Oxidative Activation in Aromatic Substitutions. Reactions of *N*,*N*-Dimethylanilines with Secondary Anilines Promoted by Thallium Triacetate

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The reactions of *N*,*N*-dimethyl-*p*-anisidine (**1a**), *N*,*N*-dimethylaniline (**1b**), and *N*,*N*-dimethyl-*p*-fluoroaniline (**1c**) toward secondary anilines **2(a−d)-H** in the presence of thallium triacetate sesquihydrate have been studied as representative of a novel oxidatively activated aromatic substitution affording 1,4-benzenediamine derivatives **3a−d**. All of the substrates considered gave substitution with diphenylamine (**2d-H**). However, with anilines **2b,c-H**, only **1a** underwent substitution, and substrates **1b,c** were practically unreactive. The observed differences in reactivity are well accounted for within a mechanistic framework wherein oxidative activation of both the substrate and the secondary aniline is regarded as alternatively (or simultaneously) possible, depending on the redox characteristics of the reactants. For instance, it can be stated, beyond any reasonable doubt, that reactions of **1a** with **2b,c-H** proceed via nucleophilic attack of the latter on **1a**$^{+\bullet}$, and that the reaction of **1a−c** with **2d-H** must involve the diphenylamino radical **2d**$^{\bullet}$.

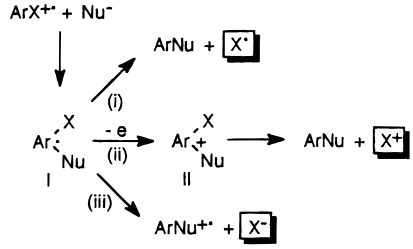
Introduction

Radical cations formed by single electron removal from neutral molecules are common reactive intermediates in a variety of thermal, photochemical, and electrochemical reactions occurring under oxidative conditions.[1−3] Among other possible reactions, these electron-poor species are known to undergo addition of nucleophiles. In fact, contrary to some theoretical considerations[4] leading to the classification of direct nucleophilic attack on a radical cation as "forbidden", kinetic measurements have demonstrated that this process can be very rapid, even approaching diffusion control.[5]

Diverse aromatic substitutions affording either hydrogen or ipso substitution products have been described as involving the addition of nucleophiles to unsubstituted or substituted positions of aromatic radical cations, respectively. Unlike conventional aromatic substitutions taking place on neutral substrates, in which the replaced group invariably keeps the electronic identity of the attacking species, a characteristic feature of these reactions is the possibility of three different electronic identities for the leaving group.

As shown in Scheme 1, the addition of an anionic nucleophile (Nu^-) to a radical cation ($ArX^{+\bullet}$) produces an uncharged nucleophilic adduct (**I**), which is none other than the homolytic adduct obtainable by addition of the radical Nu$^{\bullet}$ to the neutral substrate ArX. Thus, a first possibility for the leaving group is to dissociate from

Scheme 1



adduct **I** as a *radical* (X$^{\bullet}$) giving the substitution product ArNu (path *i*).

Because of the oxidizing conditions operating in this type of reaction, the second most likely possibility for the leaving group is to detach as an *electrophile* (X^+) from the Wheland intermediate **II** formed by oxidation of adduct **I** (path *ii*). In comparison, H-substitution reactions such as anodic cyanation and acetoxylation of anisole and other aromatic compounds,[6] pyridination of mesitylene by photoactivation of its electron donor−acceptor complex with *N*-nitropyridinium,[7] chlorination of methyl-substituted methoxybenzenes with iodine monochloride,[8] and azidation and acetoxylation of 1,4-dimethoxybenzene induced by hypervalent iodine[9] have been interpreted as nucleophilic displacements of H^+. An analogous mechanistic formulation in terms of nucleophilic deprotonation was advanced by Eberson[10] to account for the formation of H-substitution products from the direct reaction of certain nucleophiles (AcO^-, Cl^-,

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† Taken in part from the respective graduation theses.

(1) Eberson, L. *Electron-Transfer Reactions in Organic Chemistry*; Springer: Berlin, 1987.

(2) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550.

(3) Kyriacou, D. *Modern Electroorganic Chemistry*; Springer: Berlin, 1994; Chapter 2.

(4) (a) Pross, A. *J. Am. Chem. Soc.* **1986**, 108, 3537. (b) Shaik, S. S.; Pross, A. *J. Am. Chem. Soc.* **1989**, *111*, 4306.

(5) Parker, V. D.; Tilset, M. *J. Am. Chem. Soc.* **1987**, *109*, 2521.

(6) (a) Andreades, S.; Zahnov, E. W. *J. Am. Chem. Soc.* **1969**, *91*, 4181. (b) Eberson, L.; Nyberg, K. *Acc. Chem. Res.* **1973**, *6*, 106.

(7) Kim, E. K.; Bochman, T. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1993**, *115*, 3091.

(8) Hubig, S. M.; Jung, W.; Kochi, J. K. *J. Org. Chem.* **1994**, *59*, 6233.

(9) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684.

(10) (a) Eberson, L.; Larsson, B. *Acta Chem. Scand. B* **1986**, *40*, 210. (b) Eberson, L.; Larsson, B. *Acta Chem. Scand. B* **1987**, *41*, 367.

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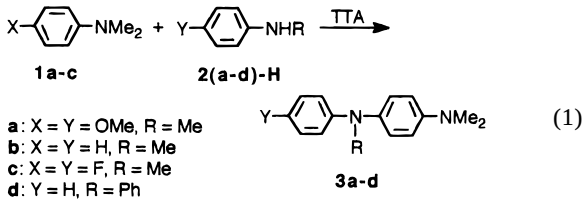
CN^-) with the tris(4-bromophenyl)aminium radical cation. Moreover, a relevant example of ipso Nu^-/X^+ substitution is the anodic cyanation of 1,4-dimethoxybenzene to give 4-methoxybenzonitrile; it was proposed in this case that the methoxyl group is lost from a cationic adduct (**II** in Scheme 1) as formaldehyde, the stable deprotonated form of the electrophile MeO^+.[6a]

The third possibility (path *iii*) is that the leaving group is expelled as a *nucleophile* (X^-) from the primary adduct **I,** thus generating the radical cation of the substitution product $ArNu^{+\bullet}$. Actually, this fragmentation is better known as part of a chain reaction mechanism, (i.e., the $S_{ON}2$ mechanism).[11,12] In this mechanism, it is followed by a single electron transfer from a new substrate molecule to the radical cation $ArNu^{+\bullet}$, thus completing the propagation sequence by giving the substitution product and regenerating the active species $ArX^{+\bullet}$. However, as pointed out by Eberson et al.,[12] simple thermochemical considerations would seem to limit the scope of this mechanism to those cases involving barely oxidizable nucleophiles and leaving groups; otherwise suspicions should arise that both Nu^- and X^- might participate in the substitution process in their oxidized forms, namely, $Nu^\bullet$ and $X^\bullet$ or X^+. Therefore, under the specific oxidative conditions commonly employed, only nucleophiles such as AcO^-, $CF_3CO_2^-$, OH^-, and CN^- and leaving groups such as F^- and Cl^- have so far been judged to be firmly compatible with the $S_{ON}2$ mechanism. Moreover, because of a common situation in oxidative substitution chemistry, namely, that the product ArNu is often more easily oxidized than the substrate ArX, clear evidence for the chain reaction attributes of this mechanism could seldom be achieved and only at a low degree of conversion[12] when ArX/ArNu ratios are high enough to sustain somehow the catalytic efficiency despite the endoergonic electron transfer from ArX to $ArNu^{+\bullet}$.

In 1988, a product study[13] aimed at identifying one of the two radical cations observed during single electron oxidation of *N*,*N*-dimethyl-*p*-anisidine (**1a**) provided us with a new example of aromatic substitution promoted by oxidation, the formation of a tetrasubstituted 1,4-benzenediamine **3** by reaction of **1a** with a secondary aniline **2-H** in the presence of thallium triacetate (TTA) as the oxidant. Relevant to the chemistry described above, we have now investigated this reaction (eq 1) in consideration of the fact that it constitutes a particularly interesting novel situation for evaluating the mechanistic variety summarized in Scheme 1.



(1)

Results and Discussion

Seeking optimum reaction conditions, we performed control experiments for the reaction of *N*,*N*-dimethyl-*p*-anisidine (**1a**) with *N*-methylaniline (**2b-H**) and TTA. Although we have already reported on the effectiveness of TTA in oxidizing *N*-methylated anisidines to the corresponding radical cations without any reference to its hydrate form,[13,14] we are now forced to specify that we had always been using sesquihydrate TTA. Fortuitous circumstances in the present research showed that anhydrous TTA was quite ineffective as an oxidant but performed better in reactions when small quantities of water were added to the solvent.[15] The oxidative activation was relatively effective in both nitromethane and acetonitrile, whereas it was substantially absent in dichloromethane. The efficiency of the MeO-substitution leading to the 1,4-benzenediamine derivative **3b** was contrasted with the concurrent demethylation of **1**, as inferred from the detection in the reaction mixtures not so much of small amounts of *N*-methyl-*p*-anisidine (**2a-H**) but primarily of **3a**, which is the product of subsequent MeO-substitution by this secondary anisidine (Scheme 2).

Scheme 2

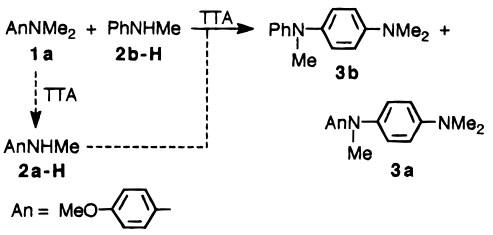


Table 1. Reaction between *N*,*N*-Dimethyl-*p*-anisidine (1a) and *N*-Methylaniline (2b-H) in the Presence of Thallium Triacetate Sesquihydrate (TTA)

run	solvent	TTA/1a	reactn time (min)	conv[a] (%)	**3b** yield[a] (%)	**3a/3b**
1	$MeNO_2$	1	20	40	47	0.26
			60	48	35	0.23
2	MeCN	1	20			1
3	$MeNO_2$	2	5	44	68	
			20	45	44	0.1
			60	47	38	
4	MeCN	2	20			0.15
5	$MeNO_2$	3	5	40	75	<0.05
			20	64	39	

[a] As determined by GC; yelds are based on the amount of substrate consumed.

Inspection of **3a**/**3b** ratios reported in Table 1 shows that more competing demethylation took place in acetonitrile and at lower oxidant-to-substrate molar ratios (TTA/1). Use of a 3-fold excess of TTA in $MeNO_2$ (entry 5) inhibited this undesired side reaction to the adequately negligible extent of less than 5%. The yields of **3b** and substrate conversions at various reaction times are also included in Table 1 and reveal that the substitution process takes place with maximum efficiency within a few minutes when conversion is less than 50%. In the case of highest oxidant excess (TTA/1 = 3), the reaction could be forced to reach a 64% conversion after a longer time (20 min), but this occurred at the expense of yield, which fell from 75% to 39%.

The reaction of **1a** with different secondary amines was thus carried out on a larger scale in $MeNO_2$ in the

(11) Alder, R. W. *Chem. Commun.* **1980**, 1184.
(12) Eberson, L.; Jönsson, L.; Wistrand, L.-G. *Tetrahedron* **1982**, *38*, 1087 and references therein.
(13) Ciminale, F.; Curci, R.; Portacci, M.; Troisi, L. *Tetrahedron Lett.* **1988**, *29*, 2463.
(14) Ciminale, F. *Tetrahedron Lett.* **1994**, *35*, 3375.
(15) In view of the two mecanisms for the oxidation of a tertiary amine with TTA reported in the next reference, it is conceivable that water might have a certain influence on the oxidative power of TTA because it would enter as a component of the metal coordination shell.

Table 2. Substitution Products from Reactions of *N,N*-Dimethylanilines (*p*-$XC_6H_4NMe_2$) 1a−c with Secondary Amines 2(a−f)-H, Promoted by Thallium Triacetate Sesquihydrate

p-$XC_6H_4NMe_2$	amine	products (yield, %)[a]	conv[b] (%)
1a (X = MeO)	**2a-H**	**3a** (40)	45
	2b-H	**3b** (44)	50
	2c-H	**3c** (53)	53
	2d-H	**3d** (35), **4** (8)	55
	2e-H	**3a** (na)	
	2f-H	**3a** (na)	
1b (X = H)	**2a-H**	**3a** (ca. 20)[c]	
	2b-H	**3b**[d]	
	2c-H	**3c**[d]	
	2d-H	**3d** (39)[e]	41[e,f]
1c (X = F)	**2a-H**	**3b**[d]	
	2b-H	**3c**[d]	
	2c-H	**3c** (ca. 10)[c]	
	2d-H	**3d** (63)[e]	31[e,f]

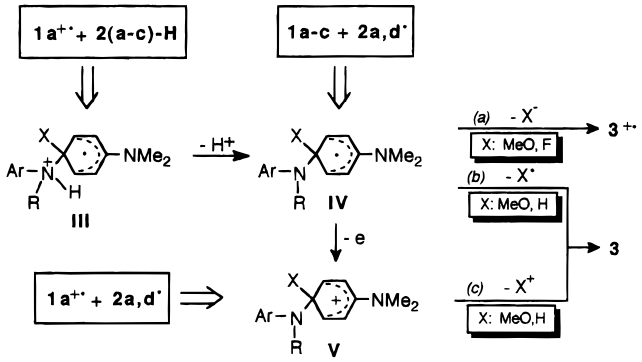
[a] Unless otherwise noted, yields refer to isolated products and are based on the amount of substrate reacted; na = not analyzed. [b] Unless otherwise noted, conversions refer to **1a−c**. [c] As estimated by GC−MS. [d] Negligible amounts. [e] As determined by ^{1}H NMR (see Experimental Section). [f] Conversion referred to **2d-H**.

presence of a 3-fold excess of TTA over ca. 10 min. As shown in Table 2, with *N*-methylanilines **2(a−c)-H**, the direct amino-demethoxylation products **3a−c** could be isolated for characterization in 40−53% yields following a reductive workup of the reaction mixtures (see Experimental Section) in which they were present in the oxidized form of radical cation. The yield of recovered **1a** was 47−55%. Similarly, reaction with diphenylamine (**2d-H**) afforded the MeO-substitution product **3d** in 35% yield at 55% conversion. This, however, could not be fully isolated but was eventually obtained in mixture with a minor (8%) nuclear H-substitution product (most likely **4**) and unreacted **2d-H**. Thus, product identification and yields were based only on GC−MS and/or ^{1}H NMR analyses of this mixture, as specified in the Experimental Section. It is important to note that in the other cases only comparatively very small amounts of H-substitution products were recognized on GC−MS spectra of the reaction mixtures.

In reactions with *N*-methyl-*p*-nitroaniline (**2e-H**) or diethylamine (**2f-H**), only relevant undetermined quantities of the same 1,4-benzenediamine **3a** were detected, indicating that **2e,f-H** are incompatible with substitution. The reasons for such an incompatibility with direct MeO-substitution should be different in the two cases and will be discussed later on.

With the support of ESR detection, we have already verified that radical cation **1a**$^{+\bullet}$ is the primary reactive intermediate involved in demethylation of **1** with TTA.[13] According to the commonly accepted mechanism for oxidative dealkylation of tertiary amines,[16] the decomposition of **1a**$^{+\bullet}$ would be triggered by its rapid deprotonation.[17] Concerning the formation of substitution products of type **3**, we have also advanced that this reaction might proceed through a nucleophilic attack of a secondary aniline on the same aminium intermediate **1a**$^{+\bullet}$. Starting from the resulting adduct **III**, a conceivable

Scheme 3



reaction pathway for this amino-demethoxylation is delineated in Scheme 3 as a proper adaptation of the general Scheme 1 on the basis of the one proton difference between related nucleophilic species. In fact, **III** should easily lose a proton to give the homolytic adduct **IV** that might get involved in the product-forming step either directly (path *a* or *b*) or by undergoing oxidative transformation into the Wheland adduct **V** (path *c*). However, it is worth considering that path *a* is not experimentally discernible from paths *b* and *c* on the basis of the competent oxidation level of the reaction product, which because of its very low oxidation potential[18] is obtained as radical cation **3**$^{+\bullet}$, even though the fragmentation of the proper precursor would imply its primary formation at the lower oxidation level, that is, as **3**.

In line with the working hypothesis of nucleophilic **2-H**/**1a**$^{+\bullet}$ interaction, the competition between demethylation and substitution referred to above seems to be governed by a balance between the basicity of the medium and the nucleophilicity of the attacking amine. In fact, the larger proportion of demethylation observed in acetonitrile at TTA/1 = 1 (entry 2 of Table 1) can be imputed to the relatively higher basicity of this solvent[20] and to the fact that a lower amount of oxidant would cause the aminium radical **1**$^{+\bullet}$ to be generated in the presence of a greater quantity of the basic parent compound. On the other hand, the substitution process is compatible with those secondary aromatic amines, **2a−c-H**, that evidently may be considered too weak as bases and good enough as nucleophiles. Moreover, with aliphatic amine **2f-H** and nitro-substituted secondary aniline **2e-H**, deprotonation is the dominant process owing to a considerable basicity of the former and a scarce nucleophilicity of the latter amine. In this case, the observed reactivity is akin to that displayed in the absence of any added secondary amine.

However, nucleophilic addition of the secondary amine **2d-H** to **1a**$^{+\bullet}$ is no longer applicable to the formation of the direct substitution product **3d** in the case of diphenylamine. In fact, judging from pK_a values[21] of the corresponding ammonium ions, **2d-H** (pK_a = 0.79) should be considered at least as feeble a nucleophile as **2e-H** (pK_a > 1)[22] and likewise incapable of adding to **1**$^{+\bullet}$. The

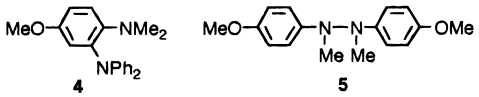
(16) Butler, R. N. *Chem. Rev.* **1984**, *84*, 249.
(17) Large deprotonation rates ($k \approx 10^4-10^5$ M^{-1} s^{-1}) have been determined for radical cations of *N,N*-dimethyl-*p*-anisidine and of related di-*p*-anisylmethylamine: (a) Zhang, X.; Yeh, S.-R.; Hong, S.; Freccero, M.; Albini, A.; Falvey, D. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, *116*, 4211. (b) Dinnocenzo, J. P.; Banach, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 8646.
(18) As a typical oxidation potential of compounds **3**, the $E_{1/2}$ value of *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine, reported in ref 19, may be considered: −0.10 V (CH_3CN, vs Ag/0.01 N Ag^+); a comparatively higher value is reported for **1a**: 0.33 V (CH_3CN, vs Ag/0.01 N Ag^+).
(19) Weinberg, N. L.; Weinberg, H. R. *Chem. Rev.* **1968**, *68*, 449.
(20) Bagno, A.; Scorrano, G. *J. Am. Chem. Soc.* **1988**, *110*, 4577.
(21) Perrin, D. D. *Dissociation Constants of Organic Bases*; Plenum Press: New York, 1965.
(22) The pK_a of *N*-methyl-*p*-nitroaniline was estimated by referring to the nonmethylated analogue: pK_a = 1.

fact that **2d-H**, in contrast to **2e-H**, is nevertheless involved in a substitution reaction might be due to its relatively lower oxidation potential [E_{ox}(**2d**) − E_{ox}(**2e**) ≅ −0.3 V],[23] suggesting that diphenylamine can actually participate in the associative step in an oxidized form. Moreover, a comparison of oxidation potentials based on $E_{1/2}$ values indicates that **2d-H** ($E_{1/2}$ = 0.39 V vs Ag/0.01 N Ag^+)[24] has an oxidation potential close to that of oxidizable **1a** ($E_{1/2}$ = 0.33 V vs Ag/0.01 N Ag^+)[19] and, consequently, its oxidation by TTA is very likely.

Reaction pathways based on other plausible combinations of active species in addition to **2-H**/**1a**$^{+\bullet}$ are also traced in Scheme 3. Thus, for oxidizable secondary amines such as **2d-H**, a suitable sequence might involve an amino radical **2d**$^\bullet$, most likely engendered by rapid deprotonation of the primary product of one-electron oxidation, **2d-H**$^{+\bullet}$. The homolytic addition of **2d**$^\bullet$ to **1a** would directly produce adduct **IV**, which in the first formulation follows the initial formation of adduct **III**, deriving from the **2-H**/**1a**$^{+\bullet}$ interaction. Another conceivable alternative for **2d**$^\bullet$ should be the coupling with **1a**$^{+\bullet}$ to give directly adduct **V** as a likely precursor of the substitution product. It is altogether reasonable to believe that a radical rather than a nucleophilic involvement of the secondary amine might be the cause of the observed different regioselectivity of **2d-H** giving relatively more conspicuous H-substitution than **2(a**−**c)-H**.

Taking advantage of the fact that, according to Scheme 3, the combination **1**/**2**$^\bullet$ is the only viable reaction pathway for substrates that, contrary to **1a**, are not amenable to oxidation, we sought to substantiate the supposed radical reactivity of **2d-H** as distinct from the nucleophilic reactivity of **2(a**−**c)-H** with recourse to analogous reactions with *N*,*N*-dimethylaniline (**1b**) and *N*,*N*-dimethyl-*p*-fluoroaniline (**1c**). These analogues of **1a**, bearing potential leaving groups (X = H, F) compatible with oxidative substitution, were chosen as appropriate substrates because they can be reasonably considered as relatively more difficult to oxidize. In fact, compared to **1a** ($E_{p/2}$[25] = 0.49 V vs SCE),[26] **1b** is reported to have a higher redox potential ($E_{p/2}$ = 0.71 V vs SCE), and its radical cation **1b**$^{+\bullet}$ is reported to be highly unstable.[26] For **1c**, we could roughly estimate an equally high redox potential ($E_{p/2}$ ≈ 0.74 V) by applying the electronic effect correlation of para substituents (σ^+ values)[27] with related $E_{p/2}$ values reported in the same electrochemical study.[26] In addition, direct evidence that **1c** is rather resistant to oxidation under our reaction conditions (i.e., TTA as oxidant) became available after several ESR attempts to detect its radical cation. Contrary to what had been observed for **1a**$^{+\bullet}$,[13] **1c**$^{+\bullet}$ turned out to be highly unstable inasmuch as to obtain it in detectable amounts it was necessary to effect the oxidation with TTA in the presence of methansulfonic acid.

As expected, substitution was found to occur with substrates **1b**,**c**, but only in reactions with diphenylamine (Table 2). H-substitution at the para position of **1b** and F-substitution on **1c** afforded the same product, **3d**, obtained by MeO-substitution from **1a**, in comparable amounts. In reactions with *N*-methylaniline or *N*-methyl-*p*-fluoroaniline, however, only negligible amounts of the corresponding substitution product **3b,c** were detected by GC−MS analysis. Other significant products that could testify for the occurrence of starting compounds oxidation were not observed except for small amounts of substrate monodemethylation products **2b,c-H**[28] and trace amounts of a *p*,*p*′-homocoupling product, tetramethylbenzidine, in the reactions of **1b**. More appreciable amounts of substitution product **3a** were detected in reactions with methylated *p*-anisidine **2a-H**, mainly in the case of substrate **1b**. Significantly, as revealed by GC−MS data, these reactions were also characterized by a markedly uneven consumption of reactants, namely, an almost complete disappearance of **2a-H** and relatively low conversions of substrates **1b**,**c**. This suggests that **2a-H** undergoes oxidation more easily than **1b**,**c**, and the aminyl radical **2a**$^\bullet$ thus formed, similarly to but to a lesser extent than **2d**$^\bullet$ in the case of diphenylamine, might be responsible for H- or F-substitution on **1b,c**. For the most part, **2a**$^\bullet$, according also to our previous ESR investigation,[14] seems to become involved in homocoupling reactions, as pointed out by the formation of small amounts of *N*,*N*′-bis(4-methoxyphenyl)dimethylhydrazine (**5**), *N*-(4-methoxyphenyl)-*N*,*N*′-dimethyl-1,4-benzenediamine (**6**), and other unidentified products of probable further oxidation.



A closing remark on the mechanistic features of our substitution reaction has to be made concerning the product-forming step. Fragmentation modes (*a* and *b* from adduct **IV** and *c* from adduct **V**) are reported in Scheme 3, each bearing reference to the leaving group(s) that may be considered as likely candidate(s) for that specific cleavage of the C−X bond, consistent with the oxidation level of the resulting X. For the fragmentation of **IV**, we suggest that F and H are the para substituents that should be ejected as X^- (path *a*) and X$^\bullet$ (path *b*), respectively, whereas MeO might be compatible with both of the possibilities. This proposal agrees with Eberson's criterion[12] as applied when considering the redox potentials for both of the fragments of C−X cleavage, namely, for **3**$^{+\bullet}$/**3**[29] and X$^\bullet$/X^- [30] couples. For X leaving as X^+ from **V** (path *c*), the proposed compatibility with MeO and H and the exclusion of F are simply in

(23) This difference in oxidation potentials was roughly estimated on the basis of $E_{1/2}$ or $E_{p/2}$ values reported in ref 19; in default of data referring to *N*-methyl-*p*-nitroaniline, the $E_{p/2}$ of the *N*,*N*-dimethyl analogue was considered.

(24) This $E_{1/2}$ value vs Ag/0.01 N Ag^+ was derived from that given vs SCE in ref 19 taking into account the difference of 0.44 V between the oxidation potentials of the two reference electrodes.

(25) Used, instead of the formerly quoted $E_{1/2}$ value, to allow a more homogeneous comparison with the available oxidation potential of **1b** given as $E_{p/2}$.

(26) 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.

(27) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979.

(28) This otherwise banal claim about detection of demethylation products must, obviously, be understood as referring to reactions in which substrate **1** and secondary aniline **2-H** are differently substituted at the para position (X ≠ Y).

(29) For a homogeneous comparison with values of ref 27, as typical redox potential of the **3**$^{+\bullet}$/**3** couple, the value of $E°$ = 0.25 V vs NHE for *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine, reported in ref 1, may be considered.

(30) Eberson, L. *Acta Chem. Scand. B* **1984**, *38*, 439.

accord with the well-known reactivity in electrophilic substitutions.

Conclusions

Three different combinations of active species are considered to account for TTA-promoted oxidative substitutions occurring at the para position of *N*,*N*-dimethylanilines **1a**−**c** by several secondary anilines **2(a**−**d)-H** (eq 1): a radical cation−nucleophile combination (**1**$^{+\bullet}$**/2-H**), a substrate−aminyl radical combination (**1/2**$^{\bullet}$), and a radical cation−aminyl radical combination (**1**$^{+\bullet}$**/2**$^{\bullet}$). Which one is in fact involved depends on whether the oxidative activation is effected on the substrate, on the secondary aniline, or on both of the reactants, respectively. The results reported herein suggest that, in the case of easily oxidizable substrate **1a**, the MeO-substitution may proceed either via nucleophilic attack at the substrate radical cation (**1**$^{+\bullet}$**/2-H** interaction) with barely oxidizable secondary anilines such as **2(b,c)-H** or via attack by the aminyl radical **2d**$^{\bullet}$ on the original (**1/2**$^{\bullet}$ interaction) and/or oxidized (**1**$^{+\bullet}$**/2**$^{\bullet}$ interaction) substrate with easily oxidizable and non nucleophilic **2d-H**. Obviously, all three reaction modes would be compatible with oxidizable and nucleophilic **2a-H**. In line with such a reactivity pattern, it was found that dimethylanilines **1b,c**, despite being relatively difficult to convert into reactive radical cations, nevertheless undergo substitution (H- and F-substitution, respectively) but only with oxidizable secondary anilines, **2a,d-H**; a **1/2**$^{\bullet}$ interaction is evidently the unique viable pathway for these substrates.

The **1**$^{+\bullet}$**/2-H** interaction is currently being investigated in more detail by a more direct approach based on isolable **1**$^{+\bullet}$ analogues.

Experimental Section

Materials. Commercially available $MeNO_2$ (Aldrich HPLC) and MeCN (Fluka purum) were used as solvents without further purification. Thallium triacetate sesquihydrate (TTA) (Aldrich) was also used as received. *N*,*N*-dimethyl-*p*-anisidine (**1a**) was prepared by methylation of commercial (Aldrich) *p*-anisidine by Me_2SO_4 following a described procedure.[31] *N*,*N*-dimethyl-*p*-fluoroaniline (**1c**) and *N*-methyl-*p*-fluoroaniline (**2c-H**) were obtained in a single preparation by methylation of neat *p*-fluoroaniline (Lancaster Synthesis) (7.2 g, 65 mmol) with CH_3I (9.2 g, 65 mmol) and flash column chromatography (hexanes/Et_2O 5:2) of the crude of reaction. **1c** (1 g): mp 33−35 °C [lit.[32] 33 °C]; IR (KBr) 3051, 2925−2805, 1611, 1515, 1347 (C−N), 1228 (C−F), 816 (substitution band) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.90 (s, 6H), 6.64−6.72 (m, 2H), 6.90−7.02 (m, 2H); MS *m*/*z* (rel abundance) 139 (M^+, 73), 138 (100), 123 (20), 122 (21), 95 (20), 75 (14), 42 (12). **2c-H** (1.5 g): oil [lit.[33] bp 136 °C (120 mmHg)]; IR (neat) 3420 (N−H), 3060, 3000−2800, 1612, 1472, 1512, 1320 (C−N), 1220 (C−F), 821 (substitution band) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.80 (s, 3H), 3.33 (bs, 1H), 6.51−6.62 (m, 2H), 6.86−6.98 (m, 2H); MS *m*/*z* (rel abundance) 125 (M^+, 78), 124 (100), 97 (19), 96 (16), 95 (15), 83 (19), 75 (16), 57 (12). *N*,*N*-dimethylaniline (**1b**) (Aldrich), *N*-methylaniline (**2b-H**) (Janssen), *N*-methyl-*p*-nitroaniline (**2e-H**) (Aldrich), and diphenylamine (**2d-H**) (Aldrich) were used without further purification. *N*-methyl-*p*-anisidine (**2a-H**) (Aldrich) was recrystallized (ligroin, 80−120 °C) before use.

(31) Bordwell, F. G.; Boutan, P. J. *J. Am. Chem. Soc.* **1956**, *78*, 87.
(32) Sellers, C.; Suschitzky, H. *J. Chem. Soc.* **1965**, 6186.
(33) Fox, B. L.; Doll, R. J. *J. Org. Chem.* **1973**, *38*, 1136.

Optimization Studies. Gas chromatographic analyses on the proceeding reaction to determine percent substrate conversions and product yields reported in Table 1 were performed according to the following general procedure. An equimolar solution (typically 6.6×10^{-2} M) of anilines **1a** and **2b-H** in 5 mL of the selected solvent was added dropwise to a magnetically stirred suspension of an appropriate quantity of TTA in 15 mL of the same solvent. The reaction solution immediately turned blue and became paramagnetic (ESR tested) as a result of the formation of the radical cation of the substitution product(s). Aliquots (4 mL) of this solution were then withdrawn at timed intervals and subjected to reducing treatment with a 10% $Na_2S_2O_3$ solution (ca. 30 mL). After the blue color faded, each aliquot was extracted with diethyl ether. The extracts were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The residue was then taken up in 0.5 mL of a 0.1 M solution of *p*-anisidine, which served as an internal standard in the subsequent quantitative GC analysis.

Isolation and Characterization of Substitution Products. The general procedure adopted to isolate substitution products **3a**−**d** is as follows. A solution of **1a** (0.25 g, 1.6 mmol) and an equimolar quantity of the appropriate secondary aniline from among **2(a**−**d)-H** in $MeNO_2$ (15 mL) was added dropwise to a stirred suspension of TTA (1.94 g, 4.7 mmol) in 60 mL of the same solvent. After the addition, the resultant blue mixture was allowed to react for 10 min, treated with a solution of $Na_2S_2O_3$ (10%, 250 mL), and extracted with diethyl ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, petroleum ether/Et_2O 5:2) of the residue gave substitution products **3a**−**c** separated from unreacted **1a** (minor materials were left unrecovered in column). Similar chromatographic treatment (eluant, petroleum ether/Et_2O 4:1), when applied to the crude of the reaction with **2d-H**, afforded **3d** mixed with unreacted **2d-H** and another substitution product (see below). All NMR spectra of substitution products were recorded in $(CD_3)_2CO$. The use of this solvent rather than $CDCl_3$ was prescribed by the occurrence in the latter solvent of spontaneous oxidation of 1,4-benzenedianmines **3a**−**d** to the corresponding radical cations (solutions took on a shade of blue), causing disturbing paramagnetic broadening of NMR resonances. Such a broadening effect was also observed in a limited fashion in uncolored $(CD_3)_2CO$ solutions but could be completely eliminated on treating the samples with powdered zinc prior to recording the spectrum.

***N*-(4-Methoxyphenyl)-*N*,*N*′,*N*′-trimethyl-1,4-benzenediamine (3a)**: 74 mg (40%) [133 mg of recovered **1a**, conv. 45%]; mp 104−105 °C (recrystallized from hexane/dichloromethane); IR (KBr) 3037, 2988−2805, 1612, 1505, 1333 (C−N), 1240 (Ar−O), 1033 (O−CH_3), 830 and 820 (substitution bands) cm^{-1}; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 2.88 (s, 6H), 3.16 (s, 3H), 3.73 (s, 3H), 6.72−6.96 (m, 8H); ^{13}C NMR (125.76 MHz, $(CD_3)_2CO$) δ 41.2 (two partially overlapped signals are distinguishable on the enlarged spectrum, 41.18 and 41.22), 55.7, 114.7, 115.1, 119.8, 124.2, 141.2, 145.2, 147.8, 154.2; MS *m*/*z* (rel abundance) 256 (M^+, 100), 241 (68), 226 (41), 120 (12).

***N*,*N*,*N*′-Trimethyl-*N*′-phenyl-1,4-benzenediamine (3b)**: 80 mg (44%) [121 mg of recovered **1a**, conv. 50%]; mp 44−45 °C; IR (KBr) 3034, 2878−2803, 1600, 1519, 1338 (C−N), 822 and 750 (substitution bands); ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 2.91 (s, 6H), 3.19(s, 3H), 6.65−6.78 (m, 5H), 6.99−7.15 (m, 4H); ^{13}C NMR (125.76 MHz, $(CD_3)_2CO$) δ 40.6, 40.9, 114.4, 115.2, 117.9, 127.5, 129.4, 139.4, 149.2, 151.2; MS *m*/*z* (rel abundance) 226 (M^+, 100), 211 (63), 196 (17), 167 (37), 77 (33).

***N*-(4-Fluorophenyl)-*N*,*N*′,*N*′-trimethyl-1,4-benzenediamine (3c)**: 114 mg (53%) [117 mg of recovered **1a**, conv. 53%]; mp 92−93 °C; IR (KBr) 3039, 2982−2804, 1609, 1504, 1340 (C−N), 1212 (C−F), 822 and 807 (substitution bands) cm^{-1}; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 2.9O (s, 6H), 3.16(s, 3H), 6.65−6.77 (m, 4H), 6.86−7.01 (m, 4H); ^{13}C NMR (125.76 MHz, $(CD_3)_2CO$) δ 40.9, 41.1, 114.5, 115.7 (d, $^2J_{CF}$ = 22.1 Hz), 117.0 (d, $^3J_{CF}$ = 7.4 Hz), 126.6, 139.8, 148.0, 149.0, 156.7 (d, $^1J_{CF}$ = 233.9 Hz); MS *m*/*z* (rel abundance) 244 (M^+, 100), 229 (73), 185 (49), 122 (20).

***N,N*-Dimethyl-*N′,N′*-diphenyl-1,4-benzenediamine (3d)**: MS *m*/*z* (rel abundance) 288 (M^+, 100), 273 (35), 167 (43), 144 (25), 77 (46), 51 (27); ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 2.87 (s, 6H). These spectroscopic characteristics were reliably extracted from proton NMR and GC−MS spectra of a chromatographic fraction (250 mg) that, in addition to **3d**, was composed of unreacted **2d-H** and a product that was identified as the H-substitution product **4** on the basis of the following spectroscopic data: MS *m*/*z* (rel abundance) 318 (M^+, 100), 303 (13), 286 (24), 77 (82), 51 (42); ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 2.47 (s, 6H), 3.65 (s, 3H). **2d-H** conversion (55%) and related product yields (**3d**, 35%; **4**, 8%) were easily estimated on quantitative ^{1}H NMR analysis of the chromatographic mixture. The OMe and NMe_2 protons of **4** were clearly distinguishable in the spectrum of the original $(CD_3)_2CO$ solution by the correct intensity ratio (1:2) of their signals. The broad singlet (δ, 7.48) of the exchangeable NH proton of **2d-H** was advantageously eliminated from the aromatic chemical shift region on treatment with D_2O. Final integrals measurement for quantitative analysis was performed after debroadening powdered Zn treatment of this solution.

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