

# Quantum Chemical Analysis of *para*-Substitution Effects on the Electronic Structure of Phenylnitrenium Ions in the Gas Phase and Aqueous Solution

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**Abstract:** Ab initio calculations for *para*-substituted phenylnitrenium ions predict larger singlet–triplet splittings, shorter singlet C–N<sup>+</sup> bond lengths, and higher singlet aromatic ring stretching frequencies for substituents with greater electron-donating character. Trends in these properties correlate linearly with *para*-substituent constants  $\sigma_R^+$ , indicating that phenylnitrenium ions closely resemble other electron-deficient aromatic systems where resonance interactions with substituents are dominant. Sensitivity to substitution is large as judged by the slope of the correlating line for aqueous singlet–triplet splittings,  $\rho = 6.4$ . For 13 of 15 substituted cases, aqueous solvation preferentially stabilizes the singlet state by 0.9 to 4.4 kcal/mol; for the *p*-CO<sub>2</sub>H and *p*-CF<sub>3</sub> cases, the triplet state is better solvated by less than 1 kcal/mol.

## 1. Introduction

Aromatic amines are oxidatively catabolized to highly reactive nitrenium cations (R–N<sup>+</sup>–R') *in vivo*.<sup>1</sup> These nitrenium ions are powerful electrophiles and, reacting out of the singlet state, covalently modify DNA (particularly guanine residues); such reactivity is carcinogenic.<sup>2–6</sup> Although isoelectronic with carbenes, nitrenium ions exhibit many different properties as a consequence of their positive charge.<sup>7–9</sup> One key example is the energy splitting between the singlet and triplet states for these biradicals and the degree to which it is affected by substitution at the divalent center.

It is well established that carbene, CH<sub>2</sub>, has a singlet–triplet (S–T) splitting of 9.0 kcal/mol,<sup>10,11</sup> while parent nitrenium, NH<sub>2</sub><sup>+</sup>, has a S–T splitting of 30 kcal/mol<sup>12</sup> (a positive sign corresponds to the triplet state being lower in energy). A combination of experimental results and well-converged quantum mechanical studies indicates that alkyl and aromatic substituents preferentially stabilize the singlet state in each system. However, while for a carbene the magnitudes of these stabilizations are about 5 kcal/mol for either substituent,<sup>7,13–24</sup> for a nitrenium ion the stabilizations are roughly 20 and 50 kcal/

mol for a methyl and phenyl substituent, respectively.<sup>7,8,25–28</sup> This large difference in the influence of substituents, particularly substituents capable of conjugating with the divalent center, is attributed to the significantly different electronegativities of C and N<sup>+</sup>.<sup>7–9,29,30</sup> Stabilization of the cationic charge in nitrenium ions by  $\pi$ -conjugation is so important that phenylnitrenium ions have been found to exhibit substantial quinoidal, i.e., iminocyclohexadienyl-cation-like, character (Figure 1).<sup>7,31</sup>

Since  $\pi$ -conjugation affects the nitrenium S–T splitting so significantly, one might expect the splitting to be sensitive to substitution on the aromatic ring. Indeed, early computational studies at low levels of theory predicted that aromatic rings substituted with  $\pi$ -electron donating groups ( $\pi$  donors) preferentially stabilize the singlet nitrenium ion better than aromatic

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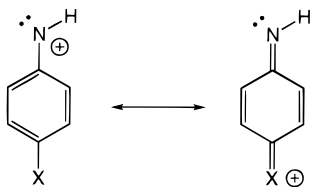
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**Figure 1.** Two key resonance structures for a *para*-substituted phenylnitrenium ion system. The mesomer on the right, formally available only to the singlet state of the nitrenium ion, rationalizes trends in substitution effects for that state.

rings substituted with  $\pi$ -electron withdrawing groups ( $\pi$  acceptors).<sup>25,29,32–34</sup> Moreover, recent experimental evidence suggests that one phenylnitrenium ion substituted with strong  $\pi$  acceptor groups has a triplet ground state.<sup>35</sup> Since it is believed that only the singlet state of aromatic nitrenium ions covalently modifies DNA, understanding the nature of aryl-substitution effects may be of practical importance in the design of aromatic amines (a functionality often occurring in pharmacophores) exhibiting minimal carcinogenicity.

The goal of this paper is to systematically compare, via quantum chemical calculations, the effects of *para* substitution on the properties of phenylnitrenium ion for a wide variety of substituents. Moreover, Gonzalez et al.<sup>9</sup> have previously examined the effects of solvation on the S-T splittings of small nitrenium ions and carbenes; this paper presents the first study of these effects on arylnitrenium ions. We explore linear free energy relationships<sup>36</sup> (LFER's) between phenylnitrenium ion S-T gaps and three model systems for *para*-substitution effects. In particular, we correlate S-T splittings with the standard  $\sigma_p$  scale<sup>37</sup> (along the lines first described by Hammett<sup>38</sup>), with the more specialized  $\sigma^+$  scale of Brown and co-workers,<sup>39,40</sup> designed specifically for electron-deficient aromatics, and with the  $\sigma_{R^+}$  scale of Ehrenson et al.<sup>41</sup> The  $\sigma_{R^+}$  scale was specifically developed for cases where the *para*-substituted aromatic ring is electron deficient and resonance is important, and considerable effort went into removing the influence of effects other than resonance on substituent constants. We also identify certain extrathermodynamic<sup>42,43</sup> relationships between these LFER descriptors and key nitrenium ion properties. Computations are carried out with density functional theory (DFT), which has been demonstrated to predict S-T splittings accurate to within about 2 kcal/mol for a variety of analogous systems.<sup>7,8,22–24,26–28,44–48</sup> Furthermore, since nitrenium ion chemistry is primarily of interest in vivo, condensed-phase effects are taken into account by using an SM5.42R aqueous solvation model,<sup>49</sup> in particular one designed for the DFT level of theory.<sup>50</sup>

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## 2. Computational Methods

All geometries were optimized by using the gradient-corrected functionals of Becke<sup>51</sup> for exchange and of Perdew and Wang<sup>52</sup> for correlation (BPW91) with the correlation-consistent polarized valence double- $\zeta$ <sup>53</sup> (cc-pVDZ) basis set. Analytic frequency calculations were performed to verify the nature of all minima and to calculate zero-point vibrational energies as well as frequencies. In cases where multiple rotameric minima exist, e.g., different orientations of  $-\text{CHO}$  relative to  $-\text{NH}$  in the plane of the aromatic ring, the lowest energy rotamer was employed in all calculations; however, rotamer energy differences were always less than 1.4 kcal/mol—usually much less.

Standard state solvation free energies  $\Delta G_s^\circ$  in water (dielectric constant  $\epsilon = 78.3$ ) were calculated with use of the SM5.42R/BPW91/DZVP aqueous model<sup>50</sup> based on Class IV charges<sup>54</sup> obtained with the DZVP basis set;<sup>55</sup> these calculations employed gas-phase BPW91/cc-pVDZ geometries (the “R” in SM5.42R implies that the model was designed to use gas-phase geometries kept Rigid in the liquid solution phase). All calculations were carried out with a locally modified version of the Gaussian 94 electronic structure program suite.<sup>56,57</sup>

## 3. Results

Optimized geometries were obtained for 30 different nitrenium ions (phenylnitrenium singlet and triplet states for each of 15 different *para* substituents:  $\text{N}(\text{CH}_3)_2$ ,  $\text{NH}_2$ ,  $\text{OH}$ ,  $\text{OCH}_3$ ,  $\text{CH}_3$ ,  $\text{H}$ ,  $\text{F}$ ,  $\text{CHO}$ ,  $\text{Cl}$ ,  $\text{CO}_2\text{H}$ ,  $\text{CO}_2\text{CH}_3$ ,  $\text{COCH}_3$ ,  $\text{CF}_3$ ,  $\text{CN}$ , and  $\text{NO}_2$ ). The electronic and zero-point vibrational energies, aqueous solvation free energies, and aqueous S-T splittings of these phenylnitrenium ions are provided in Table 1. The heavy atom bond lengths for all 30 compounds are tabulated in Table 2. The nitrenium NH bond is found to be in the plane of the aromatic ring for all of the singlets, while for the triplets it is usually rotated out-of-plane such that the CCNH dihedral angles are about  $\pm 90^\circ$ . For the nitrenium ions *para* substituted with carbonyl derivatives or  $\text{NO}_2$ , however, the NH bond is found in the plane of the aromatic ring for both spin states.

It has recently been shown that the quinoidal character of aromatic nitrenium ions can be assessed from measurement of key IR stretching frequencies.<sup>31,58</sup> Table 3 lists the computed frequencies for the normal mode corresponding approximately to the symmetric combination of two aromatic C–C stretches; in this case, the two C–C bonds are those parallel to the C–N<sup>+</sup> bond.

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**Table 1.** Electronic ( $E_h$ ) and Zero-Point Vibrational (ZPVE) Energies, Aqueous Solvation Free Energies ( $\Delta G_s^\circ$ ), and S-T Splittings for *para*-Substituted Phenylnitrenium Ions<sup>a</sup>

<i>para</i> substituent	electronic state	$E^b$	ZPVE	$\Delta G_s^\circ$ <sup>c</sup>	S-T splittings <sup>d</sup>	
					gas	aqueous
N(CH <sub>3</sub> ) <sub>2</sub>	<sup>1</sup> A	0.0	109.3	-51.6		
	<sup>3</sup> A'	29.9	107.1	-50.0	-27.7	-29.3
NH <sub>2</sub>	<sup>1</sup> A'	0.0	75.3	-60.7		
	<sup>3</sup> A''	29.9	73.3	-56.5	-27.8	-32.0
OH	<sup>1</sup> A'	0.0	67.3	-62.3		
	<sup>3</sup> A	27.3	65.4	-59.3	-25.4	-28.4
OCH <sub>3</sub>	<sup>1</sup> A'	0.0	84.2	-52.9		
	<sup>3</sup> A	28.6	82.4	-51.7	-26.7	-28.0
CH <sub>3</sub>	<sup>1</sup> A	0.0	80.5	-54.5		
	<sup>3</sup> A''	23.7	78.7	-52.5	-21.9	-23.9
H	<sup>1</sup> A'	0.0	64.1	-57.5		
	<sup>3</sup> A''	20.8	62.1	-55.8	-18.8	-20.6
F	<sup>1</sup> A'	0.0	59.4	-57.1		
	<sup>3</sup> A''	24.0	57.5	-56.2	-22.2	-23.1
CHO	<sup>1</sup> A	0.0	69.1	-59.2		
	<sup>3</sup> A	13.8	67.5	-54.8	-12.2	-16.5
Cl	<sup>1</sup> A'	0.0	58.4	-54.7		
	<sup>3</sup> A''	23.2	56.6	-53.8	-21.3	-22.3
CO <sub>2</sub> H	<sup>1</sup> A	0.0	72.8	-59.9		
	<sup>3</sup> A	18.3	70.7	-60.6	-16.2	-15.5
CO <sub>2</sub> CH <sub>3</sub>	<sup>1</sup> A	0.0	89.6	-52.0		
	<sup>3</sup> A	18.6	87.6	-49.7	-16.5	-18.8
COCH <sub>3</sub>	<sup>1</sup> A	0.0	86.1	-55.2		
	<sup>3</sup> A	15.0	84.6	-52.0	-13.5	-16.7
CF <sub>3</sub>	<sup>1</sup> A	0.0	66.6	-56.0		
	<sup>3</sup> A''	20.0	64.6	-56.8	-17.9	-17.1
CN	<sup>1</sup> A	0.0	62.9	-60.9		
	<sup>3</sup> A	19.4	61.1	-58.4	-17.5	-20.0
NO <sub>2</sub>	<sup>1</sup> A	0.0	64.8	-59.0		
	<sup>3</sup> A	18.8	62.8	-55.5	-16.8	-20.3

<sup>a</sup> All energies in kcal/mol. <sup>b</sup> Gas-phase electronic energy (including nuclear repulsion) relative to the gas-phase ground state at BPW91/cc-pVDZ level. <sup>c</sup> SM5.42/BPW91/DZVP//BPW91/cc-pVDZ level, standard state is 1 mol/L in both gas and liquid at 298 K. <sup>d</sup> S-T splittings include  $\Delta$ ZPVE; negative splitting indicates that the singlet state is lower in energy.

We have correlated some of the data in Tables 1–3 against descriptor sets developed to quantify *para*-substitution effects in various model systems. The parameter sets examined include the  $\sigma_p$  scale,<sup>37,38</sup> from which descriptors are available for all of our considered substituents, and also the  $\sigma^+$  scale of Brown and co-workers.<sup>39,40</sup> The  $\sigma^+$  scale was developed from a model system meant to be more relevant for reactions/properties involving electron-deficient aromatics. Since the nitrenium ion systems are cationic, one might expect the  $\sigma^+$  descriptor set to be more applicable than the  $\sigma_p$  set;  $\sigma^+$  descriptors are available for 12 of the examined substituents. Finally, we have correlated against the  $\sigma_R^+$  scale of Ehrenson et al.<sup>41</sup> This scale was also designed to be most applicable to electron-deficient aromatic rings, but the scale was refined in such a way that descriptor values are meant to reflect primarily the influence the *para* substituent exerts through *resonance*, not inductive, steric, or other effects. Again, such a design seems particularly appropriate for use in the nitrenium ion system; again, however,  $\sigma_R^+$  descriptors are available for only 12 of our set of *para* substituents (a different set of 12 than for  $\sigma^+$ ). Table 4 provides literature values for the various substituent constants, and Table 5 contains the correlation coefficients  $R$  associated with linear regressions of the S-T splitting, singlet C–N<sup>+</sup> bond length  $r_2$ , and singlet symmetric aromatic C–C stretching frequencies on the different descriptor sets.

As the various LFER scales were developed from reference systems in *liquid-phase solution*, one might expect properties calculated with the inclusion of solvation effects to be better

correlated with these scales than gas-phase values. For the S-T splittings, Table 5 includes correlation coefficients  $R$  for both the gas phase and aqueous solution. Since the SM5.42R model is designed to compute solvation effects with use of gas-phase geometries, we do not evaluate solvation effects on the other properties in Table 5.

We now discuss in more detail the trends in key nitrenium ion properties as a function of substitution. We begin with a focus on the qualitative effects of substitution and then examine the quantitative utility of regressing selected properties on LFER descriptors for the *para* substituents.

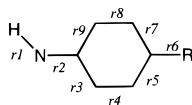
#### 4. Discussion

The data in Table 1 indicate that the S-T splittings for the *para*-substituted phenylnitrenium ions change as a function of the  $\pi$ -electron-withdrawing (or donating) character of the substituent. That change is qualitatively in the expected direction: The predicted splittings in water span a range of 16.5 kcal/mol, with strong  $\pi$  donors (e.g., –NR<sub>2</sub>, –OR) better stabilizing the singlet state relative to the triplet, while strong  $\pi$  acceptors (e.g., –CN, –NO<sub>2</sub>) are net singlet destabilizing.

Other trends in Table 1 are also of interest. The singlet nitrenium ions are calculated to have consistently larger zero-point vibrational energies than the corresponding triplets, typically by about 2 kcal/mol. This implies “stiffer” bonding in the singlets, a situation with which the quinoidal character of the singlet nitrenium ions (Figure 1) is consistent. One vibration that consistently contributes a sizable amount (~0.5 kcal/mol) to this effect is the C–N<sup>+</sup> bond, which for the singlets is computed to have a vibrational frequency of typically about 1540 cm<sup>-1</sup>, while in the triplets the same stretching frequency is more typically about 1360 cm<sup>-1</sup>. Remaining differences (~1.5 kcal/mol) are spread out among the various other normal modes.

Aqueous solvation effects on the S-T splitting are also significant. In 13 of 15 cases, the singlet is better solvated than the triplet by 0.9 to 4.4 kcal/mol. For the cases of CO<sub>2</sub>H and CF<sub>3</sub>, the triplet is better solvated than the singlet, but by only a small amount, 0.7 and 0.8 kcal/mol, respectively. Over all 15 substituents, the average preferential solvation of the singlet state is 2.1 kcal/mol. We carefully examined the differential state solvation free energies to determine whether they were correlated with, say, the partial charge on key atoms or functional groups (e.g., the NH<sup>+</sup> fragment) but did not find any particular trend. Instead, the increased magnitude of the solvation free energy for the singlet appears to be the sum of many small contributions over the whole of the molecule (in a neutral molecule, such an observation might suggest that the singlets have a higher molecular dipole or quadrupole moment than the triplets, for instance, but this is not as easily quantified for a charged system, since these moments are dependent on the chosen origin and the two spin states do not have identical geometries). The difference in the solvation free energies for the two states is almost entirely associated with the polarization free energy resulting from the electrostatic interactions between the charge distribution of the solute and the surrounding dielectric medium; differences in first-solvation-shell effects (e.g., cavitation, dispersion, nonelectrostatic components of hydrogen bonding, the hydrophobic effect, etc.) are predicted to be less than 0.2 kcal/mol in every case.

Preferential solvation of the singlet is consistent with results obtained previously by Gonzalez et al.<sup>9</sup> for small substituted nitrenium ions (e.g., dichloronitrenium), where only the polarization component was examined, and is also consistent with a

**Table 2.** Heavy-Atom Bond Lengths (Å) for *para*-Substituted Phenylnitrenium Ions<sup>a</sup>

<i>para</i> substituent	electronic state	<i>r1</i>	<i>r2</i>	<i>r3</i>	<i>r4</i>	<i>r5</i>	<i>r6</i>	<i>r7</i>	<i>r8</i>	<i>r9</i>
N(CH <sub>3</sub> ) <sub>2</sub>	<sup>1</sup> A	1.040	1.304	1.467	1.364	1.455	1.341	1.458	1.363	1.468
	<sup>3</sup> A'	1.039	1.362	1.435	1.381	1.437	1.366	1.437	1.381	1.435
NH <sub>2</sub>	<sup>1</sup> A'	1.040	1.303	1.471	1.364	1.448	1.330	1.453	1.363	1.472
	<sup>3</sup> A''	1.038	1.355	1.441	1.378	1.436	1.348	1.436	1.378	1.441
OH	<sup>1</sup> A'	1.041	1.304	1.472	1.367	1.439	1.316	1.443	1.367	1.471
	<sup>3</sup> A	1.037	1.345	1.445	1.380	1.430	1.331	1.431	1.377	1.446
OCH <sub>3</sub>	<sup>1</sup> A'	1.041	1.304	1.471	1.369	1.441	1.310	1.449	1.364	1.470
	<sup>3</sup> A	1.040	1.348	1.445	1.380	1.426	1.350	1.434	1.375	1.446
CH <sub>3</sub>	<sup>1</sup> A	1.042	1.307	1.469	1.375	1.435	1.482	1.443	1.371	1.469
	<sup>3</sup> A''	1.036	1.336	1.449	1.380	1.432	1.489	1.432	1.380	1.449
H	<sup>1</sup> A'	1.043	1.309	1.471	1.381	1.421	1.101	1.428	1.378	1.470
	<sup>3</sup> A''	1.035	1.330	1.453	1.383	1.420	1.098	1.420	1.383	1.453
F	<sup>1</sup> A'	1.042	1.306	1.472	1.374	1.424	1.311	1.431	1.371	1.472
	<sup>3</sup> A''	1.037	1.332	1.450	1.380	1.420	1.320	1.420	1.380	1.450
CHO <sup>b</sup>	<sup>1</sup> A	1.043	1.310	1.470	1.379	1.425	1.518	1.431	1.378	1.490
	<sup>3</sup> A	1.033	1.309	1.458	1.376	1.429	1.479	1.416	1.388	1.456
Cl	<sup>1</sup> A'	1.042	1.307	1.469	1.375	1.431	1.698	1.437	1.372	1.469
	<sup>3</sup> A''	1.036	1.339	1.447	1.381	1.426	1.709	1.426	1.381	1.447
CO <sub>2</sub> H <sup>b</sup>	<sup>1</sup> A	1.043	1.310	1.468	1.380	1.426	1.509	1.431	1.376	1.467
	<sup>3</sup> A	1.030	1.304	1.454	1.385	1.415	1.490	1.423	1.378	1.467
CO <sub>2</sub> CH <sub>3</sub> <sup>b</sup>	<sup>1</sup> A	1.042	1.310	1.468	1.379	1.427	1.507	1.432	1.376	1.467
	<sup>3</sup> A	1.030	1.307	1.455	1.380	1.421	1.495	1.414	1.387	1.459
COCH <sub>3</sub> <sup>b</sup>	<sup>1</sup> A	1.042	1.310	1.467	1.376	1.431	1.514	1.436	1.374	1.466
	<sup>3</sup> A	1.033	1.312	1.456	1.378	1.428	1.495	1.415	1.389	1.455
CF <sub>3</sub>	<sup>1</sup> A	1.043	1.309	1.469	1.381	1.421	1.535	1.431	1.376	1.466
	<sup>3</sup> A''	1.035	1.327	1.452	1.382	1.421	1.528	1.421	1.382	1.452
CN	<sup>1</sup> A	1.043	1.310	1.468	1.378	1.433	1.423	1.439	1.375	1.467
	<sup>3</sup> A	1.036	1.333	1.450	1.380	1.432	1.419	1.432	1.380	1.450
NO <sub>2</sub> <sup>b</sup>	<sup>1</sup> A	1.042	1.310	1.468	1.378	1.420	1.468	1.426	1.376	1.468
	<sup>3</sup> A	1.031	1.306	1.457	1.384	1.409	1.464	1.410	1.384	1.463

<sup>a</sup> BPW91/cc-pVDZ level. The CCNH dihedral angle is approximately 0° (NH in plane) for all singlets and, unless otherwise indicated, 90° (NH out of plane) for all triplets. <sup>b</sup> Triplet CCNH dihedral angle approximately 0° (NH in plane).

**Table 3.** Harmonic Vibrational Frequencies (cm<sup>-1</sup>) for the Symmetric Aromatic C–C Stretching Mode of *para*-Substituted Phenylnitrenium Ions<sup>a</sup>

<i>para</i> substituent	singlet frequency	triplet frequency
N(CH <sub>3</sub> ) <sub>2</sub>	1642	1597
NH <sub>2</sub>	1654	1628
OH	1641	1617
OCH <sub>3</sub>	1638	1606
CH <sub>3</sub>	1630	1598
H	1618	1574
F	1630	1602
CHO	1622	1547
Cl	1616	1580
COOH	1618	1565
COOCH <sub>3</sub>	1617	1560
COCH <sub>3</sub>	1608	1545
CF <sub>3</sub>	1626	1584
CN	1621	1584
NO <sub>2</sub>	1608	1551

<sup>a</sup> BPW91/cc-pVDZ level.

number of experimental studies for carbenes in nonaqueous solvents.<sup>15,59–62</sup> A previous computation of a solvent effect on

(59) Langan, J. G.; Sitzman, E. V.; Eisenthal, K. B. *Chem. Phys. Lett.* **1984**, *110*, 521.

(60) Eisenthal, K. B.; Turro, N. J.; Sitzman, E. V.; Gould, I. R.; Hefferon, G.; Langan, J.; Cha, Y. *Tetrahedron* **1985**, *41*, 1543.

(61) Sitzman, E. V.; Langan, J. G.; Griller, D.; Eisenthal, K. B. *Chem. Phys. Lett.* **1989**, *161*, 353.

(62) García-Garibay, M. A.; Theroff, C.; Shin, S. H.; Jernelius, J. *Tetrahedron Lett.* **1993**, *52*, 8415.

**Table 4.** *para*-Substituent  $\sigma_p$ ,  $\sigma^+$ , and  $\sigma_R^+$  Values (unitless)

<i>para</i> substituent	$\sigma_p^a$	$\sigma^+{}^b$	$\sigma_R^+{}^b$
N(CH <sub>3</sub> ) <sub>2</sub>	-0.830	-1.70	-1.75
NH <sub>2</sub>	-0.660	-1.30	-1.61
OH	-0.370	-0.92	
OCH <sub>3</sub>	-0.236	-0.78	-1.02
CH <sub>3</sub>	-0.170	-0.31	-0.25
H	0.000	0.00	0.00
F	0.062	-0.07	-0.57
CHO	0.220		
Cl	0.227	0.11	-0.36
COOH	0.265	0.42	
COOCH <sub>3</sub>	0.385	0.48	0.14
COCH <sub>3</sub>	0.502		0.16
CF <sub>3</sub>	0.540		0.08
CN	0.660	0.66	0.13
NO <sub>2</sub>	0.778	0.79	0.15

<sup>a</sup> Reference 37. <sup>b</sup> Reference 41.

the S-T splitting of an arylnitrenium ion found the singlet state of *N*-methyl-*N*-phenylnitrenium to be better solvated than the triplet state by only 0.4 kcal/mol in acetonitrile.<sup>8</sup> Since the effect in this case was also almost entirely polarization, and since the magnitude of the polarization effect is proportional to  $(1 - \epsilon^{-1})$  where  $\epsilon$  is the dielectric constant, results for water ( $\epsilon = 78.3$ ) would be expected to be very similar to those for acetonitrile ( $\epsilon = 37.5^{63}$ ). This suggests that the magnitude of the preferential solvation calculated for nitrenium ion singlet states may be

(63) *CRC Handbook of Chemistry and Physics*, 75th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 1995.

**Table 5.** Correlation Coefficients  $R$  (unitless) for Regression of *para*-Substituted Phenylnitrenium Properties on  $\sigma_p$ ,  $\sigma^+$ , and  $\sigma_R^+$  Values<sup>a</sup>

property	$\sigma_p$	$\sigma^+$	$\sigma_R^+$
S-T splitting <sup>b</sup>	0.842 (0.834)	0.909 (0.951)	0.946 (0.943)
singlet bond length $r_2$ <sup>c</sup>	0.878	0.926	0.954
singlet <i>sym</i> aromatic CC stretch <sup>d</sup>	0.865	0.913	0.885

<sup>a</sup> Substituents for which  $\sigma^+$  or  $\sigma_R^+$  values are not available were not included in the respective correlations (see Table 4). <sup>b</sup>Data from Table 1. Values are tabulated as aqueous solution (gas-phase). Corresponding  $\rho$  values are 8.9 (9.3), 5.3 (5.6), 6.4 (6.6). <sup>c</sup>Data from Table 2. <sup>d</sup>Data from Table 3.

substantially reduced for cases where the nitrenium nitrogen is not protonated, as is true for many biologically relevant nitrenium ions.

Turning now to geometrical trends in the substituted phenylnitrenium ions, the most striking substitution effect is found within the triplet series, where *para* substitution by a nitro or carbonyl group causes the N–H bond to remain in the plane of the aromatic system, while for all of the other substituted triplets that bond rotates through 90° so as to be out of the aromatic plane. In the case of the singlets, the N–H bond is always found in the aromatic plane, and for that spin state the explanation for this preference is obvious. The singlet state nitrenium ion is a closed-shell state with two electrons in an in-plane orbital, which at roughly 33% s character is much lower in energy than the pure p out-of-plane orbital that is unoccupied in the singlet. For the triplet, however, both orbitals are singly occupied, and the hybridization of the nitrogen becomes nearly sp (as judged by CNH bond angles typically between 150° and 160° for this state).

The issue then becomes which of the singly occupied orbitals in the triplet can best interact with the aromatic  $\pi$  system. Recalling that the energy gain from the interaction of two orbitals is proportional to the overlap between the two and inversely proportional to the energy separation between the two,<sup>64</sup> one can see that there are opposing considerations for the nitrenium triplet. Overlap will be greater for the pure p orbital, which is perfectly parallel with the aromatic  $\pi$  system as opposed to slightly tilted away, but the alternative orbital will be somewhat lower in energy (by virtue of some s character) and thus closer in energy to the highest occupied  $\pi$  orbital of the aromatic ring. These effects appear to be very finely balanced—rotational barriers about the N–H bond in the triplets are usually well below 2 kcal/mol. When the energy of the highest energy aromatic  $\pi$  orbital is high (i.e., when a donor substituent is present), overlap appears to be the dominant consideration. On the other hand, when the energy of the highest energy aromatic  $\pi$  orbital drops, the reduction in the energetic separation between the two interacting orbitals is the controlling influence on the geometry. Note that this analysis presupposes the nitro and carbonyl derivative groups to be the strongest electron withdrawing groups, a point to which we return below. [A reviewer suggested that N–H orientations in the triplets might instead be controlled by dipolar interactions between the N–H and substituent groups (thus in-plane groups would tend to enforce in-plane N–H rotamers, while cylindrically symmetric groups such as CN would allow intrinsic N–H rotameric preferences to be exhibited). However, the two possible in-plane conformations for *para* carboxaldehyde, for example, one being dipole aligned and the other opposed, are

both minima; they differ in energy by 0.4 kcal/mol. A similar situation exists for all triplets having nonsymmetric in-plane substituents. This suggests that while such distant dipole–dipole interactions may certainly influence the rotational coordinate, they do not dominate it.]

A different geometric issue of key importance is the length of the C–N<sup>+</sup> bond ( $r_2$  in Table 2) in the various singlets. To the extent that *para* substitution stabilizes the quinoidal mesomer in Figure 1, this should be reflected in increasingly shorter bond lengths  $r_2$  with increased  $\pi$ -donating power of the *para* substituent. This trend is indeed observed;  $r_2$  takes on its smallest value of 1.303 Å in *p*-aminophenylnitrenium and its largest value of 1.310 Å in the nitro- and carbonyl-substituted phenylnitreniums. Although the magnitude of the substitution effect is rather small at 0.007 Å, it is smooth over the range of substituents studied here (see below). It is moreover clear that while *para* substitution does influence the weight of the quinoidal mesomer for the singlet state (as judged by this geometric criterion), the absolute weight of that mesomer is still quite large even in those phenylnitreniums substituted with  $\pi$  acceptors— $r_2$  for these species being considerably smaller than the typical C–N single bond length of about 1.4 Å.

A separate measure of quinoidal character may be had from analysis of the IR frequency associated with the normal mode that represents the symmetric combination of the C–C stretches for the two aromatic ring bonds parallel to the C–N<sup>+</sup> bond. As the quinoidal mesomer becomes increasingly relevant, this stretch would be expected to move to higher frequency since the bonds involved would have more double bond character. Table 3 shows that this is the case. The highest frequency, 1654 cm<sup>-1</sup>, is obtained for *p*-aminophenylnitrenium, and the lowest frequency, 1608 cm<sup>-1</sup>, is obtained for both the nitro- and acetyl-substituted phenylnitreniums. The magnitude of this stretching frequency is less consistently dependent on substitution in the triplets—correlation with respect to substituent electron-donating or -withdrawing power is reduced (see below).

Similar behavior is found in the singlets for the frequency associated with C–N<sup>+</sup> bond stretching; here again there should be increased double bond character with substitution by more powerful  $\pi$  donors, and this is observed for this stretch, which ranges from 1537 to 1588 cm<sup>-1</sup>. However, the intensity of this band is always predicted to be very small, and it is unlikely to be observed experimentally.<sup>58</sup> The symmetric aromatic stretch, on the other hand, is predicted to have moderate to strong intensity, and has been observed experimentally in those few instances where IR data are available for phenylnitrenium ions.<sup>31,58</sup>

To calibrate the importance of *para* substitution in these systems compared to others, and also to better understand the nature of that influence, we have correlated the most obvious trends in energies and properties against different series of LFER descriptors associated with *para* substituents. As already noted in the above discussion, the trends in S-T splittings, bond lengths  $r_2$ , and aromatic C–C stretching frequencies are qualitatively those expected from the resonance analysis of Figure 1. The correlation coefficients for these data regressed on the descriptors in Table 4 provide a measure of the degree to which substitution effects in phenylnitrenium ions manifest themselves in a fashion similar to those observed in the model systems from which these descriptors were developed.

We note first that the correlation coefficients associated with  $\sigma_p$  are quantitatively fairly good, but are always statistically inferior to either  $\sigma^+$  or  $\sigma_R^+$ . The reference reaction for the development of  $\sigma_p$  (ionization of substituted benzoic acids) is

(64) Dewar, M. J. S. *The PMO Theory of Organic Chemistry*; Plenum: New York, 1975.

more sensitive to inductive effects and less sensitive to resonance effects than the models used to develop  $\sigma^+$  (ionization of substituted benzylic substrates to benzyl cations) and  $\sigma_{\text{R}}^+$  (a complicated statistical analysis of different reference reactions primarily sharing benzyl-cation character as a common feature), suggesting that the resonance mode of interaction is more important in the nitrenium ion series. This result agrees with intuition. Note that it is not simply an artifact from having slightly different sets for which substituent descriptors are available. Over the same data sets as those used for the  $\sigma^+$  and  $\sigma_{\text{R}}^+$  correlations, the correlation coefficients for regression on  $\sigma_p$  remain significantly smaller in every instance.

A measure of the importance of substitution effects which can be set in the context of other systems is the slope of the regression line for the S-T splittings in solution. For a true LFER, this value,  $\rho$ , has been compiled for many different reaction rates and equilibria. For the different descriptor sets,  $\rho$  ranges from 5.6 ( $\sigma^+$ ) to 9.3 ( $\sigma_p$ , see footnote *b* of Table 5), which is consistent with a property that is extremely sensitive to substitution effects. For comparison, the magnitude of the  $\rho_{\sigma_p}$  value for rates of ionization of singly *para*-substituted diphenylmethyl chlorides in ethanol, a reaction involving essentially unit charge buildup on a benzylic carbon, is 5.1.<sup>65</sup>

Another feature of the S-T splitting correlations is that they are insensitive in two cases out of three to whether the regression is on the data for aqueous solution or for the gas phase (in the case of  $\sigma^+$ ,  $R$  is 4% smaller in solution). Thus, the *relative* charge-donating or -accepting characters of the substituents appear to be unaffected by solvation. However, the absolute magnitude of the interaction difference between a *para* substituent and the electron-deficient center in singlets vs triplets is in every case *reduced* by aqueous solvation, as indicated by smaller  $\rho$  values in solution than in the gas phase for all three descriptor sets. Such a trend is consistent with the notion that solvation assists in stabilizing charge differences between the two spin states, and thereby mitigates substitution effects, but the magnitude of the amelioration is only 3–5%.

Turning to the geometric and vibrational properties in Table 5, the slopes of the regressions are not particularly meaningful, since there are few other such regressions against which to compare (of course, the *sign* of the slope is critical, since it describes the nature of the substitution response as discussed above). However, the qualities of the correlations, as measured by the values of  $R$ , are comparable to the S-T splitting correlations. Regressions of properties other than those listed in Table 5 (e.g., other bond lengths, bond angles, atomic partial charges, etc.) on the three descriptor sets were examined for both states, but none proved sufficiently significant to generate  $R$  values larger than 0.8. No property intrinsic to the triplet state correlated well against any  $\sigma$  scale (the triplet frequencies in Table 3 show one of the best correlations against  $\sigma_{\text{R}}^+$ , with  $R = 0.804$ ). Thus, it is the singlet state that appears to respond to substitution in a manner most analogous with other physical organic reactions/equilibria, and this response extends to geometric and vibrational analysis.

For the cases of the  $r_2$  bond length and the symmetric C–C stretching vibrational frequency, the relative performances of

(65) Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 191.

the  $\sigma^+$  and  $\sigma_{\text{R}}^+$  parameter sets are about equal. However, this comparison is probably not definitive, as each descriptor set lacks values for certain substituents that *are* covered in the other. A potentially more meaningful assessment of this point is to reconsider the *triplet* geometries vis a vis the rotations about the C–N bond observed for this state. In the  $\sigma^+$  descriptor set, CN is considered to be a stronger  $\pi$  acceptor than any carbonyl derivative, but rotation of the N–H bond out of the aromatic plane is not observed. While a parameter for the CF<sub>3</sub> group is not available in the  $\sigma^+$  descriptor set, based on comparison to the  $\sigma$  descriptor set one would expect it too to be larger in magnitude than values assigned to carbonyl derivative substituents, but C–N bond rotation is not observed in that case either. With the  $\sigma_{\text{R}}^+$  parameter set, on the other hand, the systems showing N–H rotation out of plane are precisely those with the maximum positive values of  $\sigma_{\text{R}}^+$ —values for CN and CF<sub>3</sub> are just slightly smaller. This suggests that overall the  $\sigma_{\text{R}}^+$  parameter set is probably best suited for evaluating substitution effects in this and any similar systems.

## 5. Conclusions

Phenylnitrenium ions are predicted to be sensitive to *para*-substitution effects; substituent groups exert their influence primarily on the singlet state and do so via charge-stabilizing interactions with the highly electronegative nitrogen atom of the nitrenium ion. Electron-donating groups donate electronic charge to nitrogen, which stabilizes the singlet state over the triplet, and also leads to increased quinoidal character for the nitrenium ion singlet. This quinoidal character manifests itself both in the C–N<sup>+</sup> bond length and in the infrared frequency for a specific, intense aromatic ring stretching mode.

The trends in singlet–triplet splittings, singlet C–N<sup>+</sup> bond lengths, and the singlet aromatic stretching frequencies all correlate well with linear free energy descriptor sets developed on the basis of the behavior of other *para*-substituted systems:  $\sigma_p$ ,  $\sigma^+$ , and  $\sigma_{\text{R}}^+$ . Correlation is strongest with  $\sigma^+$  and  $\sigma_{\text{R}}^+$ , implying that charge-donating/withdrawing interactions between *para* substituents and the nitrenium ion nitrogen atom are dominated by resonance and that the phenylnitrenium ion system closely resembles other systems where a phenyl ring is attached to a highly electron-deficient center.

In addition to being stabilized by *para* substitution of electron-donating groups, the singlet state is usually also preferentially stabilized by aqueous solvation. For 13 substituents, the magnitude of this stabilization varies from 0.9 to 4.4 kcal/mol. Substituents CO<sub>2</sub>H and CF<sub>3</sub> are exceptions to this rule; the triplet state for these systems is predicted to be better solvated by less than 1 kcal/mol.

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