Factors Controlling Regioselectivity in the Reduction of Polynitroaromatics in Aqueous Solution

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Regioselectivities in the bisulfide reduction of 10 polynitroaromatics (PNAs) to monoamine products have been determined; four of these compounds have also been reduced by anoxic sediments in heterogeneous aqueous solution, and the same regioselectivities are observed. Analyses of Austin Model 1-Solvation Model 2 electrostatic potential surfaces for the radical anions of these polynitroaromatic compounds provides a reliable method of predicting the regioselectivity of their reduction. In particular, at their minimum-energy geometries in aqueous solution, it is the more negative nitro group that is selectively reduced. This is consistent with a mechanism where regioselection occurs upon kinetic protonation at the site of maximum negative charge in the radical anion formed after the first electron transfer to the neutral PNA. Inclusion of solvation effects is critical in order to confidently predict the electrostatic preference for the reduction of one nitro group over the others. Sterically uncongested nitroaromatic radical anions have gas-phase geometries in which the nitro group is coplanar with the aromatic ring. However, ortho substituents and solvation effects both oppose this tendency and can lead to nitro groups that are rotated out of the ring plane and pyramidalized.

Introduction

Nitroaromatics comprise an important class of potential environmental contaminants because of their wide use in agrochemicals, textile dyes, munitions, and other industrial applications. As a result, there is considerable interest in determining the fate pathways of nitroaromatics in soil and aquatic environments (1). Nitroaromatics are known to be susceptible to reductive transformations to aromatic amines in anoxic (i.e., oxygen-depleted) environments (2, 3). The reduction of nitroaromatics occurs through a series of electron transfer reactions and protonations with nitroso compounds and hydroxylamines as highly reactive evenelectron intermediates (4).

A number of environmentally significant nitroaromatics contain two or more nitro groups. For such polynitroaromatics, the rate of reduction of the first nitro group is generally much more rapid than the rate of reduction of the remaining nitro groups (Scheme 1); in most cases, the rate of subsequent reduction is so slow that the process is effectively stopped after the first nitro group is reduced. The ability to predict the regiospecificity of reduction (if any exists) is important for environmental assessment needs because the regiomeric reaction products can exhibit very different chemical (5) and toxicity (6) characteristics.

Regioselective reductions of polynitroaromatics to form nitroaromatic amines that are resistant to further reduction have been observed in several laboratory studies. For example, Weber and Adams (7) observed that the chemical and sediment-mediated reduction of 2-bromo-4,6-dinitroaniline, an important textile dye intermediate, was selective for the nitro group in the 4-position. The resulting reaction product, 3-bromo-5-nitro-1,2-diaminobenzene, did not undergo further reduction. Only a trace amount of the substrate resulting from the reduction of the nitro group in the 6-position was observed in anoxic sedimentwater systems. Similar results have been observed for the chemical (8, 9) and enzymatic (10, 11) reduction of 2,4dinitrophenol and 2,4-dinitroaniline and its N-phenyl derivative. Finally, the chemical (8), sediment-mediated (5), and microbial reduction (12) of 2,4,6-trinitrotoluene occurs at the nitro group in the 4-position.

We report here measurements of reduction selectivities for 10 polynitroaromatics. All compounds in the study were reduced in homogeneous aqueous solutions containing bisulfide (which has been proposed to be a slow but important reductant in anoxic environments (3, 13)). In several cases, micromolar amounts of juglone were also present. Juglone is a quinone that acts as an electrontransfer mediator to shuttle electrons between the sulfide and the nitroaromatics (13). An electron shuttle system involving dissolved organic matter has been postulated to account for the facile reduction of nitroaromatics in natural systems (14). Some data are also presented here for reductions carried out in reducing sediments.

We also report here quantum mechanical calculations using the Austin Model 1–Solvation Model 2 (AM1–SM2) semiempirical molecular orbital method (*15*) that rationalize the observed selectivities. We hypothesize that the step that establishes the regioselectivity is the first proton transfer to the radical anion that is created after the initial oneelectron reduction of the starting material (Scheme 2) and that the nitro group that is selectively protonated proceeds irreversibly to the completely reduced amine product. Localization of charge in the initial radical anion will influence the site of protonation. A key point to be made here is that, because of the Coulomb repulsion between electrons, charge would *not* necessarily be expected to

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localize in the gas phase. In aqueous solution, however, the favorable effects of solvation can overcome the tendency of electronic charge to delocalize over the molecular framework because localized charges are more effective at inducing favorable electric polarization of the solvent. Thus, a significant amount of charge can localize on one or both nitro groups, and the nitro group with the greater negative charge localization is likely to be the one most readily protonated. Visualization of the electrostatic potential on the van der Waals surface is used as an aid to conclude that charge localization does indeed occur and that it provides a predictive diagnostic of the regiospecificity of the protonation step.

Experimental Section/Theoretical Methods

Chemicals. Standard-grade chemicals, purchased from a variety of commercial sources, were used without further purification. Stock solutions (0.01 M) of the nitroaromatic compounds were prepared in MeOH and routinely monitored for degradation. Stock solutions of 0.01 M juglone and 1.0 M Na₂S were prepared in MeOH and ultrapure (18 M Ω /cm) water, respectively, and stored in serum bottles sealed with Bellco butyl rubber stoppers. No loss of the nitroaromatic compounds or juglone to the butyl rubber stoppers could be detected.

Chemical Reductions. Reductions of substituted nitroaromatics by Na₂S were performed in anaerobic culture tubes sealed with Hungate butyl rubber stoppers. All reactions were carried out in 50 mM phosphate buffer at pH 7.0 with the exception of 2,4-dinitrophenol, for which 5 mM phosphate solutions were either buffered to pH 2.5 to ensure predominance of the conjugate acid (i.e., the phenol) or buffered to pH 11.0 to ensure predominance of the conjugate base (i.e., the phenolate). A 10-mL volume of buffer solution was de-oxygenated by bubbling an H₂/ N_2 (5%/95%) gas mixture through the solution for 20 min. Appropriate amounts of the Na₂S stock solution and juglone were added to the buffer and allowed to equilibrate for at least 12 h. Reactions were initiated by spiking with 50 μ L of the nitroaromatic stock solution for an initial concentration of 50 μ M. Aliquots were removed via syringe and analyzed by HPLC for both the parent compound and the reduction products. The latter were identified by comparison to HPLC retention times for the known anilines. Control studies demonstrated that the reduction was quenched upon contact with the HPLC eluent.

Sediment-Mediated Reductions. For four compounds, reductions were also performed in sediment–water slurries. These slurries were collected from a eutrophic pond

(Cherokee Park) in the vicinity of Athens, GA, and were wet-sieved through a 1-mm mesh. Aliquots of the stirred slurry were added to serum bottles and then crimp sealed with butyl rubber stoppers. The aqueous volume of the slurry was estimated, and an appropriate volume of nitroaromatic stock solution was added to achieve an approximate 50 μ M initial concentration. Control experiments indicated that sediment concentrations varied at most by 10% from experiment to experiment. At selected sampling times, a representative sample aliquot was withdrawn and centrifuged at 14 000 rpm. The supernatant was analyzed by HPLC.

Analytical Methods. HPLC analyses were performed on a Gilson 305 gradient HPLC equipped with a variable wavelength UV detector (Applied Biosystems). Analyses were run on C18 (Phenomenex ODS-30) or polymer (Hamilton PRP1) reverse-phase columns typically under isocratic conditions (using mixtures of acetonitrile and H_2O as the mobile phase). For analysis of 2,4-dinitrophenol and phenolate, a mixture of acetonitrile and 5 mM phosphate buffer at pH 2.5 was used as the mobile phase.

Yields of the monoamine products were calculated by dividing the moles of product formed by the moles of parent compound reacted. For most of the reactions, product yields are reported for approximately 50% reaction of the starting polynitroaromatic. Despite the fact that for most compounds there was no further reduction of the monoamine compounds to a diamine product, this arbitrary 50% cutoff was chosen to ensure that the initial products were not lost to further reduction. In a few cases the yield of monoamine products was very low due to competing reaction pathways and/or subsequent (non-reductive) reaction of the product amines. Product yields were then reported based on the best yields obtained; this best product yield was typically from earlier reaction times when loss of the starting compound from competing reaction pathways was minimal.

Semiempirical Computational Methods. Gas-phase geometries and electronic wave functions of polynitroaromatic radical anions were fully optimized with the halfelectron restricted Hartree-Fock (HE) approximation (16) using the semiempirical Austin Model 1 (AM1) Hamiltonian (17, 18). Use of the unrestricted Hartree-Fock (UHF) approximation (19) for the radical anions led to excessive spin contamination of the doublet wave functions with components of higher multiplicity, so this formalism was not further explored. Aqueous solvation effects were accounted for by reoptimization of the geometries and electronic wave functions at the AM1-SM2 level (15). In the AM1-SM2 model, the electronic wave function and geometry of the solute both respond self-consistently to the electric polarization of the solvent dielectric medium. Relaxation of the wave function in the presence of the solvent reaction field can significantly alter the molecular electronic and geometric structure (20), especially in aromatic systems (21-24) as discussed further below. The model also includes localized non-electrostatic effects associated with interactions between the solute and the solvent (15, 25, 26). In particular, cavitation, dispersion, and non-electrostatic components of hydrogen bonding are included. The AM1-SM2 solvation model has been demonstrated to reliably predict solvation effects on tautomeric equilibria (27) and on the conformational energetics of polyols (28), sugars (29), and other aromatic compounds (23) where competition between inter- and



intramolecular hydrogen bonding might be expected to be an issue.

Partial charges q_k on the atoms k were calculated using the Class IV charge model 1A (CM1A) (*30*). For gas-phase calculations, the CM1A model maps AM1 Mulliken charges to high-quality partial atomic charges that closely reproduce both experimental dipole moments and also atomic charges derived from fitting to high-quality ab initio electrostatic potential surfaces (*30*). Partial charges of solvated systems were derived from CM1A mappings of AM1–SM2 Mulliken partial charges (which differ considerably from AM1 gasphase Mulliken charges as described below).

In order to visualize the electrostatic potential around the solute, we defined a curved surface surrounding the solute on which the electronic density per unit volume has decayed to 0.002 atomic units (au). Such a surface is commonly used as a way to define the critical region for interaction of the solute with nonbonded collision partners. Electrostatic potentials (*31*) were calculated on this isodensity surface from partial atomic point charges, i.e.

$$V(\mathbf{r}) = \sum_{k}^{\text{atoms}} \frac{q_k}{|\mathbf{r} - \mathbf{r}_k|}$$
(1)

Ab Initio Computational Methods. To gain insight into certain conformational issues, additional studies were carried out on the radical anions of nitrobenzene and 2-nitrotoluene with the restricted open-shell Hartree Fock (ROHF) approximation (*19*) using the 6-31G* (*32–34*) and cc-pVDZ (*35*) basis sets. When exploring specific conformational coordinates (see below), all other degrees of freedom were fully optimized. Electron correlation effects were included by restricted open-shell Møller-Plesset second-order perturbation theory (*36, 37*) in single-point calculations at the ROHF geometries.

Density Functional Theory Computations. Isotropic hyperfine coupling constants for the nitrobenzene radical anion were calculated by standard methods (*38, 39*) at the B3LYP (*40*) density functional level using the 6-311G** (*34, 41*) basis set. Since the experimental measurements of the hyperfine constants were carried out in hexamethylphos-

TABLE 1

Regioselectivities and Yields for Bisulfide Reductions of Various PNAs^a

compound	[HS [–]], <i>µ</i> M	[Jug⁰], µM	% ortho	% para	% yield
2-amino-4,6-dinitrotoluene	500		100	0	16
2-bromo-4,6-dinitroaniline	5000		100	0	89
	1000	5	100	0	90
1-bromo-2,4-dinitrobenzene	1000		100	0	7
1-chloro-2,4-dinitrobenzene	100		86	14	14
	500	5	89	11	39
2,4-dinitroaniline	4500	10			С
2,4-dinitroanisole	5000		100	0	86
	500	5	100	0	17
2,4-dinitrophenol ^d	5000				С
	5000	10	98	2	100
2,4-dinitrophenolate ^e	5000	10			С
2,4-dinitrotoluene	5000		12	88	62
	500	25	8	92	80
2,4,6-trinitrotoluene	1000		0	100	74
	500	20	0	100	9

^{*a*} Reductions at pH 7.0 unless otherwise indicated. ^{*b*} Juglone (5-hydroxy-1,4-naphthoquinone). ^{*c*} No reaction after 3 days. ^{*d*} Reaction performed at pH 2.5. ^{*e*} Reaction performed at pH 11.0.

phoramide (HMPA) solvent, the effects of solvation on the ab initio wave function were approximated using a Born–Kirkwood–Onsager reaction field (42-46) with a solvent dielectric constant of 30.0 to facilitate comparison to experiment.

Computer Programs. Semiempirical calculations were carried out using a locally modified version of version 4.5 of the AMSOL computer program (47); ab initio calculations were carried out using the Gaussian92/DFT program suite (48); and visualization of the electrostatic potential surfaces was accomplished using version 3.0 of the SPARTAN computer program (49).

Results

Table 1 summarizes the experimental results for reduction of a series of substituted dinitrobenzenes and 2,4,6trinitrotoluene in bisulfide-containing systems. Half-lives

TABLE 2

Regioselectivities and Yields for Reductions of Various PNAs Carried Out in Reducing Sediments from Cherokee Park near Athens, GA

compound	% ortho	% para	% yield
2-bromo-4,6-dinitroaniline ^a 1-bromo-2,4-dinitrobenzene 1-chloro-2,4-dinitrobenzene 2,4,6-trinitrotoluene ^b	99 99 65 1	1 1 35 99	75 10 27 73
^a Ref 7. ^b Ref 5.			

for the bisulfide-mediated reduction of the dinitroaromatics ranged from several hours to days. The dinitroaromatics with half-lives on the order of 12-24 h included 2-bromo-4,6-dinitroaniline, 2,4-dinitrophenol, 2,4-dinitrotoluene, and 2,4,6-trinitrotoluene. Control experiments with mononitro reduction products (both isomers when available) indicated that reduction of the second nitro group occurred much more slowly under all of the experimental conditions. In several instances, compounds in solution were detected by HPLC that did not correspond to reduction products (as inferred from co-injection of singly and doubly reduced standards); this accounts for the lower yields reported for some substrates. In some cases, these products subsequently disappeared, suggesting them to be nitroso or hydroxylamine intermediates. For 1-bromo- and 1-chloro-2,4-dinitrobenzene, low yields are attributed to an aromatic nucleophilic substitution in which bisulfide (or another adventitious nucleophile) displaces the halogen atom on the starting material. For the bisulfide-mediated reduction of 2,4-dinitroanisole and 2,4,6-trinitrotoluene, the addition of juglone significantly lowered the yields of monoamino products-this is consistent with aromatic amines being known to undergo facile nucleophilic addition to quinones in aqueous solution (50).

Most of the 2,4-dinitroaromatics were selectively reduced at the nitro group in the ortho position; however, 2,4dinitrotoluene was selectively reduced at the nitro group in the para position. Similarly, 2,4,6-trinitrotoluene was observed to be reduced at the nitro group para to the methyl substituent. In the mixtures containing bisulfide alone (i.e., without juglone), reduction was observed for all compounds except 2,4-dinitroaniline and 2,4-dinitrophenol. In the case of 2,4-dinitrophenol, the addition of juglone to the reaction system resulted in complete and selective reduction of the phenol. The addition of juglone to all reaction systems typically accelerated reduction, but had no effect on the ortho to para distribution of reduction products. Bisulfide reduction of 2,4-dinitroaniline did not take place even after the addition of juglone-simple aqueous bisulfide reductions of 2,4-dinitroaniline and its N-substituted derivatives are known to be sluggish (51), and typically other reducing systems (vide infra) are required for these substrates (51, 52). Bisulfide reduction of 2,4-dinitrophenolate in the presence of juglone was similarly unsuccessful, in this case probably because of the unlikelihood of creating an intermediate radical dianion.

The reductions of four of the polynitroaromatics were also studied in an anoxic (reducing) sediment—water system. The distributions of reduction products are summarized in Table 2. The selectivity of the reduction of these polynitroaromatics in the anoxic sediment was not qualitatively different from that observed in the bisulfide system.

TABLE 3 Summary of Literature Data on Selectivity of Reduction of PNAs in Various Chemical and Biological Systems

reductant	% ortho	% para	ref
SnCl ₂	100	0	52
HCO ₂ H•Et ₃ N/Pd	100	0	9
HCO ₂ H•Et ₃ N/Pd	100	0	9
HCO ₂ H·Et ₃ N/Pd	100	0	9
TiCl ₃	100	0	71
HCO ₂ H·Et ₃ N/Pd	100	0	9
Na ₂ S, NH ₄ OH	100	0	8
HCO ₂ H·Et ₃ N/Pd	0	100	9
$H_2S_1C_5H_5N$	100	0	51
biotic	100	0	11
biotic	0	100	12
	$\label{eq:spectral_reductant} $$ SnCl_2 $$ HCO_2H \cdot Et_3N/Pd $$ HCO_2H \cdot Et_3N/Pd $$ HCO_2H \cdot Et_3N/Pd $$ TiCl_3 $$ HCO_2H \cdot Et_3N/Pd $$ ND_2S, NH_4OH $$ HCO_2H \cdot Et_3N/Pd $$ H_2S, C_5H_5N $$ biotic $$ bi$	% reductant % SnCl2 00 HCO2H·Et3N/Pd 100 H2S, C5H5N 100 biotic 100	$\begin{array}{c c} & & & & & \\ & & & \\ reductant & & \\ & & \\ SnCl_2 & & 100 & 0 \\ HCO_2H\cdot Et_3N/Pd & 0 & 100 \\ HC$

Finally, Table 3 summarizes available literature data on selectivity in the reduction of polynitroaromatics in various other chemical and biological systems. These selectivities are quite similar to those measured for the polynitroaromatics in this study, suggesting that the stereochemical partitioning step is relatively insensitive to the reducing agent. Table 3 includes reaction conditions that more rapidly reduce 2,4-dinitroaniline and its *N*-methylated derivatives, in contrast to our bisulfide results.

Figure 1 presents the modeling results for nine of the polynitroaromatics surveyed experimentally. Each polynitroaromatic radical anion is represented by a line drawing to the left and a ball-and-stick structure to the right illustrating the stereochemistry of the AM1-SM2-optimized structures that are the global minima in aqueous solution. The nitro group that is observed to be selectively reduced is indicated in the line drawings. At the far right of each pair of representations, the electrostatic potential is colormapped onto an isodensity surface of the optimized structure, in particular onto the hypersurface where the AM1-SM2 electronic density has a value of 0.002 au. This isodensity surface roughly corresponds to a van der Waals surface, i.e., the depiction is like a space-filling model. The electrostatic potential, calculated as described in the Theoretical Methods section, is contour mapped onto the isodensity surface using the visible spectrum so that red represents regions having maximal negative (i.e., attractive) potential for a positive point charge, while blue represents regions least attractive to a positive point charge. In every one of these nine cases, the nitro group observed to be reduced experimentally is the one predicted to have the greater localization of negative charge (and hence the most negative potential) at the AM1-SM2 level. This supports the hypothesis in the Introduction that the initial protonation of the polynitroaromatic radical anion is the product partitioning event.

It is worth noting that one alternative explanation for the observed regioselectivity could be based on a thermodynamic argument. In particular, if the first protonation step is reversible and the second electron transfer is slow, the product partitioning could simply reflect the relative stabilities of the intermediate hydroxynitroxyl radicals. We have calculated these relative stabilities in several instances by the AM1–SM2 method and find poor correlation with the observed regioselectivities for reduction, so we reject this explanation.

A second alternative explanation might invoke an essentially concerted electron transfer/proton transfer







2-amino-4,6-dinitrotoluene



2-bromo-4,6-dinitroaniline







2,4-dinitrobromobenzene







2,4-dinitrochlorobenzene







2,4-dinitroaniline



2,4-dinitroanisole



2.4-dinitrophenol



2,4-dinitrotoluene













FIGURE 1. Chemical line structures (left), ball-and-stick representations of the AM1–SM2 minimum-energy radical anion stereostructures in aqueous solution (center), and the electrostatic potentials on the 0.002 au isodensity surfaces for those structures (right) for several PNAs. The nitro group with the box around it is the one that is experimentally observed to be selectively reduced.

process. In that case, one might expect the observed regioselectivity to correlate with localization of relatively more partial positive charge on one of the nitro groups in the neutral compared to the other, i.e., a greater "local" reduction potential. While such a process is highly unlikely, insofar as the relaxation of electronic coordinates occurs orders of magnitude faster than relaxation of nuclear coordinates (*20*), we did examine the charge distribution in the solvated neutral polynitroaromatics. The average difference in nitro group charges was less than 0.01 unit and failed to correlate with the observed regioselectivities, so we reject this alternative as well.

Discussion

Solvation Effects on Electronic Polarization. The relaxation of electronic structure in response to solvation can have large effects on solute properties and reactivity (20, 53, 54). As noted in the Introduction, aqueous solvation is expected to be critical in stabilizing the localization of anionic charge on one nitro group more than another. Figure 2 illustrates this effect for the case of 1-chloro-2,4dinitrobenzene; pictured is a comparison of the electrostatic potential surfaces of the gas-phase (upper) and solvated (lower) electronic structures for the lowest energy optimized geometries in each medium. The color scale used for the two electrostatic potential surfaces is the same; thus, the larger and more intense red regions on the aqueous potential surface indicate solvent-promoted localization of anionic charge. Moreover, the solvated potential surface exhibits a quite different charge polarization by comparison to the gas-phase potential surface. The prediction that would be made based on the gas-phase surface would be opposite to that made based on the solvated surface and fails to agree with experiment; in the calculation including aqueous solvation effects on the other hand, the larger concentration of negative charge on the ortho nitro group easily rationalizes the experimentally observed reduction selectivity. The comparison may be made more quantitative by comparing the CM1A charges on the two different nitro groups. In the gas phase, the para nitro group bears 0.11 more units of negative charge than the ortho one; in aqueous solution, on the other hand, the ortho nitro group bears 0.47 more units of negative charge than the para one. This same situation, where the gas-phase electrostatic potential would lead to a different prediction than the aqueous electrostatic potential, is also observed for 2-amino-4,6-dinitrotoluene (gas phase, 0.03 more negative para;

aqueous solution, 0.62 more negative *ortho*), 1-bromo-2,4dinitrobenzene (gas phase, 0.17 more negative *ortho*; aqueous solution, 0.42 more negative *para*), and 2,4dinitroanisole (gas phase, 0.05 more negative *para*; aqueous solution, 0.55 more negative *ortho*). In every instance, it is the prediction based on the aqueous electrostatic potential that agrees with the results obtained from experiment.

Even for the remaining five molecules in Figure 1, where the polarization of the gas-phase electrostatic potential surface leads to the same prediction as does the solvated surface, there is an enhanced differentiation of the two nitro groups as a result of aqueous solvation. In particular, the average CM1A charge difference between the two nitro groups in the gas phase is only 0.07. In aqueous solution, on the other hand, the average difference is 0.58. A complete listing of all nitro group charges is provided in the supporting information.

Solvation Effects on Molecular Geometries. As illustrated in Figure 1, AM1–SM2 calculations often predict the radical anion minimum-energy stereostructures to have a nitro group rotated as much as 90° out of the plane of the aromatic ring. In most instances, the rotated nitro group is also noticeably pyramidalized. It is well established that *ortho* substituents can induce some out-of-plane twisting of nitro groups in neutral nitrobenzenes (*55*), and as discussed further below, this effect is calculated to be present in solvated radical anions as well. However, solvation effects appear to be much more important as a driving force for nitro group rotation than are steric effects—in the gas phase, with the exception of the 1-halo-2,4-dinitrobenzenes, all of the radical anions have nitro groups that are nearly coplanar with the aromatic ring.

In the gas phase, only a single minimum-energy structure exists for each of the 10 nitroaromatic radical anions considered in this paper (the nine in Figure 1 plus 2,4dinitrobenzaldehyde, which is discussed below). In aqueous solution, however, six of the compounds had two local minima, one had three, two had four, and one had six local minima (a complete listing of all minima is available in the supporting information). Typically, the energies corresponding to these minima spanned a range of about 10 kcal/mol in relative energy. In four cases out of six, the minima having energy less than 4 kcal/mol above the global minimum tended to have similar charge polarizations, i.e., one would predict the same reduction selectivity. This was also the case for six of the remaining 14 higher energy



FIGURE 2. Comparison of the electrostatic potential surfaces for the gas-phase (upper) and solvated (lower) structures of 1-chloro-2,4dinitrobenzene radical anion.

minima. Thus, we are confident that our predicted reduction selectivities are not critically dependent on a highly accurate determination of the global minimumenergy structure.

For several of the polynitroaromatics studied here, the inclusion of aqueous solvation effects also has geometric consequences on substituents other than the nitro groups or on interactions between those other substituents and the nitro groups (Figure 3). For instance, the minimumenergy geometry of the solvated 2,4-dinitroaniline radical anion has the ortho nitro group rotated perpendicular to the aromatic ring, and the amino group is approximately coplanar with the aromatic ring. This localizes anionic charge on the rotated nitro group: its CM1A charge is -0.98. In the lowest energy gas-phase structure, on the other hand, the ortho nitro group remains coplanar with the aromatic ring (which delocalizes anionic charge: its CM1A charge is -0.33) while the amino group rotates out of plane. The rotation of the amino group decreases interaction between the amino lone pair and the electron-rich π orbitals and may also improve the nonlinear hydrogen-bonding interactions between the amino group and the ortho nitro group. Although a solvated geometry similar to that found in the gas phase is a local minimum, it is 10.0 kcal/mol higher in energy than the illustrated global minimum. The situation for 2-bromo-4,6-dinitroaniline, which differs only by addition of the 2-bromo group, is essentially identical and is not illustrated.

Also shown in Figure 3 are the gas-phase and aqueous minimum-energy geometries of the 2,4-dinitrophenol radical anion. Again, the effect of aqueous solvation is to

rotate the nitro group out of the aromatic plane. In this instance, however, the nitro group rotates less completely, presumably to maintain some hydrogen bonding between the hydroxyl hydrogen and the *ortho* nitro group.

The radical anions of 2,4-dinitroanisole and 2,4-dinitrobenzaldehyde are also predicted to have significantly different gas-phase and solvated geometries. In the gas phase, the orthonitro group of the 2,4-dinitroanisole radical anion prefers to remain in the plane of the aromatic ring, and this forces the methoxy group to rotate out of that plane. In aqueous solution exactly the opposite is observed, again presumably to maximize charge localization on the rotated nitro group (-0.79 in solution vs -0.25 in the gas phase). The radical anion of 2,4-dinitrobenzaldehyde represents an especially interesting case. On going from the gas phase to aqueous solution, there is both the usual 90° rotation of the ortho nitro group out of the aromatic plane and additionally a 180° rotation of the aldehyde group so that the carboxaldehyde oxygen atom is adjacent to the ortho nitro group. The preferred proximity of the carboxaldehyde oxygen, with its negative partial atomic charge, to the similarly charged ortho nitro group illustrates the extent to which solvent induces enhanced charge localization. Moreover, it appears that this effect may play an interesting role in the kinetic protonation. The electrostatic potential surface for 2,4-dinitrobenzaldehyde indicates that the site of most negative potential is actually on the carboxaldehyde oxygen. Although it is possible that this is simply an artifact arising from the representation of the continuous charge density by atomic partial charges, it is also possible that this localization influences the observed



FIGURE 3. Comparison of the gas-phase (left) and solvated (right) minimum-energy stereoisomers of the radical anions of 2,4-dinitroaniline, 2,4-dinitrophenol, 2,4-dinitroanisole, and 2,4-dinitrobenzaldehyde.

ortho regioselectivity in the reduction step by directing protonation to this general region of the solute.

The above examples suggest that the potential for rotation of a nitro group can undergo a qualitative change when the effects of solvation and ortho substitution are included. Specifically, solvation always preferentially stabilizes an out-of-plane geometry because that geometry permits greater localization of partial negative charge on the nitro group. This effect works in concert with the steric influence of any substituent(s) to which the nitro group is ortho. Of the 10 molecules computationally studied here, the only ones not observed to be selectively reduced at nitro groups ortho to some substituent are 2,4-dinitrotoluene and 2,4,6-trinitrotoluene. In each of these cases, it is a methyl substituent to which the unreduced nitro group is ortho, and it is the nitro group para to methyl that is reduced. A likely explanation is that the hydrophobic methyl group descreens the ortho nitro group from the surrounding dielectric, while the para is fully exposed (i.e., again solvation is more important than sterics). When the methyl is replaced by a group bearing a partial negative charge (as in eight other instances) or there is an additional hydrophilic substituent on the ring (as in 2-amino-4,6dinitrotoluene), that negative group assists in organizing the solvent shells about the ortho nitro group and thus enhances the local polarization.

Ab Initio Calculations on Smaller Model Systems. In order to gain further insight into the energetics associated with nitro group rotation and also to address the issue of nitrogen pyramidalization, ab initio calculations were carried out for the radical anions of nitrobenzene and 2-nitrotoluene. Previous theoretical work has established that the preferred geometry for the former radical anion in the gas phase is a planar one having C_{2v} symmetry (56).

Figure 4 illustrates the energetic cost of nitro group pyramidalization (without rotation) for the nitrobenzene radical anion as calculated at the ROMP2/cc-pVDZ//ROHF/ 6-31G* level. Forcing the oxygen atoms out of the aromatic plane increases the energy by about 10 kcal/mol by the time the ONCC dihedral angle reaches 20°. This preference for nitro group planarity is not maintained if the nitro group itself is not coplanar with the aromatic ring. Thus, Figure 4 also shows the potential for pyramidalizing the nitro group when it is rotated to be orthogonal to the aromatic plane. In this case, a structure having ONCC dihedral angles of about $\pm 70^{\circ}$ is roughly 4 kcal/mol more stable than the perpendicular C_{2v} geometry having a planar nitro group. However, as illustrated in Figure 5, at this level of gasphase theory the barrier to rotation of the nitro group is approximately 25 kcal/mol even after accounting for pyramidalization of the rotating group.

To examine the effects of an *ortho* substituent, the energy was calculated as a function of the internal rotation coordinate for the nitro group in the 2-nitrotoluene radical anion (also Figure 5). The ROMP2/cc-pVDZ//ROHF/6-31G* calculations indicate that the methyl substituent *ortho* to the nitro group decreases the barrier to rotation by almost 12.0 kcal/mol, i.e., it is reduced by about half in the gas phase, but coplanarity is still preferred.

Electron spin resonance (ESR) experiments (57) on the nitrobenzene radical anion in HMPA solution have been interpreted as indicating that the planar geometry calculated in the gas phase is maintained in solution. To address these results, we calculated isotropic hyperfine coupling constants at the B3LYP/6-311G** level of theory. We (58) and others (59-62) have found the B3LYP level of density functional theory to be reasonably accurate for the prediction of isotropic hyperfine couplings, and we have discussed elsewhere the applicability of the 6-311G** basis set for such calculations (63). After accounting for solvation effects using a Born-Kirkwood-Onsager reaction field model with a solvent dielectric constant of 30.0 (corresponding to HMPA), this level of theory predicts carbon hyperfine coupling constants of -6.0 G at C1 and 5.4 G at C4 in the optimized planar C_{2v} geometry. Similar calculations were performed on a geometry in which the oxygen atoms were constrained to lie 20° out of the plane of the aromatic ring and the coupling constants in this case were found to be 5.8 G at C1 and 3.0 G at C4. The experimentally determined



FIGURE 4. Energetics of nitro group pyramidalization for the nitro group fixed in the plane of the aromatic ring (left) and orthogonal to the plane of the aromatic ring (right) for nitrobenzene radical anion. The abscissa refers to one ONCC dihedral angle (the other is related by symmetry), and all other degrees of freedom are fully relaxed. Energies are calculated at the ROMP2/cc-pVDZ//ROHF/6-31G* level.



FIGURE 5. Energetics of rotation about the C—N bond in the radical anions of nitrobenzene and *o*-nitrotoluene. All other degrees of freedom are fully relaxed. Energies are calculated at the ROMP2/ cc-pVDZ//ROHF/6-31G* level.

coupling constants in HMPA are -7.0 G at C1 and 6.1 G at C4 (*57*). Overall, then, the experimental results are in excellent agreement with the predicted planar geometry for nitrobenzene radical anion.

ESR studies of 1,3-dialkyl-2-nitroaromatic radical anions in acetonitrile solvent, on the other hand, have been interpreted as showing that the nitro group is rotated out of the plane of the aromatic ring (64). This is based on an observed increase in spin localization on the nitro group. The nitrogen was further proposed to be pyramidal for these radical anions based on the magnitudes of the observed coupling constants (64). This would appear to indicate that solvation effects, when operating in conjunction with *ortho*-substitution, can result in preferred radical anion geometries that rotate the nitro group out-of-plane. The observed planarity of the solvated nitrobenzene radical anion appears to be primarily attributable to the very high gas-phase barrier to nitro group rotation, which is reduced in substituted cases as illustrated by the *o*-nitrotoluene calculations.

The above analysis supports the reliability of the aqueous geometries predicted by the AM1–SM2 model. Of course, the successful predictions for the regioselectivity of reduction further support the validity of the modeling approach. The ability of the SM*x* series of solvation models (*15, 25, 26, 65–70*) to predict the electronic structure of reagents in solution should open the door for the study of many environmentally important reactions taking place in aqueous or other liquid media.

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Supporting Information Available

Stereostructures and relative energies for all radical anion local minima in the gas phase and aqueous solution with Mulliken and CM1A charges for each nitro group (5 pages) will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supporting information from this paper or microfiche (105×148 mm, 24× reduction, negatives) may be obtained from Microforms Office, American Chemical Society, 1155 16th St. NW, Washington, DC 20036. Full bibliographic citation (journal, title of article, names of authors, inclusive pagination, volume number, and issue number) and prepayment, check or money order for \$15.00 for photocopy (\$17.00 foreign) or \$12.00 for microfiche (\$13.00 foreign), are required. Canadian residents should add 7% GST. Supporting information is available to subscribers electronically via the Internet at http://pubs.acs.org (WWW) and pubs.acs.org (Gopher).

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