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Effect of the Electronic Structure of the Radical Anions of 4-Substituted 1,2- and 1,3-Dinitrobenzenes on the Regioselectivity of Reduction of the Nitro Groups

V. Yu. Orlov, R. S. Begunov, N. Yu. Demidova, and A. I. Rusakov

Demidov Yaroslavl State University, ul. Sovetskaya 14, Yaroslavl, 150000 Russia
e-mail: begunov@bio.uniyar.ac.ru

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Abstract—Theoretical and experimental regularities of the regioselectivity of the reduction of one of the two nitro groups in unsymmetrical dinitrobenzenes were studied. It was found that the regioselectivity of the formation of isomeric nitroanilines depends on the structure of the substrate and the nature of the reducing agent. The reduction regioselectivity model was verified, according to which radical anion protonation is the major reaction direction.

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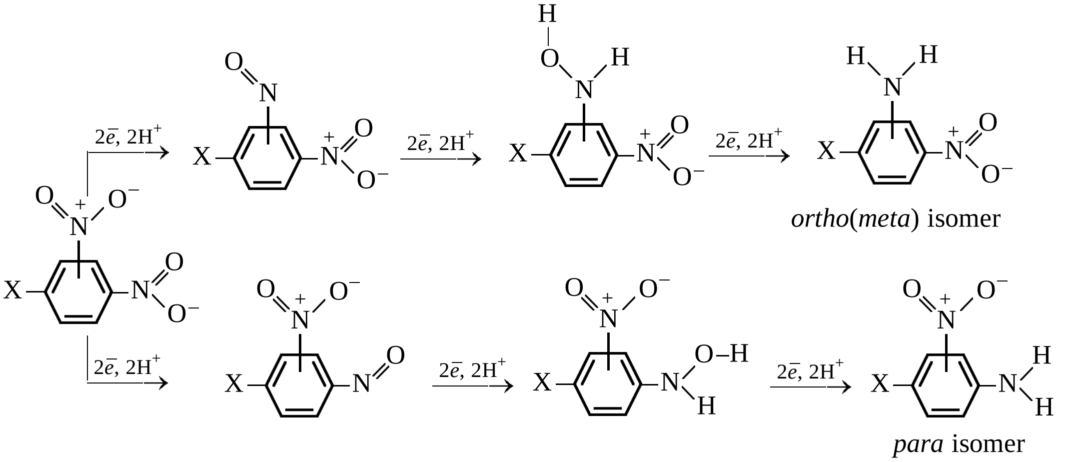
To direct a reaction to one of several potential reaction centers is an urgent problem of synthetic organic chemistry. Hence selective reduction of one of several nitro groups in polynitroaromatic compounds forms one of the basic synthetic approaches to nitroarylamines. Depending on conditions, the reaction can lead to one or another isomeric product. In the present paper we discuss the problem of selective monoreduction of 4-substituted 1,2- and 1,3-dinitrobenzenes. This reaction gives rise to a mixture of isomeric nitroanilines (Scheme 1).

Scheme 1.



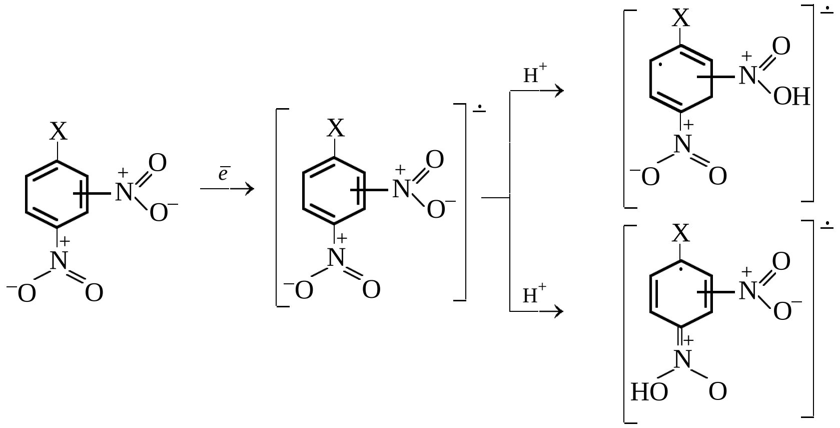
In certain specific conditions, one or the other nitro group is predominantly reduced. We previously found that the direction of the monosubstitution of 4-substituted 1,2- and 1,3-dinitrobenzenes with compounds of varied oxidation state elements depends on the structure of the substrate and the nature of the reducing agent and the solvent [1, 2].

4-Substituted 1,2- and 1,3-dinitrobenzenes were reduced to the corresponding nitroanilines with titanium(III) and tin(II) chlorides (Table 1). The reactions were performed in conditions ensuring nearly quantitative yields of the target products and no diamine formation. This allows the monoreduction regioselectivity to be measured by the ratio of nitroanilines formed, since neither starting dinitro compounds nor reaction products are consumed in side processes.

Our present data, like those reported in the literature, provide evidence to show that the monosubstitution regioselectivity is strongly dependent on the structure of the substrate and the nature of the reducing agent.

To study the effect of substrate structure of the regioselectivity of monoreduction of unsymmetrical dinitrobenzenes, we made use of a model [3, 4], according to which the reaction direction is controlled by protonation of the redical anion species formed in the first stage (Scheme 2).

Scheme 2.



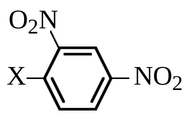
Some authors believed that the reduction direction is controlled by the steric effect of the substituent in the starting structure [5, 6]. Bil'kis and co-workers [7–10] stated, considering radical anions, that the substituent effect is complex in nature and is defined by such parameters as electronic effects, effective volume, and capacity for hydrogen bonding with the *o*-nitro group. However, such interpretation of experimental data is no more than qualitative.

In the present work we made use of quantum-chemical characteristics of corresponding radical anions to assess the effect of the structure of a compound on the direction of the monosubstitution of 4-substituted 1,2- and 1,3-dinitrobenzenes with titanium(III) chloride. The calculation method chosen was AM1. According to published data (including those in [11]), this method and its modifications fairly correctly reproduce the structure of aromatic radical anions. Obviously, monoreduction direction is difficult to correlate with any specific parameter of substituent X. Therefore, we took into consideration the substituent effects on various quantum-chemical characteristics of both reaction centers of radical anions. According to the proposed reaction model (protonation of substrate radical anion), we chose the following quantum-chemical parameters: ratio of the charges on the nitrogen and oxygen atoms of the *p*- and *o*-nitro groups [q_p(O)/q_o(O), q_p(N)/q_o(N)], as well as on the nitro groups themselves (q_p/q_o); and ratio of quantities that relate to the contributions of the oxygen and nitrogen atoms of the *o*- and *p*-nitro groups into the highest occupied molecular orbital (HOMO) of the radical anion [ratio of the squared p_z atomic contributions of the reaction centers into the molecular orbital (C^2p_z)]. The resulting values are listed in Table 2.

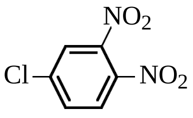
As seen from Table 2, the charge factor has almost no effect on the isomer ratio. Certain correlation is only observed with iodo-2,4-dinitrobenzene, where the preferential formation of the *para* isomer can be correlated with the charge ratio on the oxygen atoms of the nitro groups.

The orbital factor has a stronger effect (see figure). The resulting isomer ratio (3-nitro-4-X-aniline:2-X-5-nitroaniline) and the ratio of the C^2p_z contributions of the oxygen atoms of the *o*- and *p*-nitro groups into the HOMOs of 1-X-2,4-dinitrobenzene radical anions. The values for 2,4-dinitrobenzonitrile and 2,4-dinitrobenzamide do not fit into this correlation. These compounds contain substituents whose atoms contribute much into the HOMOs of the corresponding radical anions and thus are potential protonation centers. Thus, the contribution of the C^2p_z orbital of the cyano nitrogen (0.05584) into the HOMO of the radical anion of

Table 1. Effect of substrate structure on product isomer ratio in reduction of compounds **Ia**–**Ih** and **III** with $TiCl_3$ and $SnCl_2$ (molar ratios : [**Ia**–**Ih, II**] : [$TiCl_3$] = 1 : 3 and [**Ia**–**Ih, II**] : [$SnCl_2$] = 1 : 1.5, methanol–water, conversion 50%, c_{substr} 0.2 M)



Ia–**Ih**



II

Comp. no.	X	Content, %		Isomer yield, %		*p/o* (*m*)
		substrate and aniline[a]	substrate	*para*	*ortho* (*meta*)	
			Reducing agent $TiCl_3$			
Ia	F	92.7	41.07	25.75	25.97	0.99
Ib	Cl	99.8	52.00	36.30	11.70	3.10
Ic	Br	98.0	54.00	37.64	8.36	4.50
Id	I	93.3	43.86	42.36–0.71	4.27–1.54	10–50[b]
Ie	H_3C	91.8	54.17	18.89	21.01	0.90
If	H_3CO	92.0	60.43	20.34	11.22	1.80
Ig	N≡C	96.8	51.23	12.30	33.27	0.37
Ih	$H_2NC(O)$	90.1	43.42	39.16	7.52	5.20
II		97.5	65.00	15.90	19.10	0.83
			Reducing agent $SnCl_2$			
Ib	Cl	99.0	51.00	49.00	[c]	
Ie	H_3C	97.0	57.40	8.50	34.10	0.25
II		98.0	50.45[d]	11.03	23.66	0.47

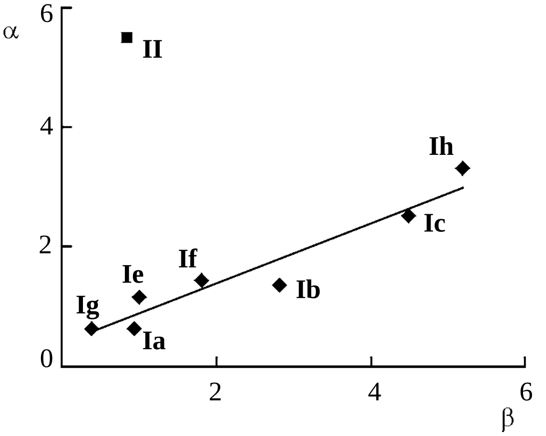
[a] In the reaction mixture. [b] The yield of the *ortho* isomer is extremely low, and its slight variations only slightly affect the nitroaniline isomer ratio. [c] The *ortho* isomer only. [d] Diamine, 12.20%, and unidentified compound, 2.66%, were also found.

Table 2. Ratios of the charges (*q*) and C^2p_z contributions of the oxygen and nitrogen atoms of the *p*- and *o*-nitro groups in the HOMOs of 1-X-2,4-dinitrobenzene radical anions

Comp. no.	*para*/*ortho*	q_p/q_o (N)	q_p/q_o (O)	C^2p_{zp}/C^2p_{zo}(N)	C^2p_{zp}/C^2p_{zo}(O)
Ia	0.99	0.99	1.03	1.19	1.16
Ib	3.10	0.99	1.05	1.39	1.35
Ic	4.50	0.99	1.04	2.20	2.50
Id	10–50[a]	0.99	1.20	48.96	58.64
Ie	0.90	1.01	1.01	1.20	1.17
If	1.80	0.99	1.04	1.44	1.44
Ig	0.37	1.01	1.07	1.56 (0.68)[a]	1.25 (0.63)[a]
Ih	5.20	1.02	0.98	0.71 (3.78)[b]	0.76 (3.34)[b]
II	0.83	0.99	1.03	76.00	5.49

[a] Parenthesized are the ratios of the C^2p_z contributions of the nitrogen and oxygen atoms of the *p*-nitro group and the nitrogen atom of the cyano group. [b] Parenthesized are the ratios of the C^2p_z contributions of the nitrogen and oxygen atoms of the *p*-nitro group and the carbon atom of the amido group.

2,4- dinitrobenzonitrile is higher of the respective contributions of the *p*-NO_2 [C^2p_z 0.03779 (N) and 0.03506 (O)] and *o*-NO_2 groups [C^2p_z 0.02415 (N) and 0.02257 (O)]. Thus, the radical anion should be preferentially protonated by the cyano nitrogen. However, as follows from the energetic characteristics of protonated 2,4-dinitrobenzonitrile radical anions, protonation by the *o*-nitro group is preferred (Δ*H*



Plot of the ratio of the para and ortho isomers (α) vs. ratio of the C^2p_z contributions of the oxygen atoms of the *p*- and *o*-nitro groups (β) in the HOMO of 1-X-2,4-dinitrobenzene radical anions.

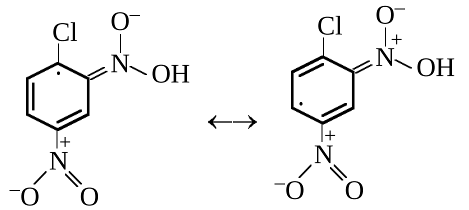
267 kJ mol^{-1}) over protonation by the cyano group (ΔH 303.8 kJ mol^{-1}). This fact suggests that, directing protonation primarily toward the cyano nitrogen, the structure of intermediate species favors protonation by the *o*-nitro group. This is associated either with the deformation of the HOMO of the species protonated by the cyano group [C^2p_z: *o*-NO_2 0.01737 (O) and *p*-NO_2 0.01158 (O)] and the preferential orientation of further protonation to the *o*-nitro group or with proton transfer from the substituent. In the latter case, an important characteristic associated with reduction orientation is the ratio of the C^2p_z values for the nitrogen (or oxygen) atom of the *o*-nitro group and the nitrogen atom of the cyano group (given in parentheses in Table 2). The same pattern is observed with such a protonation-susceptible substituent as the amido group.

Taking into account the characteristics of the possible protonation centers, we can state that the resulting isomer ratio correlates with the orbital characteristics of the 1-X-2,4-dinitrobenzene radical anions (R^2 0.9204).

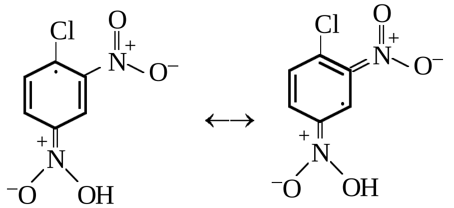
Chloro-3,4-dinitrobenzene falls out of the above correlation (see figure). The fraction of the *para* isomer is much lower and that the *meta* isomer is much higher than expected by the orbital characteristics of the radical anion. A possible reason for this fact is that the activation barrier for proton transfer between the two nitro groups in these structures is only slightly (by 5%) is higher than the respective parameter for the protonation of the radical anion with a foreign donor.

As mentioned above (see [3, 4], as well as the correlation dependence between the electronic parameters of radical anions and the isomer ratio of nitroanilines formed), a stage that predetermines the direction of selective reduction of one of several nitro groups is protonation of the radical anion of the substrate. In terms of this concept, the isomer ratio of monoreduction products is defined by competition of the nitro groups for protonation. The structural characteristics of the corresponding transition states can arbitrarily be divided into factors associated with systems to be protonated (radical anions) and factors associated with protonation products (protonated radical anions). To gain a comprehensive understanding of the pattern, we performed AM1 quantum-chemical calculations of polynitrobenzene radical species protonated by different functional groups.

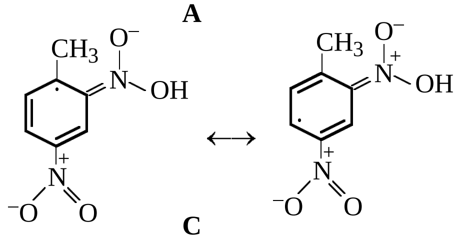
As models for calculating the protonated radical anions we chose derivatives of 1-substituted 2,4-dinitrobenzenes: 2,4-dinitrochlorobenzene and 2,4-dinitritoluene. Structures protonated by nitro groups were only taken into account (structures **A**–**D**). This is explained by the fact that atoms of the functional groups contribute much less into the unpaired electron orbital than nitro oxygen atoms; the principal parameters of these species are listed in Table 3.



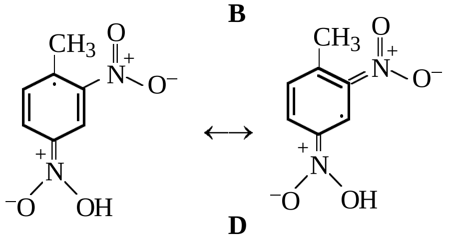
A



B



C



D

Table 3. Quantum-chemical characteristics of protonated forms **A**–**D** of 1-chloro-2,4-dinitrobenzene and 2,4-dinitrotoluene radical anions (AM1 method)[a]

Atom	*o*-NO_3			*p*-NO_3		
	q	C^2p_z	$l_{N–O}$ ($l_{O–H}$), Å	q	C^2p_z	$l_{N–O}$ ($l_{O–H}$), Å
Structure **A**						
N	0.3042	0.00083		0.5709	0.00000	
O	–0.3408	0.00098	1.33840	–0.3486	0.00000	1.20095
O	–0.2705	0.05061	1.20720	–0.3486	0.00000	1.20095
H	0.2490	0.00090				
Structure **B**						
N	0.5697	0.00004		0.3083	0.08346	
O	–0.3342	0.00007	1.19900	–0.3548	0.10745	1.33938
O	–0.3339	0.00008	1.19900	–0.2717	0.09598	1.20795
H				0.2498	0.00176	(0.97954)
Structure **C**						
N	0.2968	0.00121		0.5713	0.00000	
O	–0.3485	0.00158	1.33895	–0.3526	0.00000	1.20150
O	–0.2758	0.05189	1.20737	–0.3526	0.00000	1.20150
H	0.2460	0.00123	(0.97980)			
Structure **D**						
N	0.5700	0.00000	1.12020	0.2963	0.00214	
O	–0.3556	0.00000	1.12020	–0.3484	0.00211	1.33878
O	–0.3558	0.00000	1.12020	–0.2743	0.05406	1.20764
H				0.2464	0.00126	(0.97944)

[a] E_f, kJ: 96.5254 (**A**), 112.2170 (**B**), 85.9436 (**C**), 86.7563 (**D**); EV_{HDOMO}/E_{HOMO}: –45.036/–22.9480 (**A**), –44.8799/–23.4862 (**B**), –44.6121/–22.3563 (**C**), –44.1978/–22.2893 (**D**).

As follows from these data, the contribution of the nitro group protonated by an oxygen atom to the HOMO of these species much increases at the expense of the contributions of the other functional groups. As a result, it is this group that takes part in further reduction. Thus we obtained evidence for our model (previously based on general regularities for such processes), according to which the direction of selective reduction is determined by the site of protonation of the radical anion.

The data listed in Table 1 and reported in [12] are also indicative of a considerable effect of the nature of the reducing agent. Thus, when tin(II) chloride is used instead of titanium(III) chloride, the fraction of the reduction product by the *o*-nitro group appreciably increases both with 1-chloro-2,4-dinitrobenzene and 2,4-dinitrotoluene. This result can be explained in terms of the degree of radical ion–counterion interaction. It is known that titanium(III) ions are mostly reduced by an outer-sphere mechanism. This also applies to reduction of nitro compounds [13]. The absence of changes in the inner coordination sphere suggests absence of a strong donor–acceptor interaction between the titanium(III) ion and dinitro compound. Therefore, the resulting isomer ratio is determined by electronic characteristics of the 1-X-2,4-dinitrobenzene anion radical undistorted by interaction with the reducing agent. This is confirmed by the electrochemical reduction data in [14].

With $SnCl_2$, the reaction with 1-chloro-2,4-dinitrobenzene results in preferential formation of 2-chloro-5-nitroaniline (by contrast to 4-chloro-3-nitroaniline with $TiCl_3$) (Table 1). In this case, a strong donor–acceptor interaction of the metal ion with the substrate chlorine atom is possible, as evidenced by the fact that the *o*-nitro group is appreciably faster reduced in the presence of a number of substituents (including halogen atoms) [15]. As a result, the electronic structure of the radical anion is distorted and the monoreduction direction changes.

Thus, it was shown that the monoreduction of 1-substituted dinitrobenzenes is controlled by the electronic configuration of the radical anion, along with the structure of the substrate and reducing agent.

EXPERIMENTAL

Dinitro compounds were reduced with tin(II) and titanium(III) chlorides by the procedure in [1]. The mixtures of reduction products were studied by GLC.

Quantum-chemical calculations were performed by the AM1 method.

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