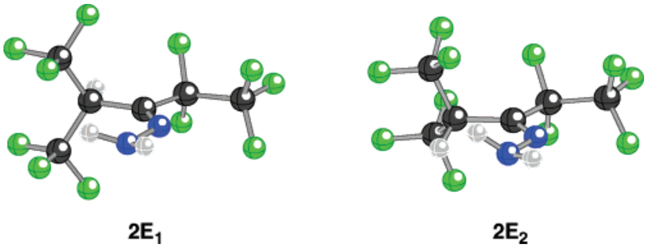


FIGURE 1. Rotamer geometries for hydrazone **2E**, calculated at the B3LYP/6-31G* level of theory.

TABLE 1. Variation with Solvent of the Rotamer Composition for Hydrazone 2E

solvent	% $2E_1$	solvent	% $2E_1$
chloroform	100	*t*-butyl methyl ether	54
bromobenzene	98	tetrahydrofuran	50
furan	97	pyridine	41
diphenyl ether	95	formamide	39
anisole	86	dimethylformamide	11
benzonitrile	63	dimethyl sulfoxide	4
acetonitrile	62	dimethylpropyleneurea	3
diethyl ether	59	hexamethylphosphoramide	~0

TABLE 2. Equilibrium (*K*) and Rate (*k*) Constants for Interconversion of the *E*- and *Z*-Isomers of Hydrazone 2

solvent	temp (°C)	K_{ZE}	$(k_{ZE} + k_{EZ}) \times 10^4\ s^{-1}$	$k_{ZE} \times 10^4\ s^{-1}$	$k_{EZ} \times 10^4\ s^{-1}$
C_6H_5Br	52	1.7	2.2 ± 0.2	1.4	0.81
CH_3CN	73	2.2			
$(C_2H_5)_2O$	50	2.3	2.7 ± 0.2	1.8	0.79
DMSO	52	14	3.8 ± 0.5	3.5	0.28
DMPU	50	30	3.5 ± 0.2	3.4	0.11
HMPA	50	v. large			

16.3 ± 0.1 kcal/mol at 84 °C, a high barrier for rotation about a single bond.

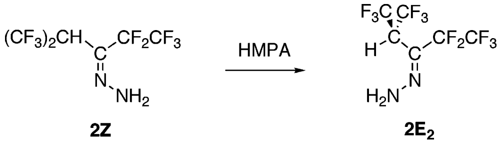
A priori, the absence of signal doubling in $CDCl_3$ could mean either that there is a single *E* rotamer in that solvent or that rotamers $\mathbf{2E_1}$ and $\mathbf{2E_2}$ interconvert rapidly at room temperature. To answer this question, a solution of **2** in methylene chloride (lower freezing point than that of chloroform) was cooled to −90 °C, but no broadening, let alone decoalescence, of the three **2E** resonances was observed. The conclusion that only one rotamer was present was confirmed by an (H, F) NOESY and a COSY experiment in $CDCl_3$. Interaction of the C−H proton with the CF_2 group, but not with the NH_2 group, was found, showing that the single rotamer is $\mathbf{2E_1}$. To assign the conformations of the rotamers in CD_3CN, it was only necessary to dilute a $CDCl_3$ solution of **2** with successive increments of CD_3CN and to observe the appearance of a second set of signals with concomitant decay of the original set. This experiment revealed that the major rotamer in CD_3CN is $\mathbf{2E_1}$, the sole one in $CDCl_3$.

We hypothesized that hydrogen bonding to the amino hydrogens by the Lewis basic solvent acetonitrile increases the effective bulk of the amino group and develops steric interactions with the flanking CF_3 groups.[5] Thus, in a relatively noninteracting medium, $\mathbf{2E_1}$ is the lower energy form, but as it becomes crowded, it approaches rotamer $\mathbf{2E_2}$ in energy. The latter rotamer presents only a hydrogen in the direction of the "oversized" amino group.

To test this surmise, we examined the NMR spectra of **2** in a series of solvents varying in Lewis basicity (Table 1). In all but chloroform, both rotamers were present, and the ratio of $\mathbf{2E_2}$ to $\mathbf{2E_1}$ correlated nicely with Lewis basicity.[6] In DMSO, for example, very little $\mathbf{2E_1}$ was present, and in HMPA, it was barely detectable. That formamide, with its extremely high dielectric constant (111.0),[7] occupies an intermediate position in the solvent series demonstrates that polarity alone does not account for the changes in rotamer populations. Pyridine stands out as an unexplained anomaly, for it behaves like formamide but is the most basic solvent in the table. Whether solvent bulk has an important influence on the rotamer ratio is not clear from our data. From signal broadening with increasing temperature for a variety of solvents in Table 1, we find that rotational barrier heights do not vary greatly from the CD_3CN value, noted above.

***E*/*Z* Isomerization.** In the extensive literature on thermal syn/anti interconversion of hydrazones, described here as *E*/*Z* isomerization, we have found a single N-unsubstituted example, discussed below.[8] There are no examples involving highly fluorinated hydrazones.

As prepared, hydrazone **2** exists as a roughly 2:1 mixture of *E*- and *Z*-isomers, respectively. A solution of this composition in HMPA at room temperature gradually shifted in composition until the *Z* form was no longer detectable by ^{19}F NMR.



Equilibrium constants for *E*/*Z* interconversion were determined in a number of other solvents, as were rate constants for equilibration at 50 °C (Table 2). In DMPU (*N*,*N*′-dimethylpropyleneurea) and DMSO, an increase in the *E*/*Z* ratio was measured starting with the hydrazone as prepared, a ~2:1 *E*/*Z* mixture. To obtain the rate constant in ether, the hydrazone was first equilibrated in DMPU to obtain a mixture highly enriched in the *E* form. The product was dissolved in ether, thoroughly washed with water to remove DMPU, and dried, and then the rate of decrease in the *E*/*Z* ratio was measured. It is apparent from Table 2 that as the Lewis basicity of the solvent increases so does the *E*/*Z* ratio at equilibrium,[5] but the rate of equilibration is quite insensitive to the nature of the solvent.

The predominance of the *E* form in all solvents indicates that the hexafluoroisopropyl group presents less steric interference

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(4) 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.5; Gaussian, Inc.: Pittsburgh, PA, 1998.

(5) Solvents that can H-bond to the N−H hydrogen of aldehyde 2,4-dinitrophenylhydrazones increase the *E*/*Z* ratio. Karabatsos, G. J.; Shapiro, B. L.; Vane, F. M.; Fleming, J. S.; Ratka, J. S. *J. Am. Chem. Soc.* **1963**, *85*, 2784.

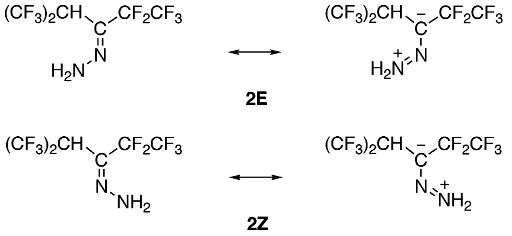
(6) Burden, A. G.; Collier, G.; Shorter, J. *J. Chem. Soc., Perkin Trans. II* **1976**, 1627.

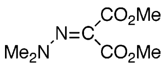
(7) *CRC Handbook of Chemistry and Physics*, 86th ed.; Lide, D. R., Ed.; Taylor and Francis: Boca Raton, 2005; p 15−17.

(8) Krebs, A.; Kimling, H. *Liebigs Ann. Chem.* **1970**, *740*, 126.

to the amino group than the pentafluoroethyl group. Though larger, hexafluoroisopropyl can rotate out of the way to a greater degree than pentafluoroethyl. As the effective bulk of the amino group is enhanced by H-bonding, the initially small difference in steric hindrance increases, causing the population of the *E*-isomer to grow.

Thermal *E*/*Z* isomerization of hydrazones can occur by either of the following two pathways: rotation about the C═N double bond or inversion at that nitrogen. If *E*/*Z* interconversion proceeded via rotation about the C−N bond, the dipolar resonance form of the hydrazone (see below) should play a greater role in the transition state than in the ground state. Because fluoro substituents stabilize the dipolar form, this mechanism must be taken seriously. However, Shvo and Nahlieli have made a strong case that hydrazone **3**, in which the dipolar form should be better stabilized, isomerizes via N-inversion.[9] Our finding that the rate of isomerization for hydrazone **2** shows little solvent dependence seems surprising, as strong H-bonding solvents, by increasing the effective size of the amino group, would be expected to destabilize the ground state relative to the transition state, whichever the mechanism. Perhaps the necessity of reorganizing the solvent en route to the transition state is a compensating factor. Strong H-bonding solvents also enhance the electron density on the terminal nitrogen, an effect that would stabilize the transition state for C═N rotation. The failure of solvents such as DMSO and DMPU to accelerate the reaction significantly gives credence to the view that *E*/*Z* isomerization in hydrazone **2**, like that in **3**, occurs via N-inversion (the lateral shift mechanism).[10,11]





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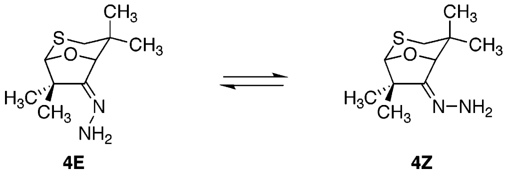
Krebs and Kimling separated and studied the interconversion of the *E*- and *Z*-isomers of hydrazone **4**, the only N-unsubstituted system in the literature for which rate data are available.[8] They found $k = 1.4 \times 10^{-4}$ s^{-1} at 144 °C ($\Delta G^{\ddagger} = 32.0$ kcal/mol) and $k = 1.0 \times 10^{-4}$ s $^{-1}$ ($\Delta G^{\ddagger} = 32.2$ kcal/mol) in benzonitrile for the forward and reverse reactions, respectively. In the four solvents for which rate data have been obtained for the isomers of hydrazone **2**, the rate constants (Table 2) are comparable to those of the German workers even though the reaction temperature was >90 °C lower. The considerable difference in *E*/*Z* interconversion barriers between the two systems is probably attributable primarily to greater ground-state steric hindrance in hydrazone **2**.



Conclusions

Both rotamer populations and equilibrium *E*/*Z* ratios for hydrazone **2** are highly solvent dependent. In the non-Lewis basic solvent chloroform, a single rotamer (**2E$_1$**) is present in the *E* form, but in hydrogen bond accepting solvents, there are two rotamers separated by a substantial barrier ($\Delta G^{\ddagger} = 16.3 \pm 0.1$ kcal/mol in CD_3CN at 84 °C). As the H-bonding ability of the solvent increases, the rotamer populations shift, culminating in virtually complete conversion to the other rotamer (**2E$_2$**) in HMPA. This trend reflects an increase in the effective size of the amino group as a result of H-bonding.

The *E*/*Z* ratio also increases with the Lewis basicity of the solvent because the *E* form is less hindered, and in HMPA, the *Z* form is undetectable. The rate of *E*/*Z* interconversion shows little dependence on solvent, however, consistent with the view that this process involves N-inversion and not C═N bond rotation.

Experimental Section

2*H*-Perfluoro-2-methyl-3-pentanone Hydrazone (2).[1] To a stirred solution of alkene **1** (9 g, 30 mmol) in acetic acid (35 mL) was added hydrazine hydrate (3 g, 60 mmol) dropwise while maintaining the reaction mixture temperature at 0−5 °C. Vigorous stirring was continued at that temperature for 1 h, and then the mixture was heated at 45 °C for 2 h. The reaction mixture was poured in methylene chloride (100 mL), washed with water (100 mL), with saturated sodium bicarbonate solution until it was free from acetic acid, and with water again. It was dried over magnesium sulfate. Methylene chloride was taken off by distillation through a long Vigreux column. Residual solvent was removed at 600 Torr and 50 °C. The hydrazone (yield 6.36 g, 68%) was a mixture of *E*- and *Z*-isomers in the ratio 1.7:1, respectively, and was sufficiently pure for the subsequent step. ^{19}F NMR ($CDCl_3$): δ (*E*-isomer) −61.5 (s, *gem* CF_3, 6F), −81.6 (s, CF_2CF_3, 3F), −111.6 (s, CF_2, 2F). ^{1}H NMR ($CDCl_3$) 6.87 (broad s, NH_2, 2H), 4.07 (septet, $J = 9.0$ Hz, isopropyl H, 1H); (*Z*-isomer) −65.5 (s, *gem* CF_3, 6F), −84.0 (s, CF_2CF_3, 3F); −117.5 (s, CF_2, 2F). ^{1}H NMR ($CDCl_3$): 7.03 (broad s, NH_2, 2H), 3.84 (septet, $J = 7.5$ Hz, isopropyl H, 1H). GC/MS (*m*/*e*): 312 (M^+).

***E*/*Z* Isomerization of Hydrazone 2.** For the kinetic runs in DMPU and DMSO, a ∼2:1 *E*/*Z* mixture was used. In each case, a solution of the hydrazone in an NMR tube was placed in a calibrated probe maintained at the temperature shown in Table 2. Decay of the *Z* form was followed by measuring the relative concentrations of the two isomers as a function of time, using integration of their ^{19}F signals. The rate of interconversion was determined similarly in ether and bromobenzene, but for these solvents, it was necessary to begin with an isomer mixture highly enriched in the *E* form and to observe the decay of that isomer. Accordingly, a ∼2:1 E/Z hydrazone mixture (0.37 g, 1.2 mmol) in 1 mL of DMPU was stirred at 50 °C for 5 h. After cooling, the solution was split into two roughly equal batches. To one was added ether (5 mL), and the solution was washed with water until it was free from DMPU. The ether solution was dried over $MgSO_4$. To the second batch was added cold $CFCl_3$, and the solution was exhaustively washed with cold water until free from DMPU. It was dried over $MgSO_4$, and the solvent was evaporated at 300−350 Torr and room temperature.

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[9] Shvo, Y.; Nahlieli, A. *Tetrahedron Lett.* **1970**, 4273.

[10] Ab initio calculations indicate that simple hydrazones undergo *E*/*Z* isomerization via the inversion pathway. Benassi, R.; Taddei, F. *J. Chem. Soc., Perkin Trans. II* **1985**, 1629.

[11] Regarding the generality of the inversion mechanism, see: Paetzold, R.; Reichenbächer, M.; Appenroth, K. *Z. Chem.* **1981**, *21*, 421 and references therein.

Acknowledgment. The authors thank the National Science Foundation for support of this work. They are greatly indebted to Mr. Wayne Casey for guidance with NMR experiments.

Supporting Information Available: *Z* matrices and total energies at the B3LYP/6-31G* level of theory for hydrazone rotamers **2E$_1$** and **2E$_2$** and the (F, H) NOESY spectrum of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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