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Interaction of Nitroarenes with Hydroxide Ion. An AM1 Molecular Orbital Treatment

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Abstract: AM1 calculations predict that nitroarenes with more than one nitro group react with OH^- to form charge-transfer complexes with considerable radical character at the nitroarene moiety. These complexes collapse to form initially Meisenheimer complexes at the carbon atom with the lowest electron density and eventually equilibrate to form the most stable Meisenheimer complexes. Although there are large systematic errors, due to neglect of correlation and thermal energies, AM1 calculations predict correctly the relative energies of Meisenheimer complexes and provide an understanding of reactions of structurally diverse nitroarenes that form long-lived Meisenheimer complexes or substitution products.

There is experimental evidence for the intermediacy of charge-transfer complexes, formed by single-electron transfer, in overall addition and substitution reactions of OH^- with di- and trinitroarenes (see ref 2 and references cited therein). We use the AM1 general-purpose quantum mechanical model[3] to evaluate properties related to chemical reactivity and formation of charge-transfer complexes (CTC^-) and anion radicals (AR^-) with these compounds, viz. formation enthalpies, geometries, charge distribution, ionization potentials, electron affinities, and spin-orbital densities. We find that the AM1 calculations can be applied to the parent nitroarenes and related anion radicals with reasonable accuracy, so the AM1 model can be applied to nitroarenes and their derivatives.[2f] On the basis of this precedent, we applied the model to formation of CTC^- and Meisenheimer complexes (MC^-), as intermediates in aromatic nucleophilic addition and substitution, as shown in Scheme I.[2,4]

Interaction between OH^- and nitroarenes very rapidly forms a π-complex (PC^-), which by a single-electron transfer gives the charge-transfer complex between the anion radical of the nitroarene and $OH^{\bullet}$. This complex is the key intermediate which rearranges to side, inactive in overall substitution, 3-Meisenheimer complexes ($3MC^-$) or to ipso Meisenheimer complexes (e.g. $1MC^-$), which may eliminate the leaving group and give the substitution product. The first-formed MC^-, in a kinetically controlled reaction, may equilibrate to a more stable MC^- or in high $[OH^-]$ may give a dihydroxy complex (e.g. $3,5MC^{-2}$) and/or be deprotonated (e.g. $3MC^{-2}$). The overall rate of substitution is controlled by the rates of rearrangement of CTC^-, the return of inactive MC^- to CTC^-, the relative stabilities of different MC^-, and the decomposition of $1MC^-$. Nitro is a good leaving group, so polynitroarenes may form overall substitution products. However, it is generally possible to separate formation of MC^- of polynitroarenes and subsequent loss of nitro group, and we consider only formation of MC^-. In most, but not all, cases a qualitative prediction of reactivity and final reaction products can be made in terms of MC^- stabilities on the basis of simple electronic theory. We investigated the electronic structures of charge-transfer and Meisenheimer complexes to predict, at least qualitatively, reactivity in nucleophilic aromatic addition and substitution in terms of the model in Scheme I, and we apply our calculations to compounds whose reactions have been studied in detail.[2]

Calculations. Calculations were carried out on Vax 11/780 or Cray X-MP/48 (University of Illinois at Urbana-Champaign) computers, by using the AM1 model from the AMPAC program QCPE 506.[3] All calculations were made by using the unrestricted Hartree-Fock scheme. The starting geometries are discussed in detail in the next section.

Results and Discussion

Reaction Enthalpies. Calculation of gas phase reaction enthalpies, ΔH^{298}, requires evaluation of ΔE^{298}, the total energy change for the reaction as given by the sum:[5]

$$\Delta E^{298} = \Delta E_e^0 + \Delta(\Delta E_e)^{298} + \Delta E_v^0 + \Delta(\Delta E_v)^{298} + \Delta E_r^{298} + \Delta E_t^{298} \quad (1)$$

where ΔE_e^0 is the difference in ground-state electronic energies of products and reactants at 0 K, including electronic correlation effects, and $\Delta(\Delta E_e)^{298}$ is the temperature effect on that difference in going from 0 to 298 K and can be neglected when only ground electronic states are considered; ΔE_v^0 is the difference in zero-point vibrational energies of products and reactants, and $\Delta(\Delta E_v)^{298}$ is the corresponding temperature effect; ΔE_r^{298} is the difference in rotational energies, and ΔE_t^{298} is the difference in translational energies and depends on changes in the rotational and translational degrees of freedom. Solvation energies are important for reaction in solution, but they are not considered in eq 1.

Calculation of changes in electronic energies, including the correlation energies, the difference between the Hartree-Fock electronic energy which contains the average rather than the instantaneous interelectron potential, and the exact solution of the nonrelativistic Schrodinger equation, requires large flexible basis sets, e.g. 6-31G(d), in ab initio calculations, and generally can be applied only to small molecules. The zero-point vibrational energy may be calculated by using the force constants; however, at the present time this is a demanding computational task, severely limited by the size of the molecule. Semiempirical methods, such as MNDO and AM1, require much less computing time and are parameterized by using experimental data so that the calculated energies implicitly allow for correlation and thermal energies.[6] However, this allowance is an average over a set of molecules and is not specific to a given system. Although the correlation and thermal energies are usually a small fraction of the total energy, differences in them between products and reactants may be significant in discussion of chemical reactivity. But if structural changes in the given reaction are not very large, these differences may be relatively small and their explicit calculation is not essential. Relative reaction enthalpies for compounds with similar

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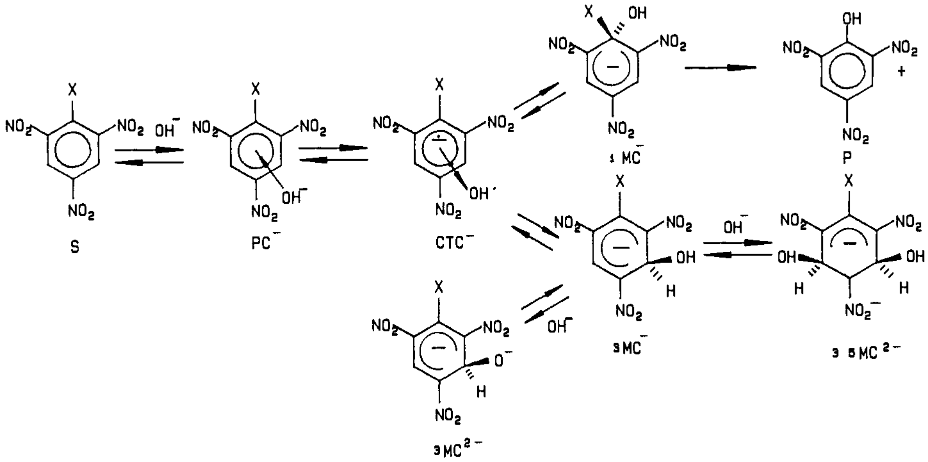
Scheme I



structure are therefore not likely to be affected by large errors and are consequently useful, at least qualitatively.

The rotational energy contribution (ΔE_r^{298}) is $0.5RT$ for each change of a degree of rotational freedom[7] and the translational contribution (ΔE_t^{298}) is $1.5RT$ for each mole change between products and reactants, Δn:

$$\Delta E_t^{298} = 1.5RT\Delta n \qquad (2)$$

The gas phase enthalpy change differs from the total energy change by

$$\Delta(PV) = RT\Delta n \qquad (3)$$

Charge-Transfer Complexes. We know of no experimental evidence on the geometry of donor-acceptor complexes of nitroarenes with n donors. Complexes of 1,3,5-trinitrobenzene with halide ions form in solution, but the equilibrium is very unfavorable and reaction enthalpies are near zero.[8] Complexes with such n donors as amines and EtO$^-$ are observed spectrophotometrically, and the equilibrium is favorable ($-\Delta H$ = 9 kcal mol^{-1}), but they also cannot be isolated because of their rapid conversion into addition products.[9] The geometry of the solid complex of iodide ion with 1-methylnicotinamide is known, but although there may be charge-transfer interactions, the crystal structure is dictated primarily by charge–charge interactions.[10]

Complexes of nitroarenes with π-donors have parallel arrangements of planar donors and acceptors in infinite stacks.[11] Similarly, crystalline complexes of Br_2 or Cl_2 with benzene form infinite stacks with the halogen situated symmetrically between the ring centers of parallel benzene molecules.[12]

A reasonable structure for a CTC$^-$ of OH$^-$ and nitroarene has the former centered over a planar aromatic ring, and exploratory calculations support this structure. We therefore used this geometry, without full optimization, because of the long computation time imposed by the UHF scheme at the AM1 level. Our conclusion agrees with that from MNDO calculations on the interaction of nucleophiles with chlorobenzene and its 4-nitro derivative.[13]

Ab initio calculations at the STO-5G level with a 3G optimized geometry for nitrobenzene led to the conclusion that there is an attractive interaction with OH$^-$, but the energy minimum was with OH$^-$ located at 1.75 Å above the plane of nitrobenzene, essentially over the midpoint of the C–NO_2 bond.[14] However our AM1 calculations for similar geometries predict a much longer distance or/and very unfavorable energies for this location of the hydroxyl.

We examined the variation of reaction enthalpy with distance for reactions of OH$^-$ with both 1,3-dinitro- and 1,3,5-trinitro-

Table I. Geometries and Electronic Structure of Charge-Transfer Complexes

compound	Δe^a	$\rho(O_{p_z})^b$	angle^c	torsion angle^d
C_6H_6 (**1**)	0.016	0.000	178.9	27.5
$C_6H_5NO_2$ (**2**)	0.766	0.978	92.1	3.6
1,3-$C_6H_4(NO_2)_2$ (**3**)	0.811	0.965	95.5	26.4
1,2-$C_6H_4(NO_2)_2$ (**4**)	0.981	0.981	93.1	30.6
1,4-$C_6H_4(NO_2)_2$ (**5**)	0.755	0.902	96.9	58.5
1,3,5-$C_6H_3(NO_2)_3$ (**6**)	0.835	0.953	100.1	35.7
1,3-$C_{10}H_6(NO_2)_2$ (**7**)	0.827	0.965	97.7	−159.5
2,4-$C_6H_3(NO_2)CN$ (**8**)	0.818	0.961	97.6	−34.9
3,5-$C_6H_3(NO_2)CN$ (**9**)	0.826	0.956	99.3	−154.7

^{a}Charge transferred from OH$^-$ to nitroarene in e. ^{b}Spin-orbital density of the p_z O orbital from hydroxyl in e. ^{c}Angle between the O–H bond and the normal to the ring in degrees. ^{d}Dihedral angle between the plane of O–H bond and the normal to the ring and the normal to the ring and the C-1 in degrees (see also Figure 2).

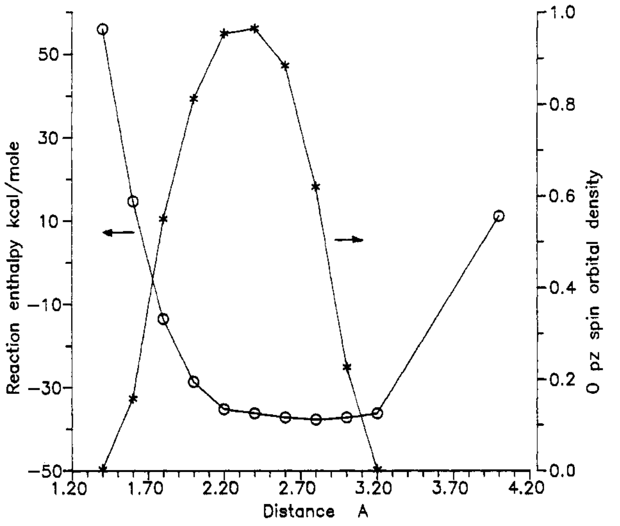


Figure 1. Dependence of the reaction enthalpy of formation of the charge-transfer complex and of the hydroxylic O_{p_z} spin–orbital density on the distance between the OH$^-$ and the center of the 1,3,5-trinitrobenzene ring.

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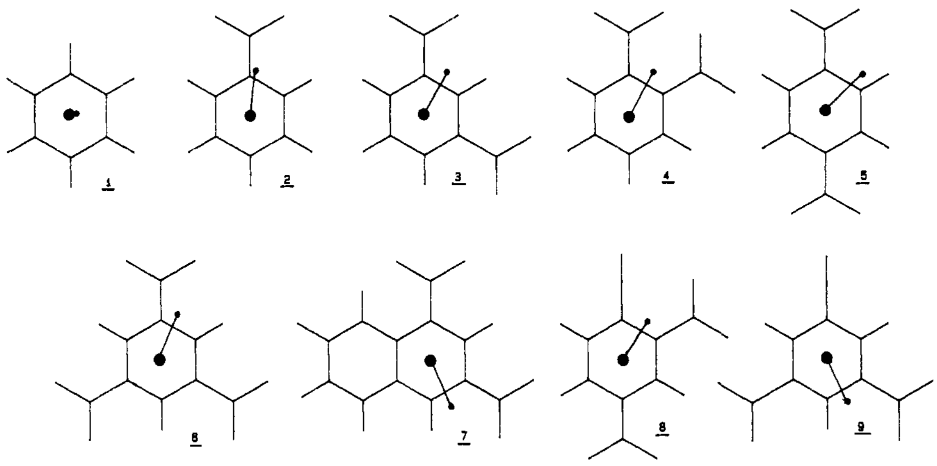
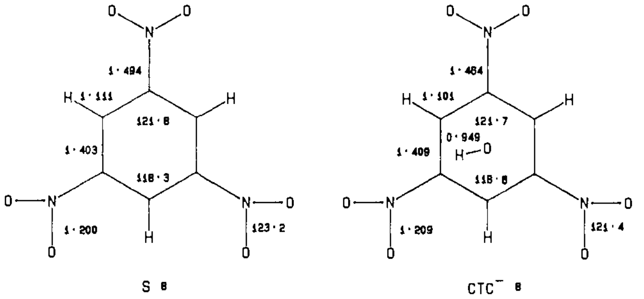


Figure 2. Projection in the ring plane of the charge-transfer complexes showing the position of the hydroxylic oxygen (large circle) and hydrogen (small circle) relative to the nitro groups. Numbering as in Table I.

Scheme II



benzene and found that there is a large minimum situated between 2.2 and 3.2 Å. However, at ca. 2.2 Å one electron is almost completely transferred from OH^- to nitroarene, and at lower or much higher distances there is much less transfer (Figure 1). As correlation and zero-point vibrational energies are not explicitly taken into account, we assumed that small changes in enthalpy are less significant than the extent of electron transfer. On the basis of these calculations, we assume that the OH moiety is 2.2 Å above the center of the aromatic ring in all CTC^-, although the optimum geometry may vary slightly from one case to another.

There is essentially no electron transfer to benzene, and probably no energy minimum. Table I gives calculated extents of electron transfer from OH^- to the arene at the assumed distance of 2.2 Å, as well as the calculated angle between the O–H bond and the normal to the ring. The angle is between 92° and 100° for those complexes in which there is extensive electron transfer, and it corresponds to the most favorable orbital overlap. The calculated dihedral angles of the OH bonds are shown in plane projections in Figure 2 and appear to be controlled largely by electrostatic interactions between the hydrogen and the oxygen atoms of the nitro groups.

The interaction at "long distance", 3.4 Å or even longer, is not accompanied by electron transfer from the OH^- to nitroarene and is a purely electrostatic interaction between the aromatic ring with its partial positive charge and OH^-. This kind of interaction has been predicted by MNDO calculations for systems having a nucleophile centered at Van der Waals distance over the aromatic nucleus of chlorobenzene and its 4-nitro derivatives.[13] We consider that these are relatively good models for the observed intermediates between nitroarenes and their charge transfer complexes, which were identified as π-complexes (PC^-, Scheme I).[2a,b,d,e] In aqueous media, these PC^- should contain a solvated OH^-, separated by water molecules from the aromatic system. The energy barrier between the PC^- and CTC^- is consequently desolvation of OH^-, which becomes free to approach the aromatic system closely.

Vibrational and rotational energies of CTC^- and corresponding nitroarenes are probably similar, because there are no major changes in geometries, as shown in Scheme II for 1,3,5-trinitrobenzene; for example torsional angles of nitro groups are close to zero in both. (For calculated geometries of other CTC^-, see the supplementary material in this paper, and for those of other nitrobenzenes, see the supplementary material in ref 2f).

Table II. Reaction Enthalpies for Formation of Charge-Transfer Complexes and Anion Radicals[a]

compound	S^b ΔH_f	CTC^{-c} ΔH_f	RA^{-d} ΔH_f	CTC^{-e} ΔH_r	RA^{-f} ΔH_r
C_6H_6 (**1**)	22.0	22.9	28.7	33.1	49.7
$C_6H_5NO_2$ (**2**)	25.3	-7.7	-9.2	0.7	8.5 -2.0^h
1,3-$C_6H_4(NO_2)_2$ (**3**)	33.4	-19.1 -23.3^h	-20.7	-20.3 -22.2^g	-11.1 -21.6^g
1,2-$C_6H_4(NO_2)_2$ (**4**)	51.6	8.9	8.0	-10.5	-0.5
1,4-$C_6H_4(NO_2)_2$ (**5**)	33.4	-22.9	-29.1	-24.0	-19.4
1,3,5-$C_6H_3(NO_2)_3$ (6)	44.9	-22.6 -28.2^h	-24.6	-35.3 -38.6^g	-26.5 -37.0^g
1,3-$C_{10}H_6(NO_2)_2$ (**7**)	53.1	-4.6	-4.8	-25.5	-14.9
2,4-$C_6H_3(NO_2)_2CN$ (**8**)	72.6	7.4	4.9	-33.0	-24.7
3,5-$C_6H_3(NO_2)_2CN$ (**9**)	69.1	8.3	5.6	-28.6	-20.5

[a] In kcal mol^{-1}. [b] Calculated enthalpies of formation of the arenes (S), ref 2f. [c] Calculated enthalpies of formation of charge-transfer complexes. [d] Calculated enthalpies of formation of radical anions (half-electron approximation), ref 2f. [e] Reaction enthalpies for charge transfer complexes based on $\Delta H_f = -33.7$ kcal mol^{-1} for OH^-.[15] [f] Reaction enthalpies for radical anions based on $\Delta H_f = 9.3$ kcal mol^{-1} for $OH^\cdot$.[15] [g] Reaction enthalpies for reactions with MeO^- based on $\Delta H_f = -36$ kcal mol^{-1} for MeO^- and $\Delta H_f = -3.5$ kcal mol^{-1} for $MeO^\cdot$.[15] [h] For reaction with MeO^-.

The AM1 method does not give a good value for the enthalpy of formation of OH^-. The calculated[3] and the experimental values[15] are -14.1 and -33.7 kcal mol^{-1}, respectively, which may overpredict the stability of CTC^- and the extent of electron transfer. However, the formation enthalpy of MeO^- is well reproduced by the AM1 method, with values of -38.8 kcal mol^{-1} for the calculated value[3] and -36 kcal mol^{-1} for the experimental value.[15] Our calculations predict that MeO^- and OH^- form very similar CTC^- with 1,3-dinitro- and 1,3,5-trinitrobenzene. (Table II).

The correlation energies may differ considerably for a nitroarene and its CTC^-, which will introduce errors in the reaction enthalpies, but we believe that they are systematic for the closely related compounds considered here, so that comparison should be mechanistically useful (Table II). Formation of a CTC^- from benzene is highly improbable, even in the gas phase, but the situation is more complex for nitrobenzene. The endothermic enthalpy for formation of CTC^- suggests that this complex is not stable. Similarly, electron transfer from OH^- with formation of the corresponding anion radical seems to be excluded. However,

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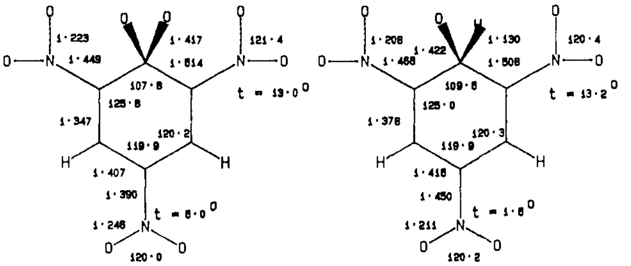
Scheme III



Experimental geomatry MC$^-$ Trinitrophenetole + EtO$^-$

Calculated geometry MC$^-$ Trinitrobenzene + OH$^-$

electron transfer from MeO$^-$ to nitrobenzene should be possible in the gas phase (Table II), due to the lower ionization potential of this anion (1.59 eV as compared with 1.83 eV for OH$^-$[16]). In polar solvents, due to the high solvation energies of anionic nucleophiles (ca. 21 kcal mol^{-1} for OH$^-$ in water[15]), this reaction is unlikely. The radical anion of nitrobenzene is formed by electron transfer from *t*-BuO$^-$ to nitrobenzene in the gas phase,[17] but it was not detected by ESR spectroscopy in *t*-BuOH or DMSO[18] or by NMR signal broadening in DMSO–D$_2$O.[2c] However, small concentrations of anion radicals should be present as transient intermediates in MeO$^-$–MeOH in reduction and radicaloid reactions.[19]

On the basis of calculated reaction enthalpies (Table II) and the enthalpy of hydration of OH$^-$, 1,3- and 1,4-dinitrobenzene should form CTC$^-$ with OH$^-$ more readily than 1,2-dinitrobenzene. The three dinitrobenzenes give NMR line broadening with OD$^-$ in DMSO–D$_2$O (7:3 v:v) due to fast electron exchange between an anion radical (AR$^-$) and/or CTC$^-$ and the parent nitroarene.[2c,20] The NMR signal of 1,4-dinitrobenzene completely disappears on addition of OD$^-$. Line broadening is more evident with 1,3-dinitrobenzene than with 1,2-dinitrobenzene, and with the former the broadening increases steadily with time, probably due to dissociation of CTC$^-$ to free AR$^-$, as predicted from the reaction enthalpies (Table II). The ESR spectra of AR$^-$ of 1,2-[21b] and 1,4-dinitrobenzene[21a,c] were observed in aqueous DMSO containing OH$^-$ and of 1,3-dinitrobenzene with *t*-BuO$^-$ in *t*-BuOH or DMSO[18] and with MeO$^-$ in MeOH.[22] Radicals were trapped in reactions of 1,4-dinitrobenzene with OH$^-$ or MeO$^-$ in aqueous DMSO,[23] and radicaloid reaction products were identified in the reaction of 1,3-dinitrobenzene with MeO$^-$ in MeOH.[22]

1,3,5-Trinitrobenzene readily forms MC$^-$ with OH$^-$ in water or aqueous dipolar solvents.[24] The equilibrium is so strongly toward addition that CTC$^-$ or AR$^-$ is not detected by ESR spectra in excess *t*-BuO$^-$ in *t*-BuOH.[18] However, NMR signals of excess substrate over OD$^-$ are broadened in DMSO–D$_2$O (7:3 v:v).[2c]

The behaviors of 1,3-dinitronaphthalene and 3,5-dinitrobenzonitrile in alkaline media seem to be in between those of the di- and trinitrobenzenes. For example, although an ESR spectrum of the AR$^-$ of 3,5-dinitrobenzonitrile was observed with MeO$^-$ in MeOH,[25] the NMR line broadening could be observed only when the substrate was in excess over OH$^-$ in DMSO–D$_2$O (1:1 v:v).[2c]

Table III. Reaction Enthalpies for Formation of Meisenheimer Complexes[a]

compound	pos	$\Delta H_f{}^b$	$\Delta H_r{}^c$	$\Delta H'_r{}^d$
C_6H_6 (**1**)	1	−35.2	−25.0	
$C_6H_5NO_2$ (**2**)	2	−65.2	−58.3	−64.3
1,3-$C_6H_4(NO_2)_2$ (**3**)	2	−78.5	−79.7	−79.7
	4	−84.1	−85.3	−85.3
	5	−68.2	−69.4	−69.4
1,2-$C_6H_4(NO_2)_2$ (**4**)	1	−75.5	−49.9	
	3	−42.6	−62.0	
1,4-$C_6H_4(NO_2)_2$ (**5**)	1	−77.5	−78.7	
	2	−74.5	−75.7	−74.6
1,3,5-$C_6H_3(NO_2)_3$ (6)	1	−70.3	−83.0	
	2	−89.9	−102.6	−99.7
1,3-$C_{10}H_6(NO_2)_2$ (**7**)	4	−69.2	−90.1	−92.5
	2	−58.7	−79.6	−86.9
2,4-$C_6H_3(NO_2)_2CN$ (**8**)	1	−45.7	−86.1	
	3	−46.7	−87.1	
	5	−52.6	−93.0	
	6	−41.0	−81.4	−77.8
3,5-$C_6H_3(NO_2)_2CN$ (**9**)	1	−31.6	−68.5	
	2	−58.5	−95.4	−93.7
	3	−38.8	−75.7	
	4	−56.2	−93.1	−98.2

[a] In kcal mol^{-1}. [b] Calculated formation enthalpies for the MC$^-$ at the indicated position. [c] Calculated reaction enthalpies for formation of MC$^-$ from substrate. [d] Relative reaction enthalpies with the formation enthalpies of 1,3-dinitrobenzene (**3**) and empirical increments for calculation of free energies of stabilization of MC$^-$[27] (benzo fusion, −7.2; ortho NO$_2$, −10.3; meta NO$_2$, −5.2; para NO$_2$, −21.0; ortho CN, −8.4; para CN, −18.5 kcal mol^{-1}).

Meisenheimer Complexes. Meisenheimer complexes (MC$^-$) have a planar conjugated system, as shown by X-ray diffraction of the complexes of alkoxide ions with 2,4,6-trinitroanisole[26a] and -phenetole.[26b] We used this geometry in our calculations, and the optimized geometry of the complex of OH$^-$ with 1,3,5-trinitrobenzene is very similar to those from the observed geometries of alkoxy complexes (Scheme III).

Reaction enthalpies of formation of Meisenheimer complexes of OH$^-$ and nitroarenes are very favorable (Table III). Similar conclusions had been drawn from MNDO calculations on complexes of *p*-nitrochlorobenzene with MeO$^-$[13] and 1,3,5-trinitrobenzene with OH$^-$.[28] The calculated values of reaction enthalpies are lower than the experimental values (up to −45 kcal mol^{-1}[29]). These differences are too large to be ascribed to solvent effects. Electronic correlation and thermal energies should be different for a planar aromatic nitroarene and the corresponding unsaturated conjugated system of the MC,$^-$ and they are not explicitly included in our AM1 calculations. However differences should be similar for the closely related compounds discussed here, and therefore relative reaction enthalpies can usefully be compared with experimental data.

Neglect of solvent effects should affect absolute reaction enthalpies but not relative values of reaction enthalpies for various complexes of the same substrate or even of similar nitroarenes. Experimental values of free energies of formation of MC$^-$ in such polar aprotic solvents as DMSO and DMF (S′) relative to such polar protic solvents as H$_2$O or MeOH (S′H) ($\Delta\Delta G = \Delta G^{S'} - \Delta G^{S'H}$) do not depend on the nature of substrate and solvent. For a series of different nitroarenes and nitrobenzonitriles, the relative stabilization free energies ($\Delta\Delta G$) fall on the same line when plotted against the molar concentration of polar aprotic solvent (DMSO

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or DMF) in polar protic solvents (H_2O or MeOH).[27] This absence of marked specific-solvent effects allows us to use calculated relative gas phase reaction enthalpies in discussions of relative stabilities in solution.

Observed stabilization free energies of formation of MC^- are additive with respect to electron-withdrawing groups and benzofusion, and the stabilization increments can be empirically predicted with a maximum error of ca. 1.5 kcal mol^{-1}.[27] With use of this increment for the relative decrease of free energies and by neglecting entropy changes, the enthalpies of MC^- of different nitroarenes can be calculated relative to the three MC^- of 1,3-dinitrobenzene (Table III). The mean difference between these values and those calculated by the AM1 method is 3.7 ± 2.2 kcal mol^{-1}, for an overall enthalpy change of ca. 40 kcal mol^{-1}. We conclude that differences in calculations of correlation and thermal energies cancel in relative reaction enthalpies so that structural effects on stabilities are reflected largely in the calculated electronic energies differences.

Two of the compounds examined form two different Meisenheimer complexes: 1,3-dinitrobenzene and 3,5-dinitrobenzonitrile (Scheme IV).

1,3-Dinitrobenzene (**3**) and MeO^- in DMSO rapidly form $2MC^-$, absorbing at 605 nm, and it disappears to form the more stable $4MC^-$, absorbing at 525 nm.[30] There is less than 1% of $2MC^-$ at equilibrium,[31] which corresponds to a free energy difference of ca. 3 kcal mol^{-1}, and the calculated enthalpy difference is 5.6 kcal mol^{-1} (Table III).

3,5-Dinitrobenzonitrile (**9**) and OH^- (MeO^-) rapidly form $4MC^-$ in DMSO–H_2O (DMSO–MeOH), as shown by UV–visible[32,30d] and NMR[33] spectroscopy, and it slowly equilibrates to give an equilibrium mixture in which $2MC^-$ predominates with a ratio between the equilibrium constants for $2MC^-$ and $4MC^-$ of 10.6 for reaction with OH^-[32a] or 9.5 for reaction with MeO^-.[31] The experimental difference in free energy of ca. 1.4 kcal mol^{-1} is close to the calculated enthalpy difference of 2.3 kcal mol^{-1}.

There is no experimental evidence for formation of MC^- of nitrobenzene with OH^- or stronger bases, e.g. NH_2^-, $CH_2(CH_2CH_2)_2N^-L^+$, and $Me_3C^-MgCl^+$.[34] The gas-phase enthalpy is −58.3 kcal mol^{-1}, calculated by the AM1 method. It appears that calculated reaction enthalpies are systematically 60–70 kcal mol^{-1} too negative, probably due to neglect of electronic-correlation and thermal energies. An empirical correction of this magnitude would give values for reaction enthalpies in the range −10 to −30 kcal mol^{-1}, which are similar to experimental values.[29]

Long-lived MC^- are not formed in reactions of 1,2- and 1,4-dinitrobenzenes in basic solutions,[34] but there is reaction at position 1, with loss of nitrite ion.[21b,c] These observations[5] are consistent with predictions of the AM1 calculations that $1MC^-$ should have lower enthalpies than the corresponding complexes, $3MC^-$ or $4MC^-$ (Table III).

The calculation predicts that the $2MC^-$ of 1,3,5-trinitrobenzene (**6**) will have a much lower enthalpy than $1MC^-$ (Table III), in agreement with experimental evidence for the formation of a long-lived $2MC^-$, rather than loss of a nitro group.[24] Overall substitution is observed only at high temperature or with UV irradiation,[35] which should favor radical or excited-state reactions.

The AM1 calculations are also consistent with results on reactions of dinitrobenzonitriles. 3,5-Dinitrobenzonitrile and OH^- give $2MC^-$ and $4MC^-$, and a relatively slow substitution to form 3-nitro-5-cyanophenol[25] is consistent with the relatively low enthalpy of the $3MC^-$. Reaction at the cyano group to give 3,5-dinitrobenzamide and -benzoic acid has also been reported.[36] 2,4-Dinitrobenzonitrile and OH^- rapidly form a MC^- with subsequent loss of the cyano group and formation of 2,4-dinitrophenol.[37] The structure of the long-lived complex is not known, but our calculations predict that it is the $5MC^-$ (Table II). There is NMR evidence for formation of a long-lived $5MC^-$ of methyl 2,4-dinitrobenzoate with acetonate ion.[38] The calculations are also consistent with addition of OH^- to the 4-position rather than the 2-position of 1,3-dinitronaphthalene to give a long-lived MC^-.[39]

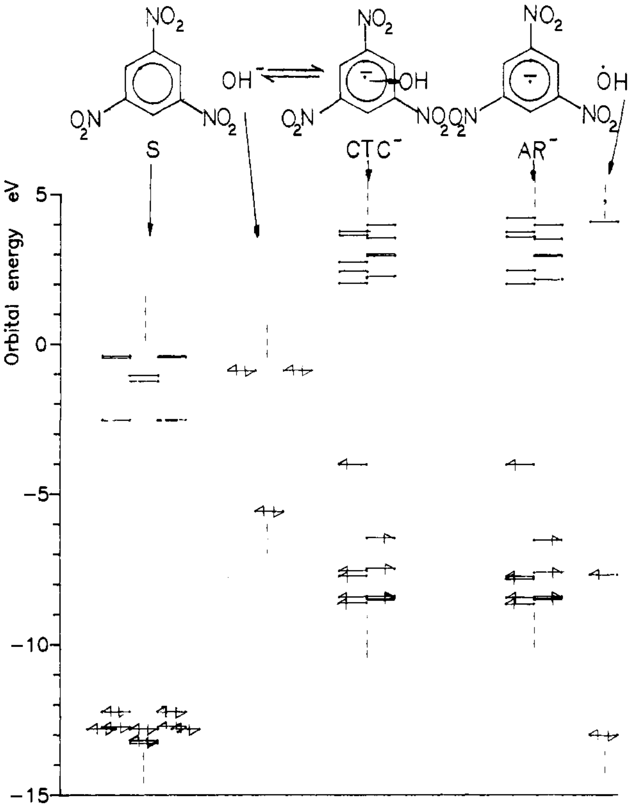

Figure 3. Frontier orbitals of 1,3,5-trinitrobenzene (S) and its charge-transfer complex (CTC^-) and anion radical (AR^-) as compared with orbitals of OH^- and $OH^\bullet$.

Despite large differences between calculated gas-phase enthalpies and observed free energies of formation of Meisenheimer complexes, the calculations successfully predict the relative stabilities of various MC^-.

Electronic Structure of the Charge-Transfer Complexes. The charge-transfer complexes (CTC^-) may collapse to form various Meisenheimer complexes (MC^-) (Scheme I), whose relative stabilities are predicted by AM1 calculations, so the next problem is the relation between the electronic structure of the CTC^- and their collapse to MC^-. It is also useful to relate the electronic structures to those of substrates and free anion radicals (AR^-).

The highest occupied (HOMO) and lowest unoccupied orbitals (LUMO) of 1,3,5-trinitrobenzene have very low energies (Figure 3). The difference between the HOMO of OH^-, calculated with the same UHF AM1 model, and the LUMO of 1,3,5-trinitrobenzene is ca. 1.65 eV, so electron transfer should be favorable. This supports previous estimates for similar systems.[40] The

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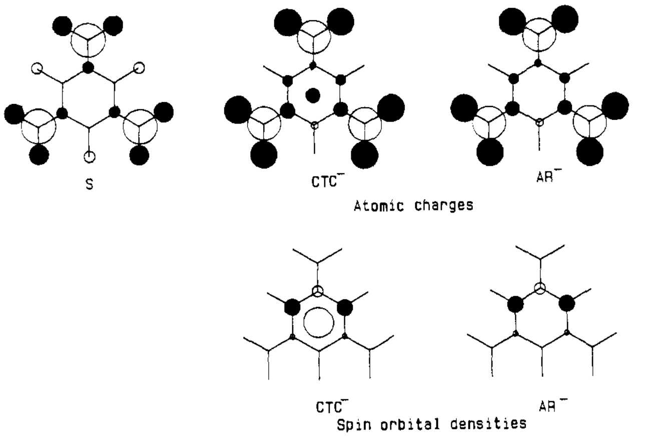
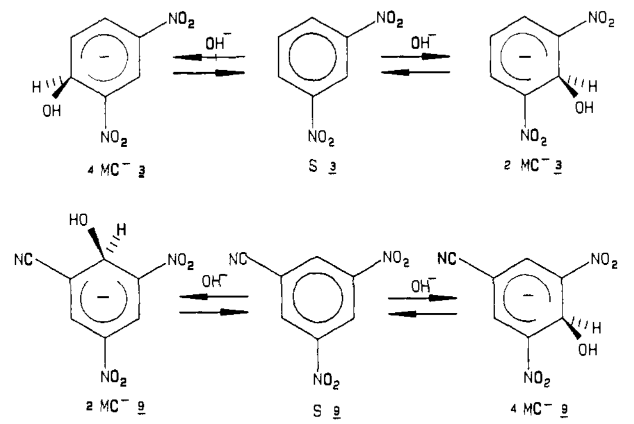


Figure 4. Net atomic charges and p_z spin–orbital densities of charge-transfer complex (CTC⁻) of 1,3,5-trinitrobenzene relative to substrate (S) and anion radical (AR⁻). The hydroxylic oxygen is shown in the center of the aromatic ring. Diameters of the circles are approximately proportional to the calculated values and negative charges are shadowed.

energies of the HOMO and LUMO of the CTC⁻ are similar to those of AR⁻, when both are calculated on the UHF scheme, and one electron has a much higher energy in both species (Figure 3). Therefore the CTC⁻ of 1,3,5-trinitrobenzene, for example, should have considerable radicaloid character. Electron transfer from OH⁻ increases electron densities on the carbon and nitro oxygen atoms, but there is little change for nitrogen atoms. Both the charge densities and spin populations of the CTC⁻ and AR⁻ are similar, as shown for 1,3,5-trinitrobenzene (Figure 4).

Scheme IV



Calculated values for all other compounds are presented in the supplementary material.

Calculated spin–orbital densities of AR⁻ are proportional to hyperfine-splitting constants,[2f] so their relative value can be used for correlation of reactivity. Consideration of the charge and spin–orbital densities of CTC⁻, as related to previously presented experimental evidence, shows that the fastest addition is at the carbon atom with lowest charge density, for example at positions 2 in 1,3-dinitrobenzene, 4 in 3,5-dinitrobenzonitrile, and 3 in 2,4-dinitrobenzonitrile (Figure 5). The calculations suggest that the CTC⁻ of 1,3-dinitronaphthalene could collapse to a short-lived 2MC⁻, and that it would then rapidly go to the more stable 4MC⁻. The short-lived 2-complex has not been identified experimentally

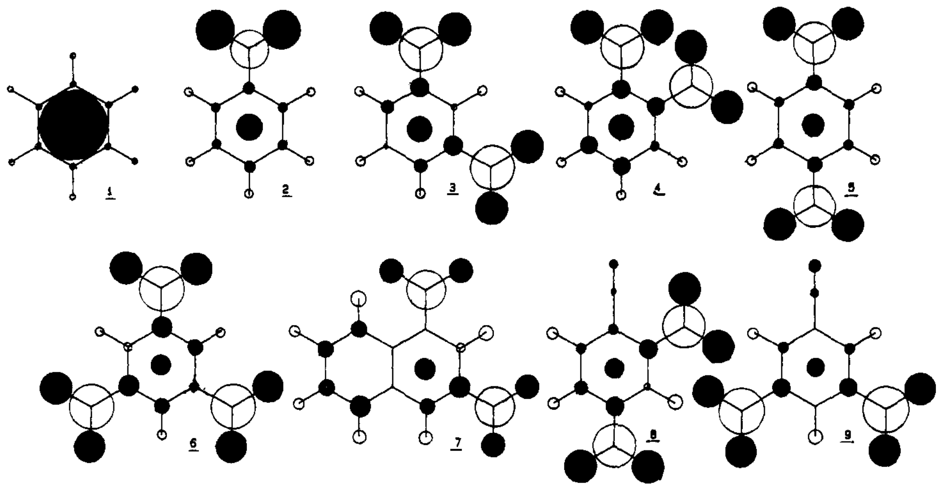


Figure 5. Net atomic charges calculated for charge-transfer complexes. The hydroxylic oxygen is shown as being above the center of the aromatic ring and negative charges are shadowed. The diameters of the circles are approximately proportional to the calculated charges.

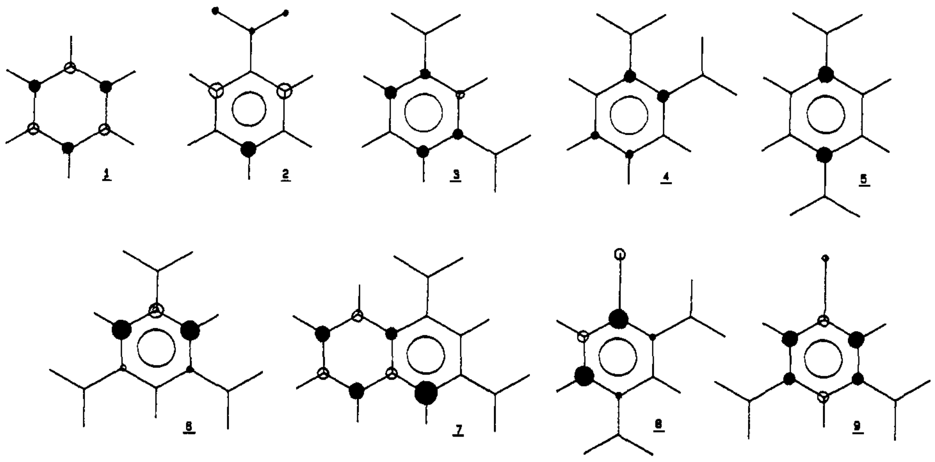


Figure 6. Spin–orbital densities of p_z orbitals calculated for charge-transfer complexes. The hydroxylic oxygen is shown as above the center of the aromatic ring, and the diameters of the circles are approximately proportional to the calculated values.

for 1,3-dinitronaphthalene, possibly due to its very low concentration or its fast conversion to the long-lived 4MC$^-$. There are kinetic and spectroscopic evidence for the existence of short-lived 3MC$^-$ in reactions of 1-chloro(bromo)-2,4-dinitronaphthalene with OH$^-$,[2e] 1-methoxy-2,4-dinitronaphthalene with MeO$^-$,[41a] or 1-(dialkylamino)-2,4-dinitronaphthalene with MeO$^-$[41b] or NR$_2$H.[41c]

The relative stabilities of the Meisenheimer complexes are shown in Table II, and comparison with data in Figure 6 shows that the most stable MC$^-$ forms at the carbon atom that has the highest spin–orbital density opposite to the oxygen of OH$^•$. If this carbon atom is bonded to a H, a long-lived MC$^-$ is formed (compounds **3**, **6–8**, Figure 6), but if there is a nitro or cyano group at this position, there is overall nucleophilic substitution with a short-lived MC$^-$ as intermediate (compounds **4**, **5** Figure 6), and no long-lived MC$^-$ is observed. In 2,4-dinitrobenzonitrile, positions 1 and 5 have almost the same spin-orbital densities, and the energies of the corresponding MC$^-$ are very similar. The CTC$^-$ collapses to the two MC$^-$, and 1MC$^-$ loses the cyano group to form the corresponding phenol.[37]

Conclusions

Molecular-orbital calculations on nitroarenes support the hypothesis that compounds with more than one nitro group react with OH$^-$ to form charge-transfer complexes of finite life and that these complexes have considerable radical character. They collapse initially to Meisenheimer complexes at the carbon atom with the lowest charge densities, but these complexes may isomerize via the charge-transfer complexes to more stable Meisenheimer complexes. The situation is different if addition is at a carbon that carries a good leaving group which can be eliminated, to give overall substitution.[2]

The AM1 method predicts geometries of nitroarenes[2f] and their Meisenheimer complexes in good agreement with experiment. There are large systematic errors in predicted reaction enthalpies, but relative values for related compounds are in reasonable agreement with experiment. The key point is that the AM1 method predicts the position of overall nucleophilic addition and substitution to a variety of nitroarenes. Qualitative theories of organic reactivity, based on inductive, mesomeric, and steric effects[4], are only partially successful in these predictions and fail to account for the observed single-electron transfer from basic or nucleophilic anions to a variety of electrophiles, including polynitroarenes and nitrogen heterocycles. There is now considerable experimental evidence that many reactions regarded as two-electron transfers actually occur by single-electron transfer via short-lived charge-transfer complexes.[42]

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Supplementary Material Available: Tables giving geometries, net atomic charges, dipole moments, spin–orbital densities, and orbital energies for 30 compounds discussed in the text (32 pages). Ordering information is on any current masthead page.

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Selective Reaction of Glycine Residues in Hydrogen Atom Transfer from Amino Acid Derivatives

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Abstract: Relative rates of reaction of the *N*-benzoylamino acid methyl esters **1a–4a** with *N*-bromosuccinimide and of **1a–4a** with di-*tert*-butyl peroxide are reported. The selective reaction of glycine derivatives in these and other reactions of *N*-acylamino acid derivatives is attributed to the relative stability of intermediate radicals produced by hydrogen atom transfer. Radicals formed by hydrogen abstraction from *N*-acylglycine derivatives may adopt planar conformations which are relatively free of nonbonding interactions and in which there is maximum delocalization of the unpaired electron, whereas radicals produced by similar reactions of derivatives of other amino acids are relatively unstable because of nonbonding interactions. In accord with this hypothesis, methyl pyroglutamate (**5a**) reacts at a faster rate than *N*-benzoylglycine methyl ester (**1a**) in reactions with either *N*-bromosuccinimide or di-*tert*-butyl peroxide. Anomalous rates of reaction of *N*-benzoylproline methyl ester (**6a**) are rationalized in terms of the regioselectivity of hydrogen atom transfer. Evidence for the mechanisms of reactions of **1a–6a** is derived from product studies and by comparison of the relative rates of reactions of **1a–6a** with those of the deuteriated amino acid derivatives **1b**, **2b**, **3b**,**c**, **5b**, and **6b**,**c**.

The preferential reactivity of glycine residues observed in the photoalkylation of peptides and proteins has been attributed to the formation of α-centered radicals by selective hydrogen atom transfer from glycine derivatives.[2] Irradiation experiments with polycrystalline and single crystal samples of amino acid derivatives have also displayed selective reaction of glycine residues.[3] Two main types of radicals are produced by irradiation, as shown by EPR spectroscopy. One of these gives EPR spectra that are broad and anisotropic. These radicals are thought to be sulfur-centered, mainly because similar spectra have been observed for a number of thiols and disulfides. The other type of radical, which displays

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