N- vs O-Protonation and the Transannular Substituent Interaction in 8-(Dimethylamino)-1-acetonaphthone

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Dynamic NMR measurements of 8-(dimethylamino)-1-acetonaphthone **1** in neutral solutions reveal a solvent dependency of the barrier to NMe group interchange similar to that reported for *N*,*N*-dimethylacetamide. Titrating **1** with TFA in solvents of varying donicities gives rise to equilibrium mixtures of N-protonated aminoketone **2** and the O-protonated transannular addition product **3**, the interconversion rate of which is slow on the NMR time scale at ambient temperature. The preference for O- or N-protonation is medium-dependent, the amount of N-protonated **2** increasing with a decrease in the nucleophilicity of the solvent. The set of equilibria which govern the interconversion of **2** and **3** in the titration mixtures are identified and their equilibrium constants evaluated from the NMR data. X-ray analysis of the crystalline trifluoroacetate salt of O-protonated **3** indicates that the transannular N···CO bond of **3** is formed to an extent of only 80%. The equilibrium distribution of **2** and **3**, paired with the tetrafluoroborate anion, depends on both the nucleophilicity and the polarity of the solvent. In $PhNO_2$ the enthalpy change **3** → **2** amounts to 2.6 kcal/mol.

Introduction

Interaction, through space, between tertiary amino and carbonyl moieties was first discovered in cyclic azaketones by Leonard and co-workers[1] in the 1950's. Since then, transannular >N···CO interplay has been observed in a number of other flexible bifunctional molecules and studied by a variety of physical, chemical, and spectroscopic methods.[2] There has been a suggestion of its potential importance in the physiological activity of relevant biomolecules.[3] The interaction, which Leonard referred to as transannular amide resonance, is believed to involve the shifting of electronic charge from the nucleophilic amino nitrogen to the antibonding π^* orbital of the electrophilic carbonyl carbon.[4]

Of great interest is a report by Dunitz et al.[5] of intramolecular donor−acceptor N···CO interaction in crystalline 8-(dimethylamino)-1-acetonaphthone **1**. Here the rigidity of the hydrocarbon framework and the particular placement of the substituents gives rise to a conformationally restricted system with a very short transannular distance and a stereoelectronic arrangement of the donor−acceptor pair that is especially conducive to through-space orbital overlap. Crystallographic analysis showed unidirectional in-plane displacements of the exocyclic substituent bonds and pyramidization of the carbonyl carbon out of the Ar/O/Me plane in the direction of the nitrogen atom. These geometric distortions were ascribed by Dunitz to the onset of sp^2 → sp^3 conversion of the carbonyl carbon.[6]

The chemistry of **1** in solution has not been investigated. Because nucleophilic addition of neutral functional groups results in higher dipole moments, the interaction between the substituents of **1** could be quite sensitive to solvent properties. For **1** dissolved in protonating media, there arises, in addition, the question of choice, as in the case of amides, between two proximate, conformationally fixed, and electronically linked protonation sites, the dimethylamino nitrogen and the carbonyl oxygen.

It was the purpose of the present work to use ^1H and ^{13}C NMR spectroscopy to investigate the behavior of the electrophile−nucleophile substituent pair of **1** in neutral and acidic nonaqueous environments.

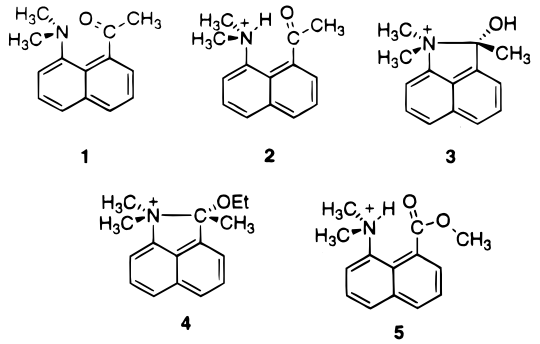

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Table 1. Rotational Barriers for *N*-Methyl Group Exchange and Solvent-Dependent ^{13}C NMR Shift Changes of 1.

solvent (ϵ)	$\Delta G^{\ddagger}$, (298.15K)	δ CO	ΔC1[a]	ΔC8[b]	E_T
$(CD_3)_2CO$ (20.7)	14.005	200.010	141.252[c]	150.568[c]	42.2
$PhNO_2$ (34.8)		200.435	−0.143	−0.241	42.0
DMSO (48.9)		200.539	−0.333	−0.150	45.0
CD_3CN (38.0)		200.856	−0.127	0.051	46.0
$CDCl_3$ (4.8)	14.057	201.540	−0.702	−0.438	39.1
CD_2Cl_2 (9.1)	14.069				
HOAc (6.2)		202.409	−1.728	−0.759	51.2
CD_3OD (32.7)	14.610	203.459	−1.081	−0.515	55.5
TFE (26.1)	15.279	205.970	−1.992	−0.919	59.5
3, $PhNO_2$		120.115	−6.081[d]	−6.016[d]	

[a] ΔC1 = δ ^{13}C1 (solvent i) − δ ^{13}C1 (acetone-d_6). [b] ΔC8 = δ ^{13}C8 (solvent i) − δ ^{13}C8 (acetone-d_6). [c] The chemical shift relative to δ $^{13}C_6H_{12}$ = 26.92. [d] ΔCi(**3**) = δ ^{13}Ci(**3**) − δ ^{13}Ci(**1**), in $PhNO_2$.

8-(Dimethylamino)-1-acetonaphthone 1 in Neutral Solvents. At ambient temperatures the ^{1}H and ^{13}C NMR spectra of **1** in neutral solvents show broadened NMe_2 resonances due to slow interchange of the *N*-methyl group environments. Experimental barriers to this exchange for **1** in CD_2Cl_2, $CDCl_3$, acetone, methanol, and TFE (2,2,2-trifluoroethanol) were obtained by dynamic ^{1}H NMR spectroscopy and are summarized in Table 1. The rate of interchange is seen to decrease with the ability of the solvent to act as H bond donor. One obtains the same linear correlation between $\Delta G^{\ddagger}$ (298 K) and the empirical solvent parameter E_T as that reported for *N*,*N*-dimethylacetamide in a more extensive series of solvents[7] except that the barrier for **1** is lower by 3.5 kcal/mol (Figure 1a).

The rotational barrier of amides has been attributed to the partial double bond character of the C−N bond which arises from resonance in the ground state of the molecule, a stabilizing interaction that is lost on rotation of the amino group. Because transannular N···CO interaction as in **1** similarly involves the delocalization of charge by means of properly oriented orbitals, it is reasonable that the rotational barriers of these two molecules could have similar solvent dependencies.

The ^{13}C shifts of **1**, measured in a more comprehensive series of neutral solvents, are given in Tables 1 and 6S (Supporting Information). Here an increase in the polarity and/or H bonding ability of the solvent leads to a progressive downfield movement of the ^{13}CO resonance with concomitant upfield shifts of the resonances of C1 and C8 ($\Delta\delta$ ^{13}C1 > $\Delta\delta$ ^{13}C8). The three shifts correlate smoothly, though nonlinearly, with E_T, except for **1** in chlorinated solvents, which are known for their anomalous effects on NMR resonances (See Figure 1b for the correlation of δ ^{13}CO). However, $sp^2 \rightarrow sp^3$ conversion of the carbonyl carbon of **1** through acid-catalyzed N−CO bond formation (**3**, vide infra) causes an 80-ppm upfield shift of δ ^{13}CO. Transannular N···CO interaction in the azaketones likewise resulted in the carbonyl shift being upfield of the shift of the corresponding monofunctional ketones. Although ^{13}C NMR shifts depend on a number of parameters, the relative contributions of which are often difficult to assess, the trend of solvent-induced downfield movements of δ^{13}CO observed here for **1** in neutral media is more in line with increasing charge separation within the carbonyl group than with additional transfer of charge from NMe_2 to CO. The direction and relative magnitudes of the shift changes of C1 and C8 of **1** support this idea because introducing positive charge within the substituent moiety of monosubstituted benzenes has been shown to cause shielding of the ipso carbon resonance.[8] In the case of 1-substituted naphthalenes,[9] there is, in addition, a smaller upfield shift of the resonance of the adjacent unsubstituted C8, as is observed here. Thus the increase in the rotational barrier of **1** may be largely the result of greater stabiliza-

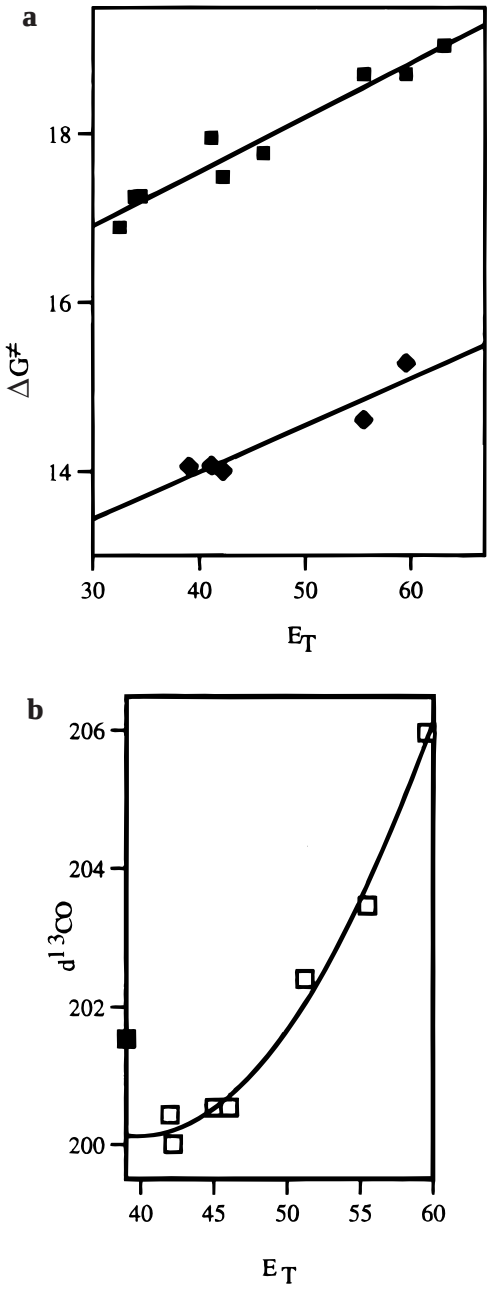

Figure 1. (a) Free energy of rotation of acetamide (■) and 8-(dimethylamino)-1-acetonaphthone 1 (♦) at 298 K. (b) Correlation of the ^{13}CO NMR shift with the solvent parameter, E_T.

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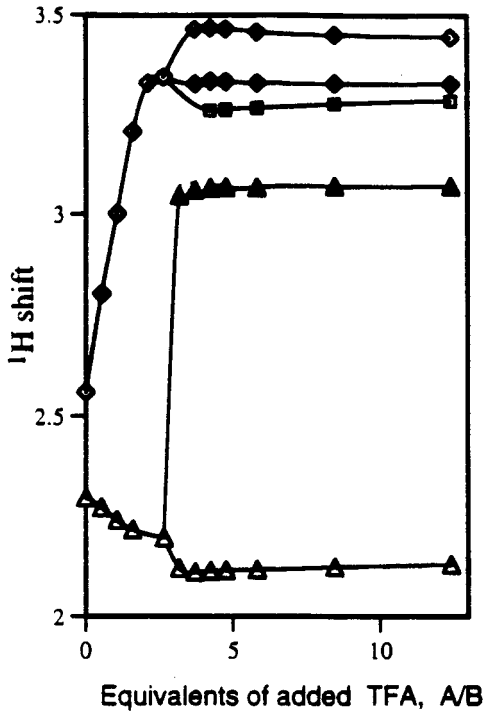

Figure 2. ^{1}H NMR shifts of NMe_A (◊), NMe_B(□), COMe of **3** (△), and of $^+NHMe_2$(♦) and COMe of **2** (▲), as function of equivalents of added TFA in the titration of **1** in CD_2Cl_2.

tion of the ground state conformation by means of increasingly favorable electrostatic interaction between the NMe_2 lone electron pair and an increasingly polarized carbonyl bond.

Protonation of Ambident Sites in 1. Spectra of **1** in neat acetic acid (pK_a = 4.75) show only hydrogen bonding between the acid and the carbonyl oxygen. However, titrating **1** with trifluoroacetic acid (TFA; pK_a = 0.51[10]) in CD_2Cl_2, $PhNO_2$-d_5, or CD_3CN produces changes in the NMR spectrum which can be ascribed to the formation of mixtures containing free base **1**, N-protonated **2**, and the O-protonated transannular addition product **3**. With fewer than 2 equiv of TFA in solution (TFA/(**1**) = A/B < 2), these species are in rapid equilibrium because the proton NMR spectrum shows only time-averaged signals. As more TFA is added, the progressive depletion of free base causes the rate of this intermolecular proton transfer to decrease.[11,12] The averaged signals gradually split into the separate resonances of **2** and **3**, and one observes coupling between the *N*-methyl and NH hydrogens of **2** which amounts to ca. 4.7 Hz, a value typical of protonated NMe_2 moieties. Figure 2 demonstrates these trends for selected ^{1}H NMR resonances of **1** in CD_2Cl_2. Similar titration curves were obtained for **1** in the other two solvents, but the titration in more basic acetone-d_6 produced only equilibrium mixtures of **1** and **3** .

X-ray analysis of the crystalline 1:1 trifluoroacetate salt of **3**, obtained by precipitation from dichloromethane−ether solution, shows the presence of two independent, nonsuperimposable mirror image molecules (ORTEP drawing, Figure 3S, Supporting Information). Table 2 lists selected geometric parameters for one of these structures. Here the transannular $^+$N−C(OH) bond length is 1.679 Å, much greater than typical $^+$N−C distances in pyrrolidinium moieties (at most, 1.507 Å)[13] or the 1.42−1.62 Å C−C single bond distance in a number of similarly strained acenaphthenes.[14] In contrast, the length of the C−O(H) bond is only 1.37 Å, compared to 1.42 Å, the typical value for the exocyclic C−O bond of glycopyranoses.[15,16] By using the experimental bond lengths of **3** in equations formulated by Bürgi et al.,[17] one obtains bond orders (*n*) of 0.76 and 1.20, respectively, for the N−CO and C−(OH) single bonds. These numbers indicate that the transannular N−CO bond in **3** has gone to only 80% completion and must, therefore, be quite labile. The two CO bonds of the trifluoroacetate counterion differ in length by an average 0.03 Å (enantiomeric ion pairs), the longer of these being that nearest the hydroxyl group of the cation. This difference is like that reported for the trifluoroacetate complex of protonated pyridine[18] and suggests the presence of inter-ion H bonding between the hydroxyl hydrogen of cation **3** and one carboxylate oxygen of TFA^-. The corresponding average O···O distance is 2.562 Å, well within the 2.5−2.8 Å range generally observed for O···H···O hydrogen bonds.[19] The other, slightly less electron-rich carboxylate oxygen of TFA^- lies 3.811 Å away from the positively charged nitrogen, allowing for favorable inter-ion electrostatic interaction.

Table 2. Selected Bond Lengths and Bond Angles of Crystalline 3,TFA$^-$

bond angles (deg)		bond lengths (Å)	
N1−C8−C9	110.2	N1−C11	1.679
N1−C8−C7	127.9	N1−C8	1.469
C11−C1−C2	130.6	N1−C13	1.503
C11−C1−C9	111.1	C11−C1	1.525
C8−C9−C1	113.2	C11−C12	1.498
C8−N1−C11	105.1	C11−O1	1.371
C1−C11−O1	110.5	C15−O3	1.215
C12−C11−O1	111.9	C15−O2	1.229

Table 3 summarizes the ^{13}C chemical shifts of **2** and **3** in solution with excess TFA and of **3** as the tetrafluoroborate salt. Included, for comparison, are the shifts of the tetrafluoroborate salts of the *O*-ethyl derivative **4** and of N-protonated methyl dimethylamino carboxylate **5**,

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Table 3. ^{13}C NMR Shifts[a] of Cations 2−5

Ci	**3**,BF_4^- $PhNO_2$	**3**, A/B = 18.5 CD_3CN	**3**,BF_4^- CD_3CN	**4**,BF_4^- CD_3CN	**2**·TFA, neat	**5**·BF_4^- $PhNO_2$	**5**·TFA, neat
C1	135.03	134.85	135.09	133.02	130.76	122.57	122.45
C2	122.09	122.08	122.09	123.09	141.23	137.42	138.92
C3	130.14	130.28	130.37	130.44	127.68	127.14	126.95
C4	127.39	127.61	127.56	127.91	140.33	137.78	138.96
C5	127.26	127.61	127.56	127.77	134.62	133.57	134.40
C6	129.21	128.85	129.08	129.14	126.51	126.13	126.54
C7	115.13	115.38	115.65	115.39	122.79	123.45	122.61
C8	144.31	144.40	144.54	145.15	138.67	138.23	137.58
C9	126.59	126.38	127.04	127.14	123.32	123.47	123.43
C10	131.53	132.00	131.73	131.83	137.44	136.16	136.65
NMe_A[b]	50.66	49.64	49.66	52.54	46.45	47.46	46.96
NMe_B	48.011	49.08	49.21	47.91			
C−O	120.115	119.22	118.56	122.64	210.59	172.71	173.65
COMe	25.302	23.71	23.91	21.84	28.98	54.80	53.57
			64.57 (O−CH_2−CH_3)				
			14.24 (O−CH_2−CH_3)				

[a] Relative to $\delta(C_6H_{12}) = 26.92$. [b] NMe_A is on same side of the aromatic plane as the acetyl methyl group.

structural analogues of **3** and **2**, respectively. The proton NMR shifts of **2**, **3**, **4**, and **5** are given in Table 4. The chemical shifts of cations **3** and **4** are quite comparable except for hydrogens and carbons nearest the site of OH → OEt substitution. This helps to confirm the assignments of the NMR resonances of **3**. Nearly identical, also, are the ^{1}H and ^{13}C shifts of the NMe_2 and aromatic atoms of the N-substituted rings of **2** and **5**, the values of the *H*−C−N−*H* coupling constants, and the shift of the NH protons: δ NH, 13.7 (**2**, $BF4^-$); 13.8 ppm (**2**, trifluoroacetate, 18.9 equivalents of TFA); 13.6 ppm (**5**, $BF4^-$), all measured in $PhNO_2$. Therefore, cations **2** and **5** must also have quite similar geometries and electronic properties. We have previously shown that the NH proton of the crystalline picrate salt of the ethyl ester related to **5**[20] is intramolecularly H bonded with the C═O oxygen in a nearly linear N−H···O arrangement, achieved through rotation of the carboxyl group from the aromatic plane by 21° (N−H−O angle, 173.7°). The NH···O distance of 1.697 Å is considerably shorter than the sum of the van der Waals radii of O and H (2.50 Å). Thus the NH···O═C hydrogen bond of the ester, and by extension, of N-protonated **2**, must be fairly strong.

The geometry of N-protonated **2**, postulated here on the basis of the NMR data, is supported by a calculation of its optimized structure which uses the density functional method of the SPARTAN program[21] with a basis set equivalent to 6−31 g**. This yielded structural parameters similar to those of the crystalline ester, 18.7° for the angle of rotation of the COMe group from ring coplanarity and 166.7° for the angle of the N−H−O hydrogen bond. The internal NH···O═C arrangement of **2** and **5** in solution is additionally confirmed by the fact that the shift of their NH proton, ca. δ 14, is so much further downfield than the usual 8−10-ppm shifts of protonated NMe_2 groups reported for monofunctional aromatics[12] or for some other 8-substituted-1-(dimethylamino)naphthalenes.[22]

The Solvent Effect on the OH (3) → NH (2) Proton Exchange Equilibrium. The mole fractions of rapidly equilibrating **1**, **2**, and **3** in the initial stages of the titration of **1** with TFA (A/B≤ 2) were calculated using the shifts of **1** in neutral solution (δ_i (B°)), the observed, time-averaged shifts δ_i of **1**, **2**, and **3** in the equilibrium mixture, and the shifts of nonexchanging **2** and **3**, δ_i (NH^+) and δ_i ($^+$HO), respectively, measured in solutions of high acid content:

$$\delta_i = f_3(\delta_i(^+\mathrm{OH})) + f_2(\delta_i(\mathrm{NH}^+)) + f_1(\delta_i(\mathrm{B}°)) \quad (1)$$

Figure 3 shows the mole fractions of **1**, **2**, and **3** in dichloromethane, thus determined, and those of **2** and **3** at the higher acid concentrations, obtained by integration of the separated resonances, as function of the number of equivalents (A/B) of TFA in solution. The plot indicates O-protonated **3** to be the major product in solutions of **1** with up to ca. 2 equiv (A/B ≈ 2) of TFA. At this point its mole fraction is a maximum 0.83, and little unprotonated reactant **1** remains in solution. Further addition of TFA, however, reverses the trend. The amount of O-protonated **3** begins to decrease, and that of N-protonated **2** increases, until in neat TFA **2** exceeds **3** by a factor of 4. Similar trends were obtained in the titration of **1** in $PhNO_2$ and in CD_3CN. These results are in contrast with the protonation behavior reported for unhindered cyclic azaketones, such as1-benzyl-1-azacyclooctan-5-one, which even in neat TFA forms exclusively the O-protonated transannular addition product.[23]

In the present case, the preference for N- or O-protonation of **1** clearly depends on the acidity of the protonating medium. The most basic available site among all species present in solution in the initial stages of the titration must be the carbonyl oxygen of **1**, by virtue of transannular N−CO bond formation which accompanies proton transfer from TFA. O-Protonation thus predominates as long as there is an abundance of **1** in solution. The product conjugate acid **3** is too weakly acidic to transfer the captured proton to any but another equally basic carbonyl oxygen so that the initial equilibrium involves mainly proton exchange between **1** and **3**. The 2:1 acid:base stoichiometry at the point of maximum **3** suggests nearly quantitative formation of **3** with homoconjugated TFA^-·TFA as the counteranion. Thereafter, any additional TFA will be complexed by this anion to form the higher aggregate $TFA^-(TFA)_2$. Such complex formation is likely to weaken OH···TFA^-·TFA inter-ion hydrogen-bonding that may be stabilizing cation **3**. With increasing amounts of the more highly acidic trimeric $TFA^-(TFA)_2$, in solution, N-protonation begins to compete with O-protonation, and the equilibrium shifts toward the formation of **2.**[24]

Figure 4 compares the mol fractions of **3** in the titration of **1** with TFA in CD_2Cl_2, $PhNO_2$-d_5, CD_3CN, and acetone-d_6. The plots show that for solutions containing excess TFA (A/B > 2), equilibrium **3** → **2** becomes increasingly biased against N-protonation as the basicity of the solvent increases: CD_2Cl_2 < $PhNO_2$ < CD_3CN < $(CD_3)_2CO$. For **1** in CD_2Cl_2, and $PhNO_2$-d_5, the following equilibria were found to fit the titration data for A/B > 2:

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(22) N-Protonated 8-Z-1-(dimethylamino)naphthalenes: Z = CN, 9.2 ppm (tetrafluoroborate salt in CD_3CN); Z = Br, 10.5 ppm (in CD_2Cl_2 with excess TFA), I. I. Schuster, unpublished results.

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Table 4. ^{1}H NMR Shifts[a] of Cations 2−5.

shift ion, solvent	δ NMe_A	δ NMe_B	δ COMe	δ H2	δ H3	δ H4	δ H5	δ H6	δ H7	δ Et[b,c] δ NH,[d] δ OH[e]
2, TFA (neat)	3.4246 (J = 4.656)		3.1217	8.8823	7.8638	8.4372	8.2728	7.8999	8.1426	14.0125[d]
2, BF_4^-, CD_2Cl_2	3.3978 (J = 4.864)		3.0613	8.7343		8.3768	8.2018	7.8726	8.1565	13.2584[d]
2, CD_2Cl_2, A/B = 12.41	3.3287 (J = 4.672)		3.0732	8.8279	7.8513	8.4470	8.2574	7.8732	8.0097	14.3617[d]
2, BF_4^-, CD_3CN	3.3043 (J = 4.850)		3.0132	8.8061	7.8541	8.4392	8.2588		8.1397	12.9672[d]
2, BF_4^-, $PhNO_2$	3.7298 (J = 4.44)		3.1766	8.9068	7.8463	8.4565	8.3939	7.9549	8.2320	13.7331[d]
2, $PhNO_2$, A/B = 18.9	3.6505 (J = 4.68)		3.1537	8.8981	7.8223	8.3733	8.3538	7.8483	8.2076	13.8497[d]
5, BF_4^-, $PHNO_2$	3.811		4.280	8.699	7.747	8.560	8.381	7.933	8.244	13.557[d]
3, neat TFA	3.5226	3.4175	2.2086	7.7327	7.8535	8.0843	8.0717	7.7996	7.6876	
3, BF_4, CD_2Cl_2	3.5650	3.2586	2.1438	7.6737	7.8035	8.0087	8.0087	7.7442	7.6253	7.5006[e]
3, BF_4, CD_3CN	3.3863	3.2590	2.1114	7.7128	7.8230	8.0819	8.0653	7.7888	7.7838	6.9504[e]
3, CD_3CN, A/B = 23.4	3.4135	3.2868	2.1257	7.7139	7.8227	8.0707	8.0707	7.7940	7.7502	
3, BF_4^-, $PhNO_2$	3.8562	3.6492	2.4956	7.9733	7.8454	7.9976	7.9976	7.8290	7.8152	
4, BF_4^-, DMSO	3.5323	3.4602	2.3143	7.9308	7.8973	8.1991	8.1651	7.8891	8.0981	3.5764, 3.5845 (CH_2)[b,c], 1.1593 (CH_3)[b]
4, BF_4, CD_3CN	3.5522	3.4807	2.3340	7.9010	7.9273	8.2133	8.1792	7.9041	8.1154	3.6068, 3.5684 (CH_2)[b,c] 1.1745 (CH_3)[b]

[a] Shifts relative to δ C_6H_{12} = 1.42. [b] *O*-Ethyl group. [c] Diastereotopic hydrogens.

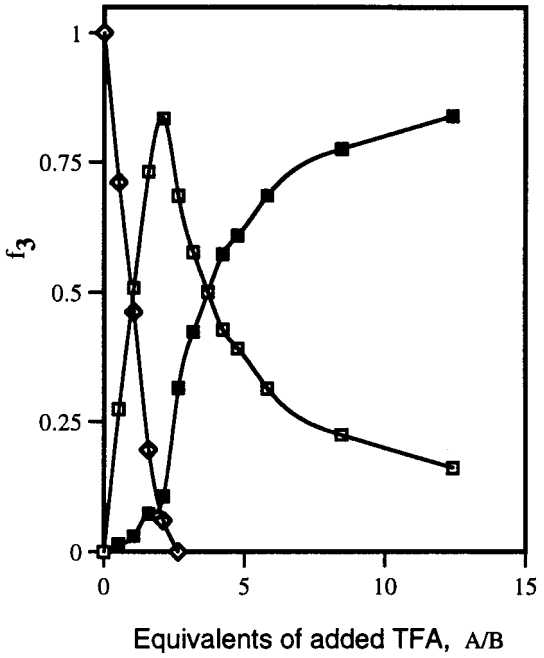

Figure 3. Mole fraction of **1** (◊), **2** (■), and **3**(□) in the titration of **1** with TFA in D_2Cl_2 at 293 K.

$$K_1\text{: } \mathbf{3},TFA^-\cdot TFA + TFA \;\Omega\; \mathbf{3},\ TFA^-(TFA)_2 \quad (2a)$$

$$K_2\text{: } \mathbf{3},TFA^-\ (TFA)_2 \;\Omega\; \mathbf{2},\ TFA^-(TFA)_2 \quad (2b)$$

$$K^d\text{: } 2\ TFA \;\Omega\; (TFA)_2 \quad (2c)$$

Values of the equilibrium constants were determined by assuming that the measured mole fraction of cation **3** is the sum of both ion-paired forms of eq 2a, and by varying trial values of K^d and K_2 until a linear plot of $\ln(f_2/K_2)/(1 - f_2a)$ versus $\ln(b - 2f)$ was obtained. This coincided with minimum deviation of the data from the correlation line. Here $a = (1 + 1/K_2)$, $b = (A/B - 2 - f_2a$), f_2 is the mol fraction of **2**,$TFA^-(TFA)_2$, and f is the fraction of TFA dimer, $(TFA)_2$, which equals $(1/8K^d)((4bK^d + 1) - (8bK^d + 1)^{1/2})$. The intercept furnished the value of K_1. The slope of the line was 1.0 which confirms the proposed stoichiometry of eq 2a. Similar strategies gave equilibrium constants for eqs 2a−c in CD_3CN, except that a better fit of the data was obtained by postulating the formation of **2**,$TFA^-(TFA)_2$ as the separated ion pair[25] in eq 2b. Therefore, a was replaced by $(1 + f_2/K_2)$ in the above equations. Figure 5 demonstrates the goodness of fit of the data to the correlation lines for the equilibria in CD_2Cl_2, $PhNO_2$, and CD_3CN. The equilibrium constants for eqs 2a−c are collected in Table 5. Here K^d = 4.78 L/mol for the dimerization of TFA in CD_2Cl_2. This figure is reasonable when compared with 1.5 L/mol for equilibrium 2c by itself in 1,2-dichloroethane.[26] TFA dimerization appears to be negligible in $PhNO_2$ and in

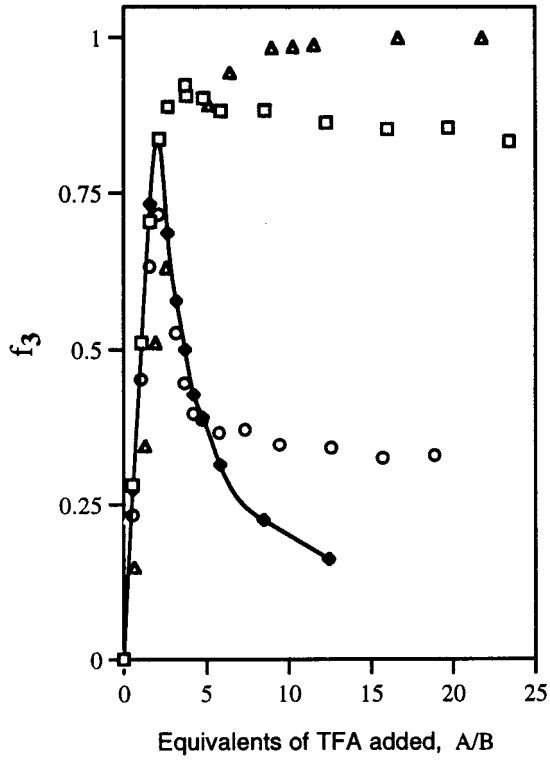

Figure 4. Mole fraction of **3** as function of added TFA in the titration of **1** in CD_2Cl_2 (♦), $PhNO_2$ (○), CD_3CN (□), and acetone-d_6 (△).

(25) Since $PhNO_2$ and CD_3CN have similar dipolar and dielectric properties, such ion separation in CD_3CN alone must be due to the greater nucleophilicity of this solvent. CD_3CN displaces $TFA^-(TFA)_2$ by coordinating with the NH hydrogen of **2**. In the case of the O-protonated cation **3** such displacement is not necessary for H bonding of its OH hydrogen by solvent to occur. See Meyer, U. *Coord. Chem. Rev.* **1976**, *21*, 159−179.

(26) Kirszenbaum, M.; Corset, J.; Josien, M. L. *J. Phys. Chem.* **1971**, *75*, 1327−1330.

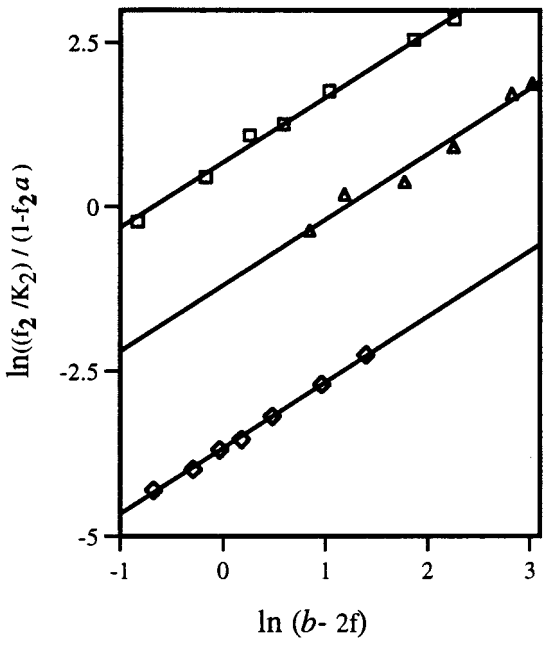

Figure 5. Correlations of eqs 2a−c in CD_2Cl_2 (◊), $PhNO_2$ (□), and CD3CN (△).

Table 5. Equilibrium Constants for 2A, 2B, and 2c in CD_2Cl_2, $PhNO_2$, and CD_3CN Solution.

K_i/solvent (DN)[a]	CD_2Cl_2 (0.0)	$PhNO_2$ (4.4)	CD_3CN (14.1)
K_1 (L/mol)	0.14	10.45	1.63
K_2	55.0	2.04	5.4×10^{-3} (mol/L)[b]
K^d (L/mol)	4.78	0	0

[a] Donor number. [b] The calculations are in better agreement with formation of **2**,$TFA^-(TFA)_2$ as the separated ions in eq 2b.

CD_3CN, probably because the acid prefers coordinating with these more basic solvents.[27] A change of solvent from CD_2Cl_2 ($\epsilon = 9.1$) to $PhNO_2$-d_5 ($\epsilon = 34.8$) increases the value of K_1 (eq 2a) from 0.14 to 10.45 L/mol, which accords with a report that anionic complexes of higher stoichiometries are favored[28] in more polar solvents. However, K_1 is only 1.63 L/mol for the equilibrium in acetonitrile ($\epsilon = 37.5$) because the formation of strong $CF_3COO-H\cdots N\equiv C$ hydrogen bonds diminishes the acidity of the protonating agent, nominally TFA.

Nucleophilic solvents can stabilize O-protonated **3** by H bonding its OH hydrogen. H-bonding of the NH proton of N-protonated **2** by such solvents is expected to be less important because this hydrogen is already intramolecularly bound to the carbonyl oxygen and is also sterically less accessible. Therefore, eq 2b is predicted to shift increasingly to the left in progressively more nucleophilic solvents. That this is the case is seen in the decreasing values of K_2 (Table 5) with increasing solvent donor number.

The onset of reaction between TFA and solvent in the titration of **1** in $PhNO_2$ and CD_3CN is evident in Figures 6a,b which show superimposed plots of δ^1 H(solvent) and mole fraction of **3** versus equivalents of added TFA. Here the solvent NMR shift reverses direction precisely at the point of maximum mole fraction of O-protonated **3** at which the concentration of free base **1** extrapolates to zero. This point is reached with 2.3 (CD_2Cl_2), 2.5 ($PhNO_2$), and 4.3 (CD_3CN) equiv of TFA in solution. These numbers follow the order of increasing solvent basicities and suggest progressively decreasing values of the equilibrium constant for the initial **1** → **3** conversion.

The titration data for **1** in acetone-d_6 best fits equilibria 3.

$$K_1:\ \mathbf{1} + TFA\ \Omega\ \mathbf{3}, TFA^- \qquad (3a)$$

$$K_2:\ \mathbf{3},TFA^- + TFA\ \Omega\ \mathbf{3},TFA^-\cdot TFA \qquad (3b)$$

Values of $K_1 = 0.46$ L/mol and $K_2 = 14.8$ L/mol were obtained by assuming that f_{OH}, the nominal mole fraction of **3** calculated by eq 1, equals the sum of the mole fractions of **3**,TFA^- (f) and **3**,$TFA^-\cdot TFA$ ($f_{OH} - f$). Trial values of K_1 were varied until a plot of $\ln((f_{OH} - f)/f)$ versus $\ln(A/B - 2f_{OH} - f)$ became linear. The slope of the line was 1.0, and the intercept furnished the value of K_2. Here the acidity-reducing effect of the solvent on the protonating agent TFA is reflected in a low value of K_1. The δ^1 H(solvent)/(A/B) correlation (not shown) was nonlinear and without break because this solvent competes successfully with unprotonated **1** for reaction with TFA throughout the entire titration.

Equilibria Involving the Tetrafluoroborate Salts of 2 and 3. Dissolving the pure tetrafluoroborate salt of **3** in solvents of varying acid−base and dielectric properties produces equilibrium mixtures of **2**,BF_4^- and **3**,BF_4^-, the ^{1}H NMR spectra of which show distinct resonances for each cation at ambient temperature. Thus, interconversion of the O- and N-protonated forms of the cation, paired with BF_4^-, is also slow on the NMR time scale. The mole fractions of N-protonated **2** in the equilibrium mixtures are summarized in Table 6. Figure 7 demonstrates that the amount of **2** again decreases with increasing donicity of the solvent. This is due to the greater acidity of cation **2** relative to that of tautomer **3**. However, there are large deviations from the correlation line for the equilibrium in solvents of low polarity ($\epsilon <$ 10). Here the amount of N-protonation is considerably less than what one would predict from the equilibrium distribution of the cations in the polar solvents. TFE, HOAc, and the chlorinated solvents of this study are all poor electron donors (DN = 0). However, the mole fraction of **2**,BF_4^- in TFE ($\epsilon = 26.1$) is 0.48, compared to only 0.20 in $CDCl_3$ ($\epsilon = 4.8$), 0.14 in HOAc ($\epsilon = 6.2$), and 0.13 in CD_2Cl_2 ($\epsilon = 8.9$). This result is similar to that obtained

Table 6. Fraction of N-Protonated 2,BF_4^- as Function of Solvent Donicity.

solvent (ϵ)[a]	donor number	f_2
CD_3OD (32.7)	19	0.0
$(CD_3)_2CO$ (20.7)	17	0.041
CD_3CN (37.5)	14.1	0.125
PhCN (25.2)	11.9	0.185
PhNO2 (34.8)	4.4	0.342
TFE (26.1)[b]	0.0	0.475
$CDCl_3$ (4.8)	0.0	0.133
CD_2Cl_2 (8.9)	0.0	0.204
HOAc (6.2)	0.0	0.139

[a] Reichert, C. *Solvent Effects in Organic Chemistry. Monographs in Modern Chemistry*; Verlag Chemie: New York, 1979; Vol. 3. [b] Kaspi, J.; Rappoport, Z. *J. Am. Chem. Soc.* **1980**, *102*, 3829−3837.

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(28) Huyskens, P.; Platteborze, K.; Zeegers-Huyskens, T. *J. Mol. Struct.* **1997**, *436*−*437*, 91−102.

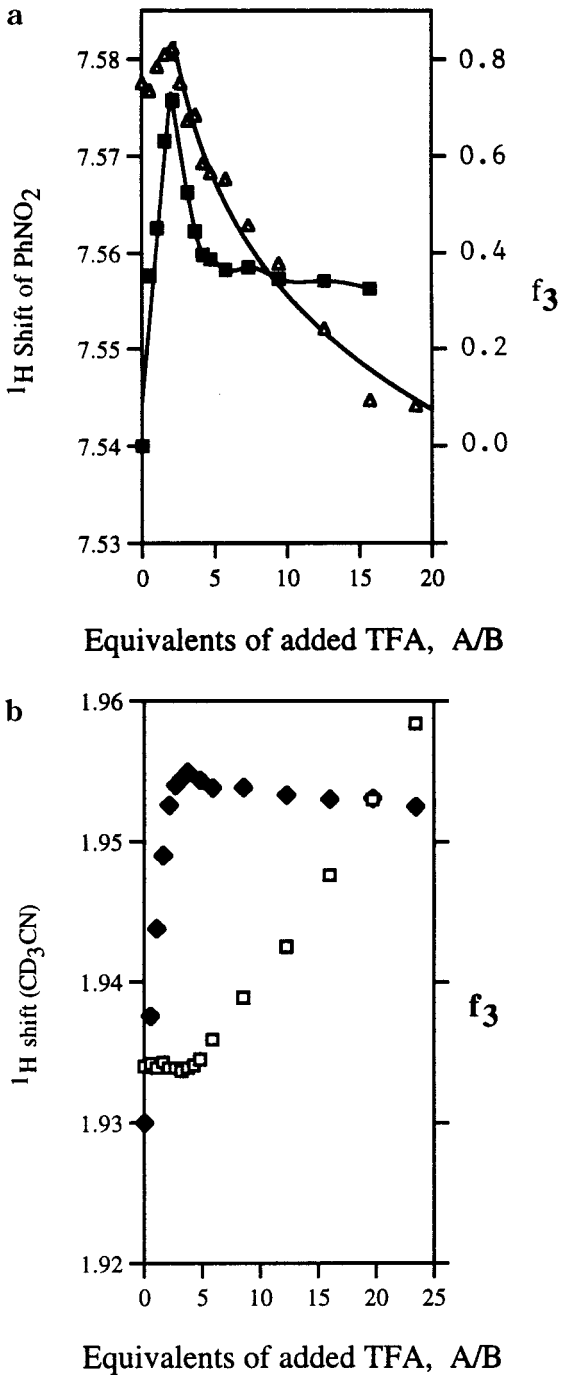

Figure 6. (a) ^{1}H NMR shift of solvent $PhNO_2$ (△) and mole fraction of **3** (■) as function of equivalents of added TFA. (b) ^{1}H NMR shift of CD_3CN (□) and of mole fraction of **3** (♦) as function of equivalents of added TFA.

in a study of amides in which the amount of O-protonation was also seen to increase in progressively less polar media.[29] In the present case, this solvent effect can be ascribed to destabilization of the more polar N-protonated tautomer in nonpolar solvents. There are no such deviations when trimeric $TFA^-(TFA)_2$ is the counterion (top correlation of Figure 7, f_2 calculated from eq 2b). The larger anion evidently confers similar polarities on the two tautomeric ion pairs, possibly through steric shielding of their polar moieties.

(29) Perrin, C. L.; Lollo, C. P. *J. Am. Chem. Soc.* **1984**, *106*, 2754−2757.

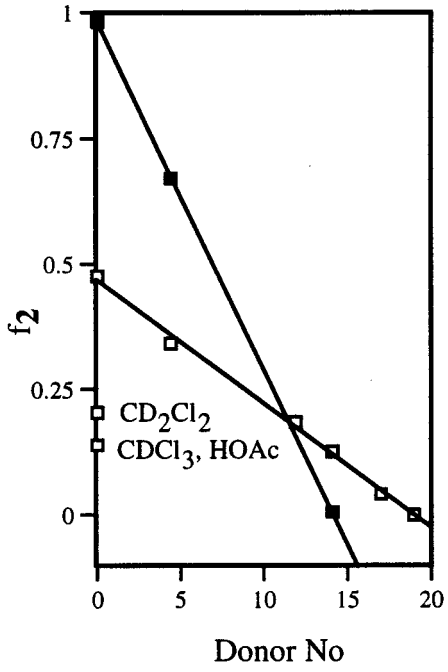

Figure 7. Mol fraction of **2**,BF_4^- (□) and of **2**,$TFA(TFA)_2$ (◊) as function of solvent donicity.

The relative contributions of $\Delta H°$ and $T\Delta S°$ to the free energy difference of equilibrium **3**,BF_4^- → **2**,BF_4^- in CD_2Cl_2 and in $PhNO_2$ were determined from its temperature dependence over ca. 50° C. Values of $\Delta H°$, $\Delta S°$ of 2.85 kcal/mol, 6.86 eu (CD_2Cl_2) and 2.56 kcal/mol, 7.58 eu ($PhNO_2$) were obtained by assuming negligible amounts of **1** present in solution. At room temperature the two terms are of nearly equal importance. It is thus understandable that even modest changes in solvent properties can reverse the relative thermodynamic stabilities of the O- and N-protonated tautomers of **1**.

The room temperature ^{1}H NMR spectra of **3**,BF_4^- in acetone, methanol, and DMSO show progressive increases in the ratio of the COMe:$NMe_{A(B)}$ signal intensities. This result is due to higher rates of N-Me group exchange because of increasing amounts of deprotonated **1** in these basic media. The degree of deprotonation **3** → **1** must be quite small in all the other solvents of this study because here the NMe and COMe NMR line widths of **3** are nearly identical and like those of O-alkylated **4**,BF_4^- which has no OH hydrogen to lose. However, spectra of **4**,BF_4^- in methanol-d_4 show deuteration of the C(O)-methyl group. This indicates that cleavage of its transannular N···CO bond is taking place. Under the same conditions, deuterium exchange within the COMe group of **3**,BF_4^- is not observed but is only evident in 1-day-old solutions. Loss of the proton from the OH group must, therefore, be considerably more facile than from COMe. Conversion of **3** to **2** then is most likely to occur by means of such O-deprotonation, followed by reprotonation at the nitrogen, rather than by direct site-to-site proton transfer following N−CO bond cleavage.

Experimental Section.

NMR Analyses. The ^{1}H and ^{13}C chemical shifts of **1**−**5** in solution were referenced to TMS or to internal cyclohexane. For the latter, conversion to the TMS scale was made using δ $^{13}C(C_6H_{12}) = 26.92$ and δ $^1H(C_6H_{12}) = 1.42$. Solution concentrations were 0.2−0.5 M (^{13}C NMR spectra) and 0.04−0.18 M (^{1}H

NMR spectra). All solvents were dried for 2 days prior to use over 3 Å molecular sieves.

Assignment of the proton NMR resonances of **1**−**5** were made by means of homonuclear decoupling experiments and by observing NOE enhancement of relevant resonances on irradiation of either the COMe or NMe_2 group hydrogens. This latter technique identified NMe_A as the *N*-methyl substituent of **3** and **4** that is cis to the C(O)Me methyl group.

Assignments of the ^{13}C resonances of the aromatic carbons were made on the basis of the three-bond H−C coupling patterns, by matching the shift values with those published for correspondingly monosubstituted naphthalenes, and by means of 2D (NOESY/COSY) experiments.

Syntheses. Compound **1** and the unprotonated methyl ester related to **5** were synthesized according to procedures published by Dunitz et al.[4] The tetrafluoroborate salt of **3** was obtained by adding an ether solution of tetrafluoroboric acid (Aldrich) to an equimolar amount of **1** in dry dichloromethane (distilled from CaH_2). After the mixture was stirred for 1 h, the volume was reduced and the precipitated salt recrystallized from methanol−ether; mp 154−155 °C. All peaks of the proton-decoupled ^{13}C NMR spectrum of the salt in solution could be accounted for by the sole presence of tautomers **3**,BF_4^- and **2**,BF_4^- in equilibrium (Figure 4S: **3**,BF_4^- in CD_3CN, Supporting Information). The salt of the corresponding ester **5** was prepared by the same procedure; mp 133−135.5 °C. The proton-decoupled ^{13}C NMR spectrum (Figure 2S: a,b; Supporting Information) confirms its purity. The tetrafluoroborate salt of **4** was obtained by addition of a 1 M dichloromethane solution of triethyloxonium tetrafluoroborate (Aldrich) to an equimolar amount of **1** dissolved in the same (dried) solvent under an inert nitrogen atmosphere. The mixture was stirred overnight, the solvent was removed, and the viscous residue was recrystallized twice from methanol−ether, yielding a white powder: mp 106−116 °C. The ^{1}H NMR spectrum showed this to be a mixture of O-alkylated **4**,BF_4^- and O-protonated **3**,BF_4^-. Several attempts were made to obtain a purer product, the best effort of which produced a compound whose proton-decoupled ^{13}C NMR spectrum (Figure 1S: a,b, Supporting Information) indicated a nearly pure product.

Crystal Structure Analysis. Crystals of **3**,TFA^- suitable for X-ray analysis were obtained by slow precipitation from a solution of **1** in dichloromethane−ether containing 2 equiv of TFA. Crystal, data collection, and refinement parameters are given in Table 1S. The systematic absences in the diffraction data were uniquely consistent for the monoclinic space group $P2_1/n$, which yielded chemically reasonable and computationally stable results of refinement. The structure was solved using direct methods, completed by subsequent difference Fourier syntheses and refined by full-matrix least-squares procedures. Two independent, but chemically equivalent, molecules per asymmetric unit are present. All non-hydrogen atoms were refined with anisotropic displacement coefficients, and hydrogen atoms were treated as idealized contributions.

All software and sources of scattering factors are contained in the SHElXTL(5.10) program library (G. Sheldrick, Siemens XRD, Madison, WI).

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Supporting Information Available: Tables of atomic coordinates, anisotropic displacement coefficients, H-atom coordinates, bond lengths and bond angles for **3**,TFA^- and details concerning crystal data, data collection, and structure refinement (Tables 1S−5S); ^{1}H and ^{13}C NMR shifts of **1** in various solvents (Tables 6S, 7S); proton-decoupled ^{13}C NMR spectra of **4**,BF_4^- in DMSO (Figure 1S: a,b), of **5**,BF_4^- in $PhNO_2$ (Figure 2S: a,b), and of **3**,BF_4^- in CD_3CN (Figure 4S); ORTEP drawing of **3**,TFA^- (Figure 3S). This material is available free of charge via the Internet at http://pubs.acs.org.

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