Electrophilic substitution of the *tert*-butyl-*NNO*-azoxy group by the bromine atom

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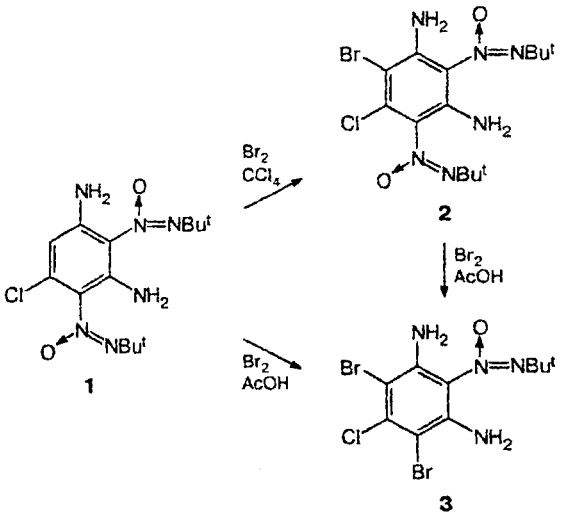
The electrophilic substitution of the *tert*-butyl-*NNO*-azoxy group by the bromine atom was observed for the first time when 6-bromo-2,4-bis(*tert*-butyl-*NNO*-azoxy)-5-chloro-1,3-phenylenediamine was treated with bromine in AcOH. The structural factors promoting this reaction are discussed. The direction of the replacement was confirmed by PM3 calculations of the heats of formation of intermediate cationic σ-adducts.

Key words: *meta*-phenylenediamine derivatives; azoxy compounds; substitutive electrophilic bromination.

Generally, the proton is a leaving group in electrophilic aromatic substitution. *ipso*-Substitution, in which an electrophile attacks the already replaced carbon atom, occurs much more rarely.[1] Usually, a leaving group readily stabilizes the positive charge (for example, Bu^t or $SiMe_3$). It is rare for electron-withdrawing groups to act as leaving groups. For example, electrophilic replacement of the sulfo group and the bromine atom were reported.[1] In this work, we report the replacement of yet another electronegative group, *viz.*, the *tert*-butyl-*NNO*-azoxy group.

In the previous study,[2] we have demonstrated that treatment of 2,4-bis(*tert*-butyl-*NNO*-azoxy)-5-chloro-1,3-phenylenediamine (**1**) with bromine in CCl_4 leads to the usual replacement of the hydrogen atom by the bromine atom to form derivative **2**. In this work, it was found that this reaction performed in AcOH was not terminated in the first stage and was accompanied by the replacement of one of the *tert*-butyl-*NNO*-azoxy groups in bromide **2** by the bromine atom to form compound **3** (Scheme 1), the rates of these two stages being comparable.

Scheme 1



When the reaction was carried out with the use of one equivalent of Br_2, the initial phenylenediamine **1** remained partially unconsumed in the reaction mixture and compounds **2** and **3** were formed. If bromination was carried out until the initial compound **1** completely disappeared, products **2** and **3** were obtained in a ratio of ~3 : 4. When two equivalents of Br_2 were added, phenylenediamine **3** was obtained as the major product. Product **3** was also formed when **2** was used as the initial compound. Note that the replacement of the azoxy group occurred under very mild conditions, *viz.*, immediately after the reagents were mixed at 20 °C.

It was established by ^1H and ^{13}C NMR spectroscopy that compound **3** has a symmetrical structure, *i.e.*, only the azoxy group, with respect to which the amino groups are in the *ortho* and *para* positions, is replaced.

Apparently, the reaction under study is ionic in character. Note that the electrophilic replacement of the azoxy group has not been observed previously. The replacement of the azoxy group is particularly surprising because molecular bromine in acetic acid exhibits rather weak electrophilic properties.[3]

Note that this reaction is sensitive to the structure of the substrate. Thus, compound **4**, containing the azoxy groups at positions 4 and 6, does not react with bromine in acetic acid even upon prolonged storage (Scheme 2).

Apparently, the replacement of the azoxy group in compound **2** by the bromine atom is substantially pro-

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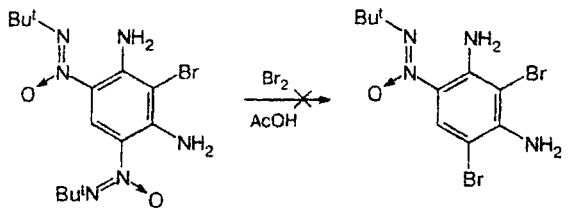
Scheme 2

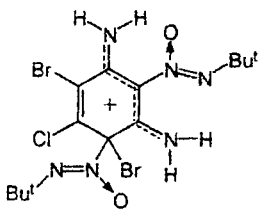


4 **5**

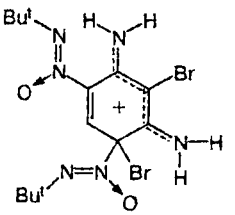
moted by the cooperative effect of two amino groups, which essentially stabilize the intermediate cationic σ-adduct **6** (Scheme 3). It is also probable that cationic σ-adduct **7**, which could cause the replacement of the azoxy group by the bromine atom at position 2, is thermodynamically less favorable than σ-adduct **6**. It can also be suggested that σ-adduct **8**, which could be formed from diamine **4**, is less stabilized than adduct **6**.

The thermodynamic stability of the isomers can be compared directly using the heats of their formation ($\Delta H°_f$). Actually, the heat of formation of σ-adduct **6**, which was calculated by the semiempirical PM3 method with full optimization of geometric parameters,[4] is ~6 kcal mol^{-1} smaller than the heat of formation of compound **7** (Scheme 3).

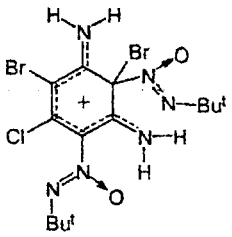
Scheme 3



6



8



7

Adduct	$\Delta H°_f$/kcal mol^{-1}
6	233.0
7	238.9

With the aim of revealing the generality of the reaction under study and explaining inertness of diamine **4** under these conditions, we performed calculations for a number of model compounds. The heats of formation ($\Delta H°_f$) of *C*-protonation products of *m*-phenylenediamine **9a,b**, compounds **10**—**13**, and cationic σ-adducts, which were obtained upon *C*-protonation or *C*-bromination of the latter compounds, are presented in Scheme 4.* Note that the heats of formation of isomers **10** and **11**, like those of compounds **12** and **13**, are virtually identical.

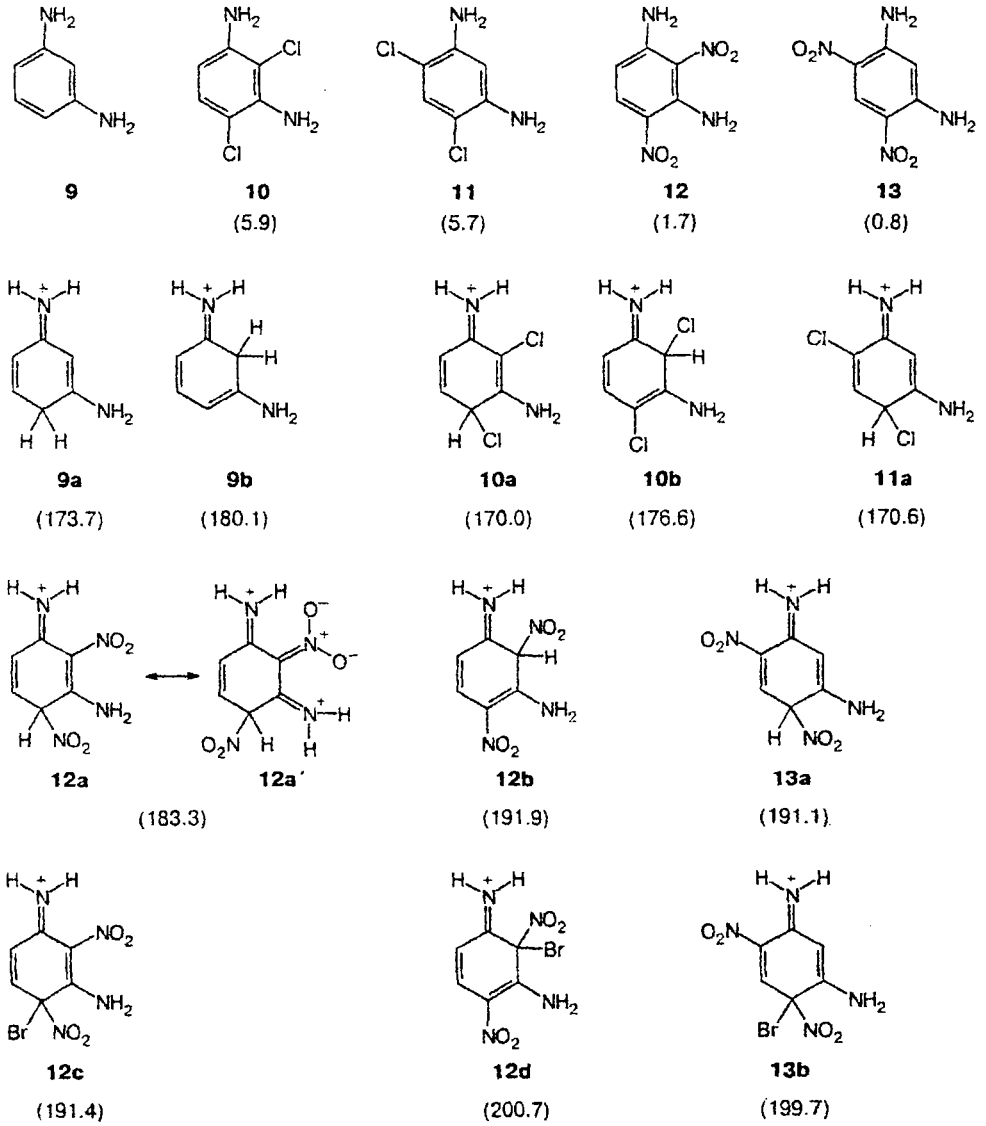
Protonation of compounds **9**—**13** at position 4 afforded σ-adducts containing the amino groups in the *ortho* and *para* positions, whereas protonation at position 2 yielded σ-adducts in which both amino groups are in the *ortho* positions with respect to the protonation site. From Scheme 4 it can be seen that 4-protonated σ-adducts **9a** and **10a** prepared from 1,3-phenylenediamines **9** and **10** are more stable than 2-protonated σ-adducts **9b** and **10b** (by ~6 kcal mol^{-1}). For σ-adducts **12a** and **12b** prepared upon protonation of diamine **12**, this difference is even larger ($\Delta\Delta H°_f$ is 8.6 kcal mol^{-1}). The difference between the heats of formation of brominated adducts **12c** and **12d** is approximately the same ($\Delta\Delta H°_f$ is 9.3 kcal mol^{-1}). Therefore, in the case of 1,3-phenylenediamines, the fact that the electrophilic attack occurs predominantly at position 4 rather than at position 2 is the common phenomenon. This agrees with the published data, for example, on azo coupling of 1,3-phenylenediamine with diazonium salts.[5]

With the aim of elucidating the reasons for the fact that the replacement of the azoxy group in diamine **4**, which is structurally similar to diamine **3**, does not occur, we performed calculations for protonated adducts prepared from the model dichlorophenylenediamines **10** and **11**. It appeared that to a first approximation the rate of the electrophilic attack for these compounds should be independent of the arrangement of the chlorine atoms, because the thermodynamic stabilities of adducts **10a** and **11a** are approximately identical. At the same time, the adducts prepared upon protonation of nitro isomers **12** and **13** are substantially different, namely, adduct **12a** is ~8 kcal mol^{-1} more stable than **13a**. The same difference in the stability is also observed for brominated adducts **12c** and **13b**. Apparently, this is attributable to the specificity of the nitro group or another isoelectronic group, for example, of the azoxy group. This specificity is clearly seen in the case of resonance structure **12a'** (Scheme 4), whose nitro group is conjugated with both amino groups. For adduct **13a**, this conjugation is impossible. The attack at position 2 of 4-nitro-1,3-phenylenediamine in the azo coupling reaction with a diazonium salt[5] can be explained analogously.

In conclusion it should be noted that the *tert*-butyl-*NNO*-azoxy group, unlike, for example, the nitro group,[6] is, apparently, eliminated irreversibly. This is associated with the ease of decomposition of the leaving cation to

* For all compounds, except for **12a**, only one of the limiting resonance structures is given in Scheme 4.

Scheme 4



Note. The calculated heats of formation (ΔH°_{f}/kcal mol^{-1}) for diamines **10**—**13** and cationic σ-adducts **9a,b**, **10a,b**, **11a**, **12a**—**d**, and **13a,b** prepared from these diamines are given in parentheses.

the *tert*-butyl cation and N_2O. It is also not inconceivable that the *tert*-butyl cation and N_2O are simultaneously eliminated upon decomposition of the cationic σ-adduct. Apparently, this irreversibility is the reason for the ease of this reaction in the case where the cationic σ-adduct is formed even at low concentration. It may be difficult to perform direct detection of cations of this type. In this connection, compounds containing the *tert*-butyl-*NNO*-azoxy group can serve as models for studying electrophilic *ipso*-substitution.

Experimental

The IR spectra were recorded on a Perkin-Elmer 577 spectrometer. The mass spectra were measured on a Kratos MS-30 instrument (EI, 70 eV); for the fragments containing the chloride and bromide anions, only signals from the ^{35}Cl and ^{79}Br isotopes, respectively, are reported. The ^{1}H, ^{13}C, and ^{14}N NMR spectra were obtained on a Bruker AM-300 spectrometer operating at 300.13, 75.5, and 21.5 MHz, respectively. The ^{14}N NMR chemical shifts are given in the δ scale relative to nitromethane. The assignment of the signals in the

^{13}C NMR spectra was made using calculation methods. The course of the reactions was monitored by TLC on Silufol UV-254 plates. The column chromatography was carried out with the use of silica gel.

Compounds **1** and **2** were prepared according to procedures reported previously.[2] Phenylenediamine **4** was prepared according to a known procedure.[7]

4,6-Dibromo-2-(*tert*-butyl-*NNO*-azoxy)-5-chloro-1,3-phenylenediamine (3). ***A.*** A solution of Br_2 (0.05 g, 0.3 mmol) in AcOH (1 mL) was added dropwise with intense stirring at 20 °C to a solution of compound **2** (0.13 g, 0.3 mmol) and AcONa (0.03 g, 0.4 mmol) in glacial AcOH (3 mL). After 5 min, the reaction mixture was poured into H_2O (50 mL), extracted with CH_2Cl_2, and dried ($MgSO_4$). The solvent was evaporated *in vacuo*. Chromatography (benzene as the eluent) of the residue afforded pale-yellow crystalline compound **3** in a yield of 0.09 g (73%), m.p. 133—135 °C (from MeOH). Found (%): C, 30.14; H, 3.24; Br+Cl, 48.53; N, 14.12. $C_{10}H_{13}Br_2ClN_4O$. Calculated (%): C, 29.99; H, 3.27; Br, 39.90; Cl, 8.85; N, 13.99. ^1H NMR ($CDCl_3$), δ: 1.50 (s, 9 H, 3 Me); 5.34 (br.s, 4 H, 2 NH_2). ^{13}C NMR ($(CD_3)_2CO$), δ: 26.0 (Me); 60.8 ($\underline{C}Me_3$); 98.1 (C-4, C-6); 136.5 (C-5); 140.9 (C-1, C-3); the signal for C-2 was not observed due to broadening. ^{14}N NMR ($CDCl_3$), δ: −48 (N(O), $\Delta\nu_{1/2}$ = 80 Hz). IR (KBr), ν/cm^{-1}: 1470 (N(O)=N); 3360, 3455 (NH_2). MS, *m/z*: 398 $[M]^+$.

B. A solution of Br_2 (0.1 g, 0.6 mmol) in AcOH (1 mL) was added dropwise with intense stirring at 20 °C to a solution of compound **1** (0.1 g, 0.3 mmol) and AcONa (0.06 g, 0.7 mmol) in glacial AcOH (3 mL). After 5 min, the reaction mixture was treated as described above. Compound **3** was obtained in a yield of 0.08 g (68%).

C. Addition of Br_2 under conditions analogous to those of method B was carried out until the initial compound **1** completely disappeared (TLC control, benzene as the eluent). After the reaction mixture was treated as described above, compounds **2** and **3** were obtained by chromatographic separation (benzene as the eluent) in yields of 0.04 g (33%) and 0.05 g (43%), respectively.

Reaction of 2-bromo-4,6-bis(*tert*-butyl-*NNO*-azoxy)-1,3-phenylenediamine (4) with Br_2. A solution of Br_2 (0.15 g, 0.9 mmol) in AcOH (1 mL) was added to a solution of compound **4** (0.12 g, 0.3 mmol) and AcONa (0.03 g, 0.4 mmol) in glacial AcOH (3 mL). The reaction mixture was kept at 20 °C for 12 h, poured into H_2O (50 mL), extracted with CH_2Cl_2, and dried ($MgSO_4$). The solvent was evaporated *in vacuo*. Unconsumed compound **4** was isolated in a yield of 0.11 g.

References

1. H. Heaney, in *Comprehensive Organic Chemistry*, Eds. D. Barton and D. Ollis, Pergamon Press, New York, 1979, V. **1**, Ch. 2.5.6.
2. A. E. Frumkin, A. M. Churakov, Yu. A. Strelenko, and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 2126 [*Russ. Chem. Bull.*, 1999, 2103 (Engl. Transl.)].
3. M. V. Gorelik and L. S. Efros, *Osnovy khimii i tekhnologii aromaticheskikh soedinenii* [*Fundamentals of Chemistry and Technology of Aromatic Compounds*], Khimiya, Moscow, 1992, Ch. 2.6.1 (in Russian).
4. M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis, and J. A. Montgomery, *J. Comput. Chem.*, 1993, **14**, 1347.
5. Z. J. Allan and F. Mužik, *Coll. Czech. Chem. Commun.*, 1958, **23**, 1927.
6. T. Urbanski, in *The Chemistry of Nitro and Nitroso Groups*, Ed. H. Feuer, Wiley Interscecince, New York, 1970, **2**, 62.
7. A. E. Frumkin, A. M. Churakov, Yu. A. Strelenko, O. Yu. Smirnov, S. L. Ioffe, and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 1307 [*Russ. Chem. Bull.*, 1999, **48**, 1295 (Engl. Transl.)].

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