



## Use of the Bell–Evans–Polanyi Principle to predict regioselectivity of nucleophilic aromatic photosubstitution reactions



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### ABSTRACT

Regioselectivity of nucleophilic aromatic photosubstitution has been shown experimentally to depend upon activation energies of the competing transition states. Computational means of determining relative activation energies were sought, therefore, in order to predict regioselectivity. Optimization of the three triplet transition states of 2-chloro-4-nitroanisole with hydroxide ion gave energies of insufficient accuracy to predict regioselectivity. Computed enthalpy changes from the first triplet transition state to the triplet  $\sigma$ -complexes correlated precisely with the experimental activation energies. This exemplifies the Bell–Evans–Polanyi Principle, and it provides an accurate means of assessing regioselectivity.

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The odd regioselectivity of photochemical nucleophilic aromatic substitutions of the  $S_N2$  Ar\* type was apparent in the first reported example: photohydrolysis of nitrophenyl phosphates proceeded much more efficiently for the *meta* than for the *para* isomer.<sup>1</sup> A new phenomenon named the ‘*meta* effect’ was advanced<sup>2</sup> in recognition that substituents appeared to transmit electronic effects to positions *meta* to the substituent on aromatic rings in the excited state. Many  $S_N2$  Ar\* reactions are now known.<sup>3,4</sup> Models for predicting the regioselectivity of these reactions focus on the electronic structures and calculated properties of the reactants alone.<sup>5</sup> Wide acceptance of these models is evidenced by the use of them in a prominent textbook of organic photochemistry<sup>6</sup> to interpret reactivity in  $S_N2$  Ar\* reactions. It seemed a significant oversight that these models and their descriptions do not mention transition states and relative activation energies, which must comprise the fundamental basis for regioselectivity.

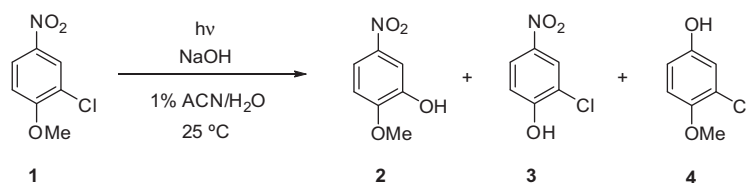
It has been known since the 1930s that photoexcitation of molecules in solution rapidly produces thermally relaxed excited states, and that reaction rates from such states ‘would be governed by the Arrhenius equation.’<sup>7</sup> Our work on the element effect of halogens in the photosubstitutions of 2-halo-4-nitroanisoles<sup>8</sup> revealed the series to be well suited for study of photochemical regioselectivity. The study showed that the photochemical nucleophilic substitutions, like the thermal counterparts,<sup>9</sup> displayed an inverse kinetic element effect, that is,  $F \gg Cl > Br > I$ . This shows that the reaction is step-wise, and the rate-limiting step is formation of the bond. The chlorine compound (**1**) upon irradiation

in aqueous media with hydroxide ion gives products **2**, **3** and **4**, in chemical yields of approximately 70%, 15% and 15%, respectively, (Scheme 1). We showed<sup>5</sup> that the temperature dependence of the distribution of the three products may be predicted exactly by use of the Arrhenius equation with the respective activation energies. This demonstrates that relative activation energies indeed control regioselectivity in this reaction.

With this fact clearly established, we sought a rapid computational means of estimating regioselectivity. Each of the three photoproducts in Scheme 1 stems from the triplet state of **1**. Adiabaticity of the initial bonding steps is required. There is no lower triplet energy surface, and intersystem crossing is too slow to occur during bond formation.

Each product pathway in the triplet manifold entails three possible stationary points: an entry transition state (TS1), a  $\sigma$ -complex, and an exit transition state (TS2). The nine species are depicted in line drawings in Table 1. The first challenge of computing the relative energies of these species is that entry 2, the triplet  $\sigma$ -complex at C–Cl, was difficult to optimize. Others<sup>10</sup> have reported this outcome for this species at the B3LYP/6-311+G(d) and the MP2/6-31+G(d) levels of theory, and have concluded incorrectly that the photosubstitution of chlorine in **1** is concerted. This photoreaction in solution is step-wise as shown by the inverse element effect.<sup>5,8</sup> We also could not optimize entry 2 with B3LYP. Optimized structures with normal bond lengths were obtained with semi-empirical computations or Hartree–Fock computation with a small basis set (STO-3G). Hartree–Fock computations with larger basis sets failed to optimize the structure. This difficulty is associated with the excellent nucleofugality of chloride ion. Known

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**Scheme 1.** Photosubstitution reactions of 2-chloro-4-nitroanisole with hydroxide ion.

**Table 1**  
Photohydrolysis triplet stationary point species and enthalpy changes computed by different methods relative to transition state 1 at the C–Cl bond

Entry	Species <sup>a</sup>	MP2/6-311+G** $\Delta H^\circ$ (kcal/mol)	HF/6-31+G* $\Delta H^\circ$ (kcal/mol)	MP2/6-31+G* $\Delta H^\circ$ (kcal/mol)
1	 TS1 at C-Cl	0	0	0
2	 $\sigma$ -cx at C-Cl	-34.98	-27.74	-34.24
3	 TS2 at C-Cl	-37.04	-27.46	-37.27
4	 TS1 at C-O	1.40	9.18	1.36
5	 $\sigma$ -cx at C-O	-20.88	-14.33	-20.77
6	 TS2 at C-O	-6.67	3.19	-6.66
7	 TS1 at C-N	-0.29	3.94	-0.05
8	 $\sigma$ -cx at C-N	-13.79	-7.49	-12.42
9	 TS2 at C-N	-0.42	6.96	0.97

<sup>a</sup> Imaginary frequencies (HF/6-31+G\*) for entries 1, 3, 4, 6, 7 and 9 are: 646, 117, 634, 693, 679 and 725  $\text{cm}^{-1}$ , respectively.

solution intermediates such as certain singlet ground state  $\sigma$ -complexes with chlorine or bromine as ligands also could not be optimized by density functional computation.<sup>11</sup> The difficulty of finding such intermediates at energy minima may be related to the strong tendency of density functional computations to underestimate energy barrier heights.<sup>12</sup> Entry 2 could be optimized with a constraint on the C–Cl bond at a normal single bond length of 1.82 Å. This constraint was used for our computations of entry 2. B3LYP computations, however, also could optimize neither entry 3 nor entry 8. In view of these shortcomings of B3LYP for this system, we used Hartree–Fock computations, and corrected for

electron correlation with Møller–Plesset computations.<sup>13</sup> Optimizing entry 3 with Hartree–Fock was also problematic. A structure with a correct imaginary frequency but a long C–Cl distance of 2.654 Å was obtained by HF/6-31G(d), and this structure was used for the higher order HF and MP2 computations in single point energy mode.

An additional problem is that a suitable reference structure and optimized energy for the triplet reactants could not be found. We optimized several plausible prereaction species having hydroxide ion and triplet state **1** weakly associated in a  $\pi$ -complex or a hydrogen-bonded complex. The structures, however, showed extensive ionization of the hydroxide oxygen, and total energies 20–40 kcal/mol below what is required by the experimental activation energies of the reactions.<sup>8</sup> We are not the first to encounter this problem.<sup>11c</sup> It is inherent in using gas phase computations to model an ionic reaction that occurs in water. Following the precedent of earlier workers,<sup>11c</sup> we used the energy of the lowest energy transition state as the reference. Because we compare to Arrhenius activation energy, the energy computed is standard enthalpy. In our case the reference is the enthalpy of TS1 at C–Cl (entry 1, Table 1), -680265.29 kcal/mol according to MP2/6-31+G(d).

Computations were carried out with Spartan '14 software<sup>14</sup> in the Windows 7 operating system. In the regime of Hartree–Fock followed by Møller–Plesset computations on the nine structures of Table 1, we found by the criterion of approach to small changes in the computed MP2 energy differences of entries 2–9 from entry 1, that the 6-31+G(d) basis set was an adequate level of theory. The 6-311+G(d,p) basis set in the same sequence of HF and MP2 computations produced nearly the same energy differences, as shown in Table 1. That variation of energy differences becomes small with increases in level of theory occurs because of cancellation of computational errors. These errors did not cancel adequately for smaller basis sets lacking diffuse functions such as STO-3G, 3-21G(\*) and 6-31G(d). Enthalpies by HF were found by optimizing to yield total energy, conducting a frequency calculation and adding calculated corrections for enthalpy changes from 0 to 298 K and zero point energy.<sup>15</sup> In all cases, the frequency calculation for transition states yielded a single imaginary frequency that corresponded to the required atomic movement. MP2 computation was done on each HF structure as single point energy, each using the same basis set. Corrections for zero point energy and enthalpy from the HF computation were added to the MP2 correlation energy result.

The experimental activation energies leading to **2**, **3** and **4** are 1.83, 2.35 and 2.68 kcal/mol, respectively.<sup>8</sup> Inspection of entries 1, 4 and 7 in Table 1 reveals that the determinations of transition state energies relative to entry 1 are insufficiently accurate to predict regioselectivity. The results with the 6-311+G(d,p) basis set are no better. The approach within 1 or 2 kcal/mol of the experimental activation energy differences corresponds roughly to the limitation of the accuracy of such computations. The use of gas phase conditions to model aqueous solution reality no doubt contributes to the deviations.

Since transition states are harder than intermediates to specify and optimize, we examined the intermediates, entries 2, 5 and 8. Figure 1 shows the relationships of the computed standard enthalpy differences by HF and MP2 methods (abscissa) to the

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