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Direct Evidence on Nucleophilic Reactivity of Secondary Anilines toward an Aminium Radical

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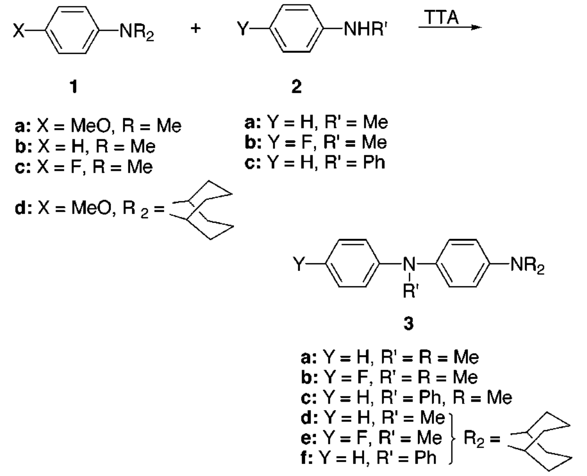
Recently we reported[1] a mechanistic study of the reaction between a few *N,N*-dimethylanilines and secondary anilines, using the product study as a tool. This is an aromatic substitution reaction (Scheme 1) that occurs under oxidative conditions with thallium triacetate sesquihydrate (TTA). *N,N*-Dimethyl-*p*-anisidine (**1a**, $E_{p/2} = 0.49$ V vs SCE)[2] turned out to undergo methoxyl substitution with *N*-methylaniline (**2a-H**), *N*-methyl-*p*-fluoroaniline (**2b-H**), and diphenylamine (**2c-H**). The less oxidizable substrates, *N,N*-dimethylaniline (**1b**, $E_{p/2} = 0.71$ V vs SCE)[2] and *N,N*-dimethyl-*p*-fluoroaniline (**1c**, $E_{p/2} \approx 0.74$ V),[1] under the same reaction conditions, were found to react only with diphenylamine, giving hydrogen substitution at C-4 and fluorine substitution, respectively.

Our mechanistic proposals were based on the relative oxidation potentials of the amines participating in the reaction and ESR evidence about the formation of radical cations from the *N,N*-dimethylanilines. In the case of **1a**, the radical cation $\mathbf{1a}^{+\bullet}$ was recognized as the active species that would undergo nucleophilic attack by secondary amines. However, in view of the pK_a value denoting a scarce nucleophilicity for diphenylamine, it was evident that the capability of **2c-H** to give substitution with **1a** could not be explained in terms of nucleophilic attack at $\mathbf{1a}^{+\bullet}$. We associated the reactivity of **2c-H** with the ease to oxidize this amine to the corresponding radical cation, which by loss of a proton gives an aminyl radical, $\mathbf{1c}^{\cdot}$. Thus the plausible hypothesis was that **2c-H** could react not as a nucleophile with $\mathbf{1a}^{+\bullet}$, but as a radical that would be able to attack either $\mathbf{1a}^{+\bullet}$ or **1a**. The unique possibility for **2c-H** to react in the oxidized form of an aminyl radical was indirectly evidenced in reaction with hardly oxidizable substrates **1b**,**c** in which the only viable reaction pathway would involve the combination of the neutral substrate with the aminyl radical of an oxidizable secondary amine as diphenylamine.[3]

Scheme 1



We now report more direct evidence on the possibility that, in our reactions of methoxy substitution, the anilines **2a,b-H** act as nucleophiles toward *p*-anisidinium radical while **2c-H** does not. To gain this kind of evidence we planned to observe the interaction between radical cation and secondary aniline directly.[5]

For that purpose, the dialkyl substitution at nitrogen of **1a** was modified using the 1,5-cyclooctylene group, which is electronically very similar to the dimethyl substitution of the previous substrate and at the same time provides the kinetic stabilization necessary to isolation of the radical cation. Because the lifetime of tertiary amine radical cations is expected to be principally controlled by its rate of deprotonation, the structural feature of the new substrate, 9-(*p*-anisyl)-9-azabicyclo-[3.3.1]nonane (**1d**), that greatly increases the lifetime of the corresponding radical cation, results in a far slower α-deprotonation due to the fact that bridgehead protons are forced to lie perpendicular to the unpaired electron bearing orbital.[6] Moreover, cyclic voltammetry measurements testified that 1,5-cyclooctylene substitution also confers a certain thermodynamic stabilization to the radical cation inasmuch as the half peak potential of **1d** was found to be 65 mV lower than that of **1a**.

However, structural characteristics of **1d** had no significant effect on its reactions with secondary anilines **2(a−c)-H** in the presence of TTA which resulted very similar to the analogous reactions of **1a**.[1]

We were able to isolate $\mathbf{1d}^{+\bullet}$ as a tetrafluoroborate salt upon oxidation of **1d** with silver tetrafluoroborate (see Experimental Section). While the salt in solid state is indefinitely stable, the changes in the UV−vis spectrum shown in Figure 1 indicate that the radical cation concentration slowly decreases with time, such a decrease being probably due to reduction of the radical cation to the starting amine.

Reactions of the aminium tetrafluoroborate with **2a**,**b** afforded the radical cation of the product of anilino-demethoxylation **3d**,**e**. This transformation occurred rapidly and was easily monitored by color changes from

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[1] Ciminale, F.; Ciardo, A.; Francioso, S.; Nacci. A. *J. Org. Chem.* **1999**, *64*, 2459.

[2] Seo, E. T.; Nelson, R. F.; Fritsch, J. M.; Marcoux, L. S.; Leedy, D. W.; Adams, R. N. J. *Am. Chem. Soc.* **1966**, *88*, 3498.

[3] An alternative hypothesis contemplates the interaction of the neutral substrate with the nitrenium ion $\mathbf{2c}^{+}$, which is another possible product of the oxidation of **2c-H**.[4] This, however, was implicitly ruled out in our previous mechanistic discussion,[1] when the fragmentation modes of the C−F bond on different adducts were judged on the oxidation level of the resulting F fragment: accordingly, the Wheland adduct formed upon $\mathbf{2c}^{+}$/**1c** interaction should be considered unlikely as direct precursor of the substitution product.

[4] Serve, D. *Electrochim. Acta* **1976**, *21*, 1171.

[5] For similar interaction of a nitrogen-centered reagent with a persistent arylaminium radical, see: Engel, P. S.; Hoque, A. K. M. M.; Scholz, J. N.; Shine, H. J.; Whitmire, K. H. *J. Am. Chem. Soc.* **1988**, *110*, 7880.

[6] Nelsen, S. F.; Kessel, C. R.; Brien, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 702.

10.1021/jo0156619 CCC: $20.00

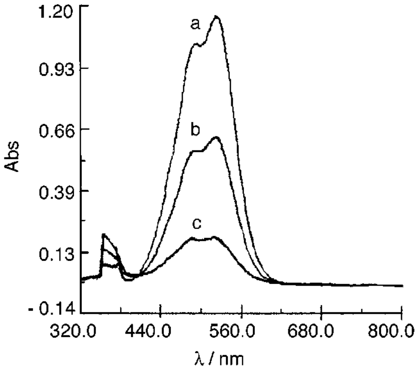


Figure 1. Time-dependent UV−vis spectra of a solution of **1d**$^{+\bullet}$BF$_4^-$ (MeNO$_2$, 10^{-4} M): $\Delta t_{(c-a)} = 5$ h.

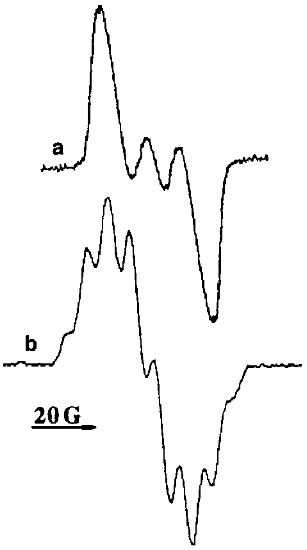
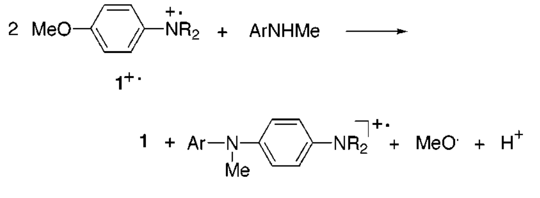


Figure 2. ESR spectral change of reaction of **1d**$^{+\bullet}$BF$_4^-$ (7.2 10^{-4} M) with **2b-H** (7.5 10^{-4} M): (a) recorded after mixing; (b) recorded after 2.5 h.

a deep red to a deep blue solution. The conversion of the initial paramagnetic species into that of the substitution product could be clearly evidenced by ESR spectroscopy as shown in Figure 2,[7] which refer to the reaction with *N*-methyl-*p*-fluoroaniline.

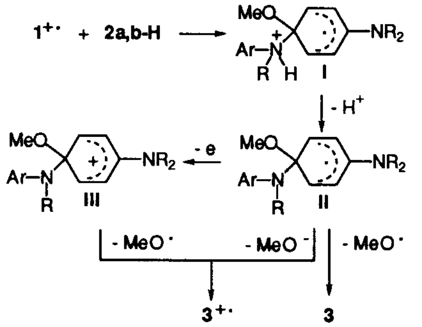
Conversion and yield for reaction with **2b-H** were determined; they were based on cyclooctyleneanisidine and the corresponding *p*-phenylendiamine, as obtained after reductive workup of the final blue reaction mixture. A 50% yield of the recovered cyclooctyleneanisidine is indicative of a stoichiometric ratio between the aminium salt and the secondary amine of 2:1 according to the eq 1.



(1)

On the side of products, the electronic balance of this equation requires the presence of *p*-phenylendiamine radical cation and of a methoxyl group in the oxidized form of the radical. From a mechanistic point of view this stoichiometry would imply that fragmentation of the C—O bond takes place on radical adduct II (Scheme 2) by ejection of the methoxyl group either as an anion or as a radical: in the first case the product is left as a radical cation and the second molecule of the starting aminium radical serves to oxidize the methoxide ion to a methoxyl radical; in the latter case *p*-phenylendiamine is left in neutral form and should immediately be oxidized to a radical cation by the 1 molar excess of starting aminium radical.

Scheme 2



However, in view of a presumably easy oxidation of the radical adduct to the cationic adduct III it cannot be ruled out that fragmentation might involve the latter adduct to give the methoxyl radical and the product radical cation: also in this case the stoichiometry of the above equation would be accounted for by the excess of aminium tetrafluoroborate serving to oxidize the radical adduct.

As for the reaction of cyclooctylene-*p*-anisidinium tetrafluoroborate with diphenylamine, the results were in agreement with the previous hypothesis about a nonnucleophilic behavior of this amine toward the aminium radical: in fact, we found that only traces of substitution product could be detected. Moreover, running the ESR spectrum of the reaction mixture at timed intervals one could simply observe a decrease in paramagnetic resonances of the starting radical cation, without any new signal appearing. Such a decrease would reflect a possible electron transfer from **1d**$^{+\bullet}$ to the oxidizable amine **2c-H**. In reactions with amines **2a,b-H**, a similar electron transfer can be ruled out in consideration of the redox characteristics of the reactants. Further, according to the results of a kinetic investigation concerning reactions of aromatic radical cations with amines,[11] the electron transfer from **1d**$^{+\bullet}$ to **2a,b-H** should be incompatible with the observed nucleophilic substitution.

In conclusion, the reactions between **1d**$^{+\bullet}$BF$_4^-$ and secondary amines **2(a−c)-H** have provided direct evidence that for our oxidatively activated aminodemethoxylation reactions the reactivity of non-nucleophilic **2c-H** is only apparently similar to that of nucleophilic **2a,b-H**. In fact, the mechanistic proposal about involvement of nucleophilic interaction between a secondary amine and the radical cation of the methoxy substituted tertiary amine is reliable only for **2a,b-H**. Thus, a different

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[7] ESR spectra (a and b) of **1d**$^{+\bullet}$ and **3e**$^{+\bullet}$ radical cations containing the 9-azabicyclononane (9-ABN) group appear broader than those of the corresponding dimethylamino substituted paramagnetic species **1a**$^{+\bullet}$[8] and **3b**$^{+\bullet}$.[9] Most likely this is due to unresolved couplings with the numerous protons of the 9-ABN group (for β-bridgehead, γ and δ splittings in the 9-ABN moiety of related systems see ref 10). However, a rough value of $a_N \approx 11$ G could be estimated from spectrum a. On the other hand, the broad octet ($a \approx 6.5$ G) of spectrum b is consistent with **3e**$^{+\bullet}$ inasmuch as it can be interpreted in terms of accidentally equivalent (or nearly so) couplings with two nitrogen and three hydrogen nuclei, typical of the *p*-phenylendiamine system.[8]

mechanism such as that based on the oxidability of the secondary amine indirectly gains reputation in the case of non-nucleophilic **2c-H**.

Experimental Section

Materials. Commercial $MeNO_2$ (Aldrich HPLC) was used as solvent without further purification. 9-(*p*-Anisyl)-9-azabicyclo-[3.3.1]nonane (**1d**) was obtained by reaction of cycloocta-2,6-diene[12] with *p*-anisidine followed by Wolff−Kishner (W−K)-reduction of the resulting 9-*p*-anisyl-9-azabicyclo[3.3.1]nonan-3-one. For both the steps, procedures were used that are described in the literature for analogous compounds.[13,14] By W−K reduction of 9.4 g of the azabicyclononanone, **1d** was obtained along with the corresponding hydrolysis product, 9-(4-hydroxyphenyl)-9-azabicyclo[3.3.1]nonane. Flash column chromatography (hexane/Et_2O 5:2) of the crude of reaction gave 1.45 g (16.4%) of pure **1d**: mp 46−48 °C; IR (KBr) 2983−2831, 1514, 1248 (Ar−O), 1039 ($O-CH_3$), 822 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.82 (s, 4H), 3.94 (s, 2H), 3.76 (s, 3H), 2.11−1.95 (m, 6H), 1.68−1.60 (m, 6H); MS *m*/*z* (rel abundance) 231 (M^+, 63), 202 (39), 188 (100), 149 (58), 134 (34). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.65; H, 8.93; N, 5.88.

Synthesis of 9-(*p*-Anisyl)-9-azoniaylbicyclo[3.3.1]nonane Tetrafluoroborate ($1d^{+\bullet}BF_4^-$). A solution of **1d** (0.240 g, 1.04 mmol, 10 mL of CH_2Cl_2) was added drop by drop at room temperature to 0.182 g (0.94 mmol) of silver tetrafluoroborate held in suspension in 30 mL of CH_2Cl_2 by magnetic stirring. The reaction mixture immediately became deep red in color while a silver mirror was formed. After the addition, the reaction mixture was concentrated (50% vol) in vacuo, filtered, and then poured into dry ether (50 mL) at − 25 °C to precipitate the azoniayl salt, which was filtered off after the mixture had warmed to room temperature. The deep red crystals were washed with dry ether: 205 g (62%), mp 102−105 °C. Anal. Calcd for $C_{15}H_{21}NOBF_4$: C, 56.63; H, 6.65; N, 4.40. Found: C, 53,81; H, 6.63; N, 4.06.

Reaction of $1d^{+\bullet}BF_4^-$ with *N*-Methyl-*p*-fluoroaniline (2b-H). A 100 mg (0.314 mmol) amount of $\mathbf{1d}^{+\bullet}BF_4^-$ was allowed to react with 41 mg (0.314 mmol) of **2b-H** in $MeNO_2$ (20 mL) at room temperature. The initial red-colored solution of the radical cation $\mathbf{1d}^{+\bullet}$ within 5 min turned to the typical deep blue color of the radical cation of the anilinodemethoxylation product. After 15 min the resultant blue solution was treated with a solution of $Na_2S_20_3$ (10%, 100 mL) and extracted with diethyl ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, hexane/Et_2O 9:1) of the residue gave 36 mg of **1d** (50% conv of the starting tetrafluoroborate) and 29 mg (57%) of the substitution product, 9-[*p*-(*p*-fluorophenyl)methylaminophenyl]-9-azabicyclo[3.3.1]-nonane (**3e**): mp 123−125 °C (recrystallized from ethanol); IR (KBr) 2940−2850, 1511, 1297 (C−N), 1217 (C−F), 823 cm^{-1}; ^1H NMR (200 MHz, $(CD_3)_2CO$) δ 6.67−6.98 (m, 8H), 4.05 (bs, 2H), 3.18 (s, 3H), 2.28−1.88 (m, 6H), 1.75−1.54 (m, 6H); MS *m*/*z* (rel abundance) 324 (M^+, 100), 281 (51), 242 (28). Anal. Calcd for $C_{21}H_{25}FN_2$: C, 77.74; H, 7.77; N, 8.63. Found: C, 77.77; H, 7.88; N, 8.23.

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