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Temperature Dependence of Regioselectivity in Nucleophilic Photosubstitution of 4-Nitroanisole. The Activation Energy Criterion for Regioselectivity

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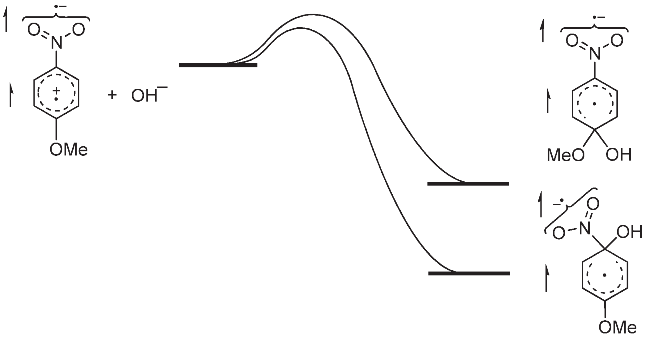

Photosubstitution of the nitro group vs the methoxy group of triplet 4-nitroanisole by hydroxide ion in water leads to product yields of about 80% 4-methoxyphenol and 20% 4-nitrophenol. The ratio depends slightly on temperature from 3 to 73 °C. The slight temperature variation in the yield ratio is reproduced almost perfectly with a simple Arrhenius model for a mechanism involving bonding of hydroxide ion with the triplet state of 4-nitroanisole. The competing transition states have activation energies of 2.2 and 2.6 kcal/mol, respectively. Correct prediction of regioselectivity can be done for this case by quantum chemical calculation of the competing triplet transition-state energies, or those of the corresponding triplet σ-complexes. Other models for aromatic photosubstitution regioselectivity in mechanisms of the S_N2Ar^* type, such as those based on calculated electron densities, HOMO/LUMO coefficients, or energy gap sizes, are discussed and shown to be inferior to the relative activation energies model. The photoreaction in alcohol solvents, claimed by others to generate the same products as in water and to have an exceedingly large variation of the product ratio with temperature, may reflect chemical changes other than those reported.

Introduction

When it became clear that photochemical reactions in condensed phases occurred typically from thermally relaxed, electronically excited molecules, pioneering photochemists suggested that the temperature dependence of reaction rate constants from excited states would be governed by the Arrhenius equation.[1] Many studies have shown the usefulness of this model in the investigation of photochemical reaction mechanisms.[2−5] It seemed odd that, despite the long history of attempts to explain the regioselectivity of nucleophilic aromatic photosubstitution reactions,[6−13] no one to our knowledge had examined the utility of relative

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(2) Fischer, E. *J. Am. Chem. Soc.* **1960**, *82*, 3249.
(3) Encina, M. V.; Lissi, E. A.; Lemp, E.; Zanocco, A.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 1856.
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(5) Gonzales, C.; Pincock, J. *Photochem. Photobiol.* **2006**, *82*, 301.
(6) Zimmerman, H. E.; Somasekhara, S. *J. Am. Chem. Soc.* **1963**, *85*, 922.
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(9) van Reil, H. C. H. A.; Lodder, G.; Havinga, E. *J. Am. Chem. Soc.* **1981**, *103*, 7257.
(10) Mutai, K.; Nakagaki, R.; Tukada, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2066.
(11) Cantos, A.; Marquet, J.; Moreno-Mañas, M; González-Lafont, A.; Lluch, J. M.; Bertrán, J. *J. Org. Chem.* **1990**, *55*, 3303.
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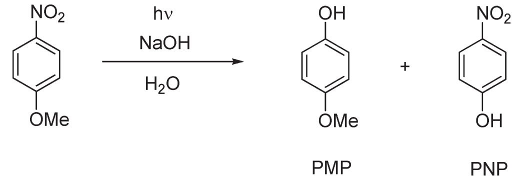
activation energies. Although it was not aimed directly at this question, a recent study[14] of the temperature dependence of regioselectivity of photosubstitution on 4-nitroanisole by hydroxide ion, which claimed a large dependence on temperature of relative product yields, aroused our interest. A subsequent report[15] added a claim of a large temperature dependence of photosubstitution regiochemistry for the same photoreaction.

Our investigation[16] of the element effect of halogen leaving groups in nucleophilic aromatic photosubstitution of 2-halo-4-nitroanisoles had shown normal, fast, elementary rate constants for the photosubstitutions of the nitro and methoxy groups of triplet 4-nitroanisole by hydroxide ion in aqueous solution. These findings for 4-nitroanisole extended and agreed with those of the original investigation of these photoreactions.[17] That study found that hydroxide ion in aqueous media displaced the nitro group and the methoxy group of triplet 4-nitroanisole in a ratio of about 4:1 at 26 and 3 °C. That photolysis of 4-nitroanisole in solutions of sodium hydroxide in alcohol solvents was reported[14] to give product ratios varying from 99:1 at −20 °C to 0.6:1 at 196 °C was very surprising. That the photoreactions were reported to give rise exclusively to hydroxide ion photodisplacement products was also unexpected. Prototropy would cause such solutions to contain little hydroxide ion and much alkoxide ion that would be expected to generate photoproducts. We now report that the temperature dependence of photosubstitution regioselectivity in pure water is modest and that alkoxide ion products are major photoproducts in alcohol solutions.

SCHEME 1. Photosubstitution Reactions of Hydroxide Ion with 4-Nitroanisole



Results

Photolyses of 4-nitroanisole (2.0×10^{-4} M) in air-saturated 5% acetonitrile/water containing 0.010 M NaOH were carried out initially at 313 nm (Scheme 1). We found by UV−vis monitoring of the reactions that the absorption of the 4-nitrophenoxide ion (PN$\bar{\text{P}}$) product (λ_{max} 400 nm, ε 18,300) was easily identifiable, but that of the 4-methoxyphenoxide ion (PM$\bar{\text{P}}$) product (λ_{max} 306 nm, ε 2920) was obscured by absorptions of unknown origin centered at 350 nm.[18] This result had been noticed by the original investigators of this reaction,[17] who attributed the unknown absorptions to degradation of the PM$\bar{\text{P}}$ product. They found that the photoreaction gave the two products shown in Scheme 1 quite cleanly if air was excluded. We confirmed this result, and we found that use of a uranium glass filter (λ > 330 nm) further improved the cleanness of the reaction.

Overlaid UV−vis spectra (225−500 nm) for the photolysis at ~25 °C of 4-nitroanisole (5.4×10^{-5} M) in argon-purged pure water solution with 0.10 M NaOH through the uranium filter are shown in Figure 1. The isosbestic points at 365 and 262 nm indicate a single-stage, simple reaction, after which the absorptions of the 4-nitrophenoxide ion at 400 nm and the 4-methoxyphenoxide ion at 306 nm are clearly visible. These absorptions allowed quantitative monitoring of the two products. The isosbestic point at 365 nm was sharp under all temperature conditions. The isosbestic point at 262 nm was sharp at 3 °C, but slightly ragged at 37 °C and at 73 °C. When samples were irradiated exhaustively at 3 °C, the UV−vis absorptions of the two products in three runs

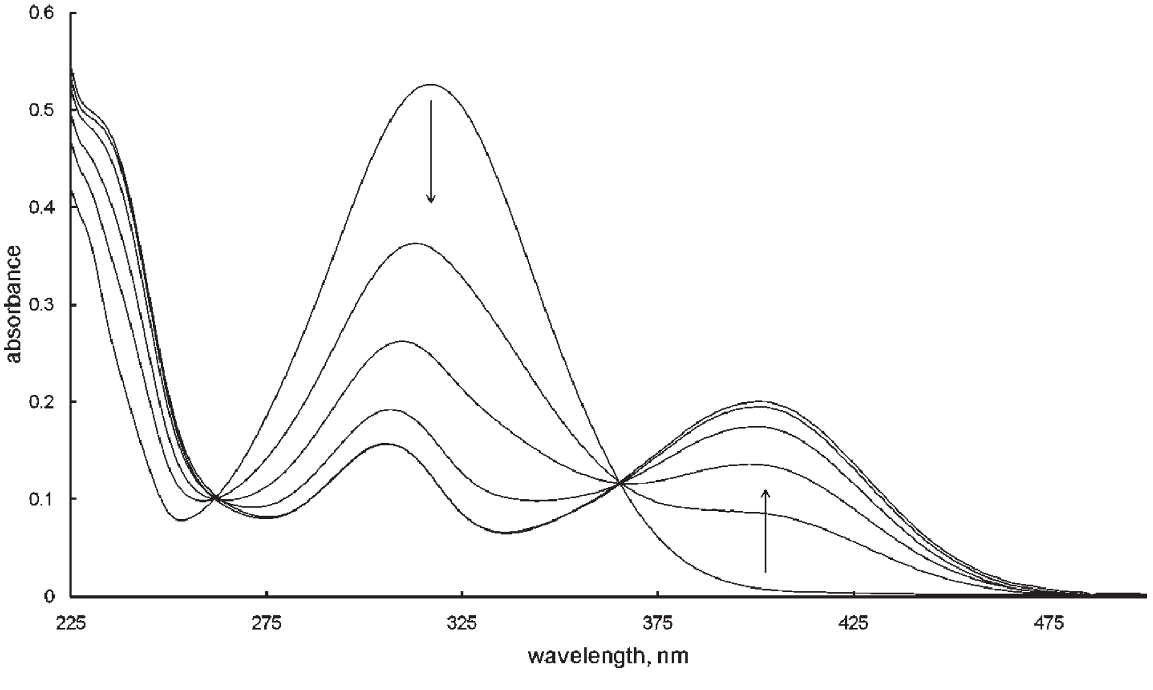


FIGURE 1. Electronic spectra for photolysis of 4-nitroanisole (5.4×10^{-5} M) in aqueous 0.10 M NaOH after irradiation for 0, 2, 4, 8, 16, and 24 min at 25 °C.

TABLE 1. Photolyses of 4-Nitroanisole (5.4×10^{-5} M) in Water Containing 0.020 M NaOH

trial	T, °C	A_∞, 400 nm	PN$\bar{\rm P}$, M ($\times 10^5$)	% PN$\bar{\rm P}$	mean % PN$\bar{\rm P}$	mean % PM$\bar{\rm P}$
1a	3	0.190	1.04	19.1	19.0	81.0
1b	3	0.189	1.03	18.9		
2a	37	0.203	1.11	20.4	20.5	79.5
2b	37	0.204	1.12	20.6		
3a	73	0.214	1.17	22.1	21.8	78.2
3b	73	0.215	1.18	21.5		

accounted for 99.6, 99.4, and 97.2% of the moles of 4-nitroanisole. This indicates a quantitatively clean reaction giving two products. At the higher temperatures, the two product absorptions accounted for about 95% of the reactant, owing to some slight thermal or photochemical degradation of the 4-methoxyphenoxide product, as reported previously.[17] At all temperatures, therefore, we used the clearly quantifiable amount of 4-nitrophenoxide as the measure of methoxide ion displacement, and the difference from the total molarity of 4-nitroanisole as the quantitative measure of nitrite ion displacement, giving 4-methoxyphenoxide ion. The results of exhaustive irradiations at three temperatures for the two product yields determined in this way are shown in Table 1. A control experiment showed that PN$\bar{\rm P}$, a possible thermal hydrolysis product, was not formed detectably by UV–vis monitoring when 4-nitroanisole was heated in the dark in aqueous 0.020 M NaOH at 80 °C for a time period equal to that of the photochemical reaction.

It is clear that temperature increases cause a modest increase in the yield of the methoxy displacement product, PN$\bar{\rm P}$, and a corresponding decrease in the amount of the nitro displacement product, PM$\bar{\rm P}$.

If the two reactions represent a simple competition between two pathways from the triplet having different activation energies, it should be possible to reproduce the changes in product yields as a function of temperature with Arrhenius theory. The rate constants were obtained from results we reported for triplet 4-nitroanisole and hydroxide ion at approximately 25 °C in 33% acetonitrile/water.[16] The sum of the two reaction rate constants from the triplet state of 4-nitroanisole is 9.6×10^7 M^{-1} s^{-1} for displacement of the nitro group and displacement of the methoxy group.[16] The total rate constant was obtained by Stern–Volmer kinetics, which depend on reactant disappearance as the photoproducts are formed. We judged[16] the intermediate σ-complex for nitro displacement to partition fully to product because nitrite ion is far superior to hydroxide ion as a nucleofuge.[19] The σ-complex for methoxy displacement is expected to partition between product and reactant in a ratio of about 1:1 because the methoxide and hydroxide nucleofuges are comparable. In such cases in the absence of complicating effects, nucleofugality is related to acidities of the conjugate acids,[20] which are very similar.[21] The actual rate constant for attack at the methoxy-bearing carbon, therefore, should be a factor of 2 greater than that inferred from the yield of PN$\bar{\rm P}$. That is, the total rate constant for loss of starting material (9.6×10^7 M^{-1} s^{-1}) is equal to $k_{\rm nitro} + 0.5k_{\rm methoxy}$. We also know from the observed product yields of 80% and 20% that $k_{\rm nitro}/0.5k_{\rm methoxy}$ is equal to 4. The solution of the simultaneous equations yields the nucleophilic attack rate constants at 25 °C of 7.68×10^7 M^{-1} s^{-1} for attack at the nitro-bearing carbon ($k_{\rm nitro}$), and 3.84×10^7 M^{-1} s^{-1} for attack at the methoxy-bearing carbon ($k_{\rm methoxy}$). We assume that the A factor in the Arrhenius equation ($\ln k = -(E_{\rm a}/RT) + \ln A$) is the fastest intermolecular reaction in the medium at 25 °C, which is approximated by the diffusion rate constant. For reactants in water with no ionic attraction or repulsion, that rate constant is 3×10^9 M^{-1} s^{-1}.[22] On this basis we calculated the activation energies for the two operative reactions. The values are 2.17 kcal/mol for attack at the nitro-bearing carbon and 2.58 kcal/mol for attack at the methoxy-bearing carbon. We then calculated the rate constants for each displacement reaction at the various temperatures. The results and the consequent product ratios are given in Table 2. The agreement of the product yields at various temperatures calculated by using the Arrhenius equation with those of experiment is excellent. This supports the view that the nucleophile attacks the triplet at two sites that are differentiated by slight differences of activation energy.

TABLE 2. Arrhenius Theory Calculations for Nitro vs Methoxy Substitution by Hydroxide Ion in Triplet 4-Nitroanisole with Activation Energies of 2.17 and 2.58 kcal/mol, Respectively

temperature, °C	$k_{\rm nitro} \times 10^{-7}$	$0.5k_{\rm methoxy} \times 10^{-7}$	% PN$\bar{\rm P}$	% PM$\bar{\rm P}$
3	5.74	1.36	19.1	80.9
37	8.85	2.27	20.4	79.6
73	12.8	3.51	21.6	78.4

The large temperature effects on photosubstitution ratios in 4-nitroanisole by hydroxide ion in alcohol solvents were attributed[14] to nitro displacement occurring with a very low activation energy and methoxy displacement involving a considerable activation energy. The claimed changes from a product ratio (nitro:methoxy) of 99:1 at −20 °C, to 9:1 at 25 °C, to 0.6:1 at 196 °C cannot be rationalized, however, with an Arrhenius model. With the activation energies needed to give a 9:1 ratio at 25 °C, as reported,[14] the change to the ratio of 99:1 by Arrhenius theory would require a temperature below −200 °C, and a temperature of 500 °C would predict a product ratio of only 1.3:1. In fact, a temperature nearing infinity could cause the product ratio only to

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[16] Wubbels, G. G.; Brown, T. R.; Babcock, T. A.; Johnson, K. M. *J. Org. Chem.* **2008**, *73*, 1925.

[17] Letsinger, R. L.; Ramsay, O. B.; McCain, J. H. *J. Am. Chem. Soc.* **1965**, *87*, 2945.

[18] The phenolic products, PMP and PMP, are ionized completely by the alkaline medium to PM$\bar{\rm P}$ and PN$\bar{\rm P}$ after they are formed.

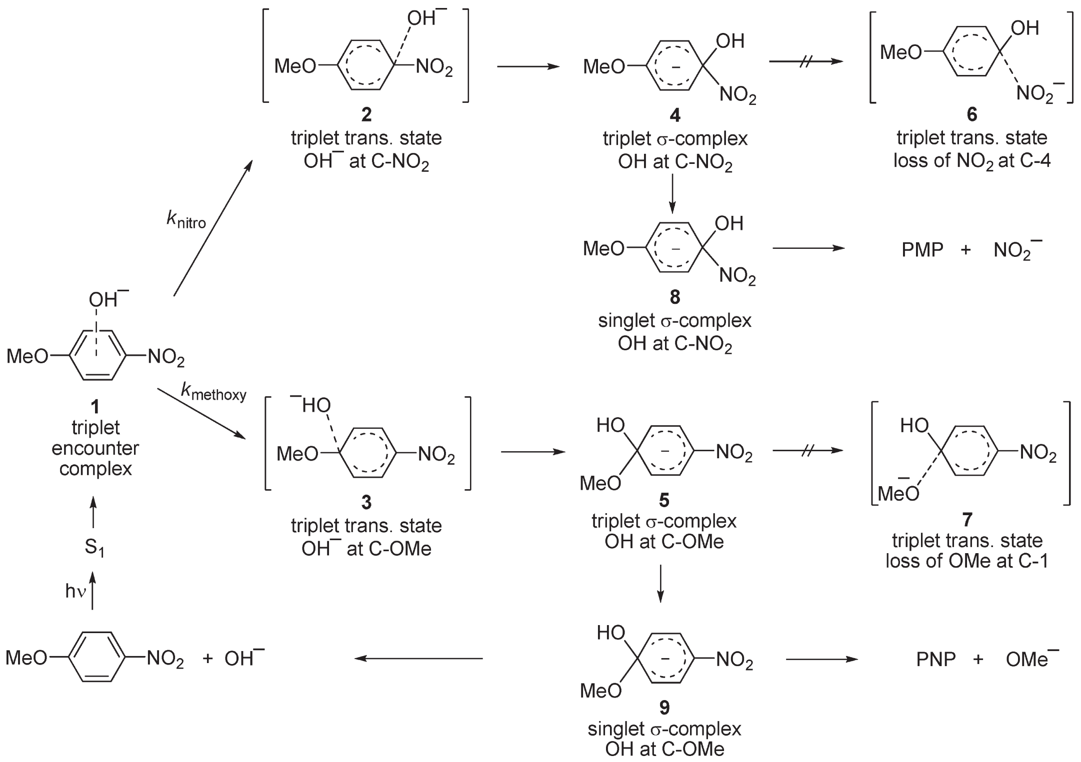
[19] Broxton, T. J.; Muir, D. M.; Parker, A. J. *J. Org. Chem.* **1975**, *40*, 3230.

[20] Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198.

[21] Ballenger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795.

[22] (a) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1. (b) Weller, A. *Z. Physik. Chem.* **1958**, *17*, 224.

SCHEME 2. Photoreaction Species and Sequence for 4-Nitroanisole and Hydroxide Ion



approach 1:1. This suggested that products other than those claimed were being measured. That the reaction system could give other products could be inferred from a prototropic equilibrium effect that was not noted in the report.

Ethanol has acidity comparable to that of water. With acidity constants of 1.3 and 1.8×10^{-16} M^{-1} for ethanol and water, respectively,[21] the prototropic equilibrium in the reported medium of pure ethanol (or the other primary alcohols used) containing 0.2 M NaOH can be calculated quickly to have about 2% of the base in the form of hydroxide ion, with most of it in the form of alkoxide ion. We verified only that the products of photolysis of 4-nitroanisole in 0.2 M NaOH in absolute ethanol were indeed complex. In our hands, GC/MS analysis of the photolysis products indicated 4-ethoxyanisole (41%), 1-ethoxy-4-nitrobenzene (7%), 4-methoxyphenol (38%), and 4-nitrophenol (9%). We also detected minor amounts of photoreduction products such as 4-methoxyaniline and 4,4′-dimethoxyazoxybenzene, a process with precedent for other nitroaromatics in alcoholic alkali.[23] As in the earlier work,[14] we did not dehydrate our absolute ethanol. Adventitious water may be the cause of the substantial yields of photosubstitution products of hydroxide ion.

Because we were interested in a model for regioselectivity with predictive power, we carried out quantum chemical calculations on the reactants, transition states, and intermediates of the probable mechanism to see if the regiochemical findings could be discovered by calculation. The Spartan ’08 quantum chemical software at the Hartree−Fock/3-21G$^{(*)}$ level of theory efficiently found the molecular species postulated. They are identified in the reaction sequence in Scheme 2, and the calculated structures and Gibbs free energies at 298 K are shown in Table 3. The Gibbs energies are calculated from the total energy, after calculation of the vibrational frequencies, by correcting for the zero-point vibrational energies, and the entropy and enthalpy changes from zero to 298 K. We also calculated most of the species at higher levels of theory including Hartree−Fock 6-31G*, 6-31+G*, and DFT-B3LYP/6-31G*. These more costly calculations did not produce significantly different or more reasonable energy increments or geometries. We could not apply solvation models to open-shell species, but we could for triplet transition states. The energy differences of solvated vs nonsolvated transition states were comparable, implying that calculation errors and solvation effects canceled each other out for comparable species. The vibrational frequencies for the transition states included the expected imaginary frequency for stretching the nucleophile−carbon bond, with the exception of entry 6. This calculation converged to an energy maximum saddle point but did not give an imaginary frequency. Of several encounter complexes found, we have shown as entry 1 only the one of highest energy.

Discussion

It has been shown by photosensitization[24] and transient spectroscopy[16] that the excited state of 4-nitroanisole populated rapidly and efficiently by photoexcitation in water is the triplet ($E_t \approx 60$ kcal/mol).[25] Kinetic[17] and quenching[26] evidence suggested that nucleophiles react directly with

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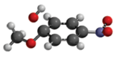
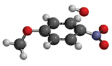
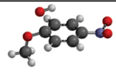
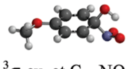
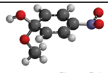
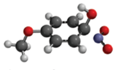
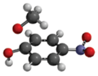
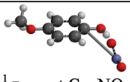
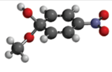
(23) Frolov, A. N.; Kuznetsova, N. A.; El’tsov, A. V.; Rtishchev, N. I. *Zh. Organ. Khim.* **1973**, *9*, 963.

(24) Letsinger, R. L.; Steller, K. E. *Tetrahedron Lett.* **1969**, 1401.

(25) Brinen, J. S.; Singh, B. *J. Am. Chem. Soc.* **1971**, *93*, 6623.

(26) Bonhila, J. B. S.; Tedesco, A. C.; Nogueira, L. C.; Diamantino, M. T. R. S.; Carreiro, J. C. *Tetrahedron* **1993**, *49*, 3053.

TABLE 3. 4-Nitroanisole−Hydroxide Ion Reaction Species Calculated by Hartree−Fock/3-21G(*)

entry	species	total Gibbs free energy 298 K (au)	ΔG vs. encounter cx. (entry 1) (kcal)	ΔG vs. -619.824577 au reactant energy (kcal)
1	 ^{3}enc. cx. at C – OMe	-619.842582	0	-11.3
2	 ^{3}TS OH$^-$ at C – NO$_2$	-619.821320	13.3	2.0
3	 ^{3}TS OH$^-$ at C – OMe	-619.816301	16.5	5.2
4	 $^3\sigma$-cx. at C – NO$_2$	-619.854510	-7.5	-18.8
5	 $^3\sigma$-cx. at C – OMe	-619.845486	-1.8	-13.1
6	 ^{3}TS loss of NO$_2$ at C-4	-619.831639	6.9	-4.4
7	 ^{3}TS loss of OMe at C-1	-619.815777	16.8	5.5
8	 $^1\sigma$-cx. at C – NO$_2$	-619.931799	-56.0	-67.3
9	 $^1\sigma$-cx. at C – OMe	-619.862846	-12.7	-24.0

triplet nitrophenyl ethers. The halogen element effect evidence[16] indicated that the initial steps of nucleophilic photosubstitutions proceeded within the triplet manifold through triplet σ-complexes. That is, reaction of the triplet with the nucleophile appeared to be adiabatic, leading rapidly to a σ-complex of the same multiplicity. Nonadiabatic reaction was unlikely because there is no electronic triplet state below the ground state triplet, and intersystem crossing was expected to be too slow to account for the nucleophilic reaction rates. The reaction rates approach the diffusion rate, and spin−orbit coupling effects of halogens on the nitroaromatics could not be discerned in the rates of nucleophilic attack.[16]

The photosubstitutions of triplet nitrophenyl ethers and many other nitroaromatics with nucleophiles have been the subject of many attempts to explain the reactivity and regioselectivity.[6−13] The unusual orientation effect of substituents in nucleophilic reactions, (and other reactions) of excited aromatic molecules was recognized early by the name, the “meta effect”.[6] The effect was rationalized[6] by suggesting the occurrence of meta-bridged valence bond structures for zwitterionic excited-state reactants. This rationale, however, was mostly symbolic since it could not accommodate the open-shell nature of the excited states and the triplet multiplicity.

The suggestion that charge density in the excited singlet state could explain regiochemistry in electrophilic and nucleophilic photosubstitutions was put forward by Havinga and Kronenberg.[27] This rationale lost relevance when it became clear that the nitroaromatic nucleophilic photosubstitutions proceeded from the triplet state.[24] A reexamination of the charge criterion using the triplet-state charge densities, however, concluded that the charge criterion was still unsatisfactory.[9] Application to the photosubstitutions of 4-nitroanisole was noted as a particular failing of the approach. That calculated charge at nuclear positions is unrelated to predominant regioselectivity of substitution could be inferred also from the absence of regiochemical effects of charge of nucleophiles. In the case of triplet 4-nitroanisole, for example, the negatively charged nucleophile, hydroxide ion, displaces mainly at the positive charge favored nitro-bearing carbon, but the neutral nucleophiles, ammonia and pyridine, displace exclusively at that position.[7,17]

Epiotis and Shaik[8] suggested on the basis of frontier molecular orbital theory (FMO) that the regioselectivity of nucleophilic aromatic photosubstitution could be predicted by the ring carbon atom (bearing a displaceable group) calculated to have the largest orbital coefficient (or electron density) in the HOMO of the ground state singlet.[28] The model was extended[11,12,29] to photoreactions involving electron transfer from the nucleophile as the initial step (S_N(ET)Ar*),[30] wherein the regioselectivity was claimed to be related to the maximum LUMO coefficient of the ground-state reactant.

The simple FMO model, or more sophisticated versions such as those based on spin-polarized Fukui functions,[13] predicts the major products of many nucleophilic aromatic photosubstitutions of nitrophenyl ethers, but it fails in several cases. It seldom accounts for the ordering of minor products,[16] and it predicts incorrectly for the cases of 4-nitro- and 2-nitroanisole.[13] Allowing for the absence of a nucleofuge at the meta position, it predicts, as observed, that the favored photodisplacement site for 4-nitroanisole and hydroxide ion is the nitro-bearing carbon. It does not predict correct regioselectivity for the photoreaction of 4-nitroanisole with cyanate or cyanide ion.[7,16] It should be noted that these regioselectivity predictions for the nitrophenyl ethers are not risky, and yet they display a high level of error. The simple generalization that S_N2Ar^* reactions occur meta to the nitro group and S_N(ET)Ar* reactions occur para to the nitro group does as well as the FMO model or its extensions to predict regioselectivity. It is possible that the HOMO and LUMO criteria amount only to a cumbersome method of identifying the positions meta and para to the nitro group.

We question the FMO model for regioselectivity first because the relationship of electron density in the ground state singlet HOMO or LUMO to reaction from an excited state triplet should be faint. The orbitals of the ground state upon which the predictions rest do not even exist in the reacting, excited molecule. Moreover, the bond formation with the nucleophile in S_N2Ar[3] is electron-paired and probably has nothing to do with the singly occupied, excited state

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[27] Havinga, E.; Kronenberg, M. E. *Pure Appl. Chem.* **1968**, *16*, 137.

[28] This was originally stated as the maximum difference of the squares of the HOMO and LUMO coefficients. The authors, however, use the square of the HOMO coefficient (HOMO electron density) as a sufficient measure.

[29] Bunce, N. J.; Cater, S. R.; Scaiano, J. C.; Johnston, L. J. *J. Org. Chem.* **1987**, *52*, 4214.

[30] Mutai, K.; Kobayashi, K.; Yokoyama, K. *Tetrahedron* **1984**, *40*, 1755.

HOMO, or the LUMO, to say nothing of the ground state HOMO or LUMO. More importantly, it suffers the powerful weakness of predicting favored reaction transition states solely on the basis of properties of the reactant. This idea has an inglorious history in the annals of reactivity and regioselectivity discussions. It is analogous to inferring the regioselectivity of electrophilic aromatic substitution reactions from the resonance structures of reactants, a method that has long been proscribed.[31] Standard practice for use of the resonance model is to consider the relative resonance stabilization of cationic intermediates rather than the delocalization or polarization of reactants to gain insight about the relative energies of the preceding transition states. This logic rests on the Bell–Evans–Polanyi principle,[32] which holds that activation energy and enthalpy change are correlated for a set of comparable, elementary reaction steps.

Dewar has emphasized[33] that there is no theoretical justification for reactivity or regioselectivity predictions in alternate or nonalternate π-electron hydrocarbon systems based on reactant properties at nuclear positions such as free valence, self-polarization (charge density), and applications in perturbation theory of HOMO coefficients of frontier orbital theory. The successes that occur owe to the coincidence of calculated positional properties and relative transition-state energies. The sorting of preferred pathways occurs on the basis of energy. Energy of a molecular species can be defined only for the whole and not for particular nuclear positions. Estimating the contribution of certain positional properties of reactants to prospective competing transition states is clearly inferior to estimating directly the energies of the competing transition states.

Another model for regioselectivity of S_N2Ar^* reactions claimed that the energy gap law for radiationless electronic transitions should govern the favored pathways.[9] The energy gap law in electronic spectroscopy states that internal conversions between states close in energy are faster than those between states far apart in energy. Since singlet meta-to-nitro σ-complexes or those for displacement of the nitro group have little resonance stabilization, they are much higher in energy than the delocalized ortho or para σ-complexes. Thus the transition from the triplet encounter complex to the less stable (meta) σ-complexes was thought to be faster than to the more stable (ortho or para) σ-complexes.[9]

The energy gap law applies primarily to internal conversion processes that are fast. The application to photosubstitution regioselectivity[9] required intersystem crossing during nucleophilic attack on the triplet nitroaromatic leading to the singlet σ-complex. With rate constants of nucleophilic attack approaching the rate of diffusion, the processes appeared to be much too fast to permit intersystem crossing.[16] Moreover, spin–orbit coupling effects of attached halogens that should have facilitated the intersystem crossing correlated inversely with the observed rate constants.[16] For reaction within the triplet manifold, the energy gap law would predict the wrong regioselectivity since the para triplet σ-complex was found by calculation[9] to be much higher in energy than the favored meta triplet σ-complex. We concluded[16] that the energy gap interpretation of regioselectivity of these reactions was not correct. Indeed, the evidence pointed to nucleophilic aromatic photosubstitution of nitrophenyl ethers occurring within the triplet manifold, that is, adiabatically. Evidence of the element effect on the elementary rate constants and the relative nucleophilicities of different attacking reagents suggested, moreover, that the bond formation process was electron-paired formation of a σ-bond by the nucleophile with the triplet nitroaromatic molecule.

A recent theoretical study[13] of the orientation rules emphasized photohydrolysis of nitrophenyl ethers including 4-nitroanisole. It modeled the reactions with density functional theory by calculating the geometries and energies of all the likely encounter complexes, σ-complexes, and transition states within the ground state singlet or triplet manifolds. It found local energy minimum σ-complex intermediates for the reactions that had oxygen nucleofugic groups. For triplet 4-nitroveratrol (3,4-dimethoxynitrobenzene) and hydroxide ion, the triplet transition state leading to the favored meta σ-complex was found by B3LYP calculation to be 6.1 kcal lower in energy than the triplet transition state leading to the para σ-complex. A Møller–Plesset calculation of the same species, however, reversed the energy difference (to -5.0 kcal). Both methods of calculation corroborated at high levels of theory the earlier finding[9] that the meta triplet σ-complex for 4-nitroveratrol and hydroxide ion was lower in energy (by 9.5 kcal) than the para triplet σ-complex. By confining its view to relative energies of successive species within spin manifolds, however, it omitted consideration of whether triplet σ-complexes might undergo intersystem crossing before completing the substitution reaction. For the case of 4-nitroanisole, the regiochemical discussion ignored the predominant nitro displacement process. The regioselectivity conclusions of the calculations of this study were mixed, but it was the first to use quantum chemical methods to estimate the relative energies of competing photosubstitution transition states of the same multiplicity.

Our experimental results for the temperature dependence of the product ratio from 4-nitroanisole and those calculated with a simple Arrhenius model agree very well. This validates the model of competing transition states in the triplet manifold, and it provides a sound experimental basis for assessing regioselectivity by quantum chemical calculation of the relative energies of transition states.

We found several energy minimum encounter complexes of triplet 4-nitroanisole with hydroxide ion. The one calculated to have the highest energy, shown as entry 1 in Table 3, placed hydroxide ion near the methoxy-bearing carbon of triplet 4-nitroanisole. The transition states (entries 2 and 3) lie 13.3 and 16.5 kcal above the energy of this encounter complex, at the Hartree–Fock 3-21G$^{(*)}$ level. The correct reference energy of the excited-state reactants appears from experiment to be about 2 kcal below the energy of the first transition state (entry 2), and we have shown energies referenced to this value in column 5 of Table 3. Reaction species discussed below are referenced to this excited reactant energy level (-619.824577 au). The difficulty of finding the correct reference energy of the reactants by calculation is not unexpected because significant calculation errors occur between species having different solvation, charge distributions, and

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(31) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; McGraw-Hill: New York, 1968; p 387.

(32) Bruckner, R. *Advanced Organic Chemistry*; Harcourt/Academic Press: San Diego, 2002; p 10.

(33) Dewar, M. J. S. *The Molecular Orbital Theory of Organic Chemistry*; McGraw-Hill: New York, 1969; p 362.

numbers and types of bonds. For closely comparable species, however, such as two transition states or two σ-complexes, the error in the calculated energy difference should be much smaller because of cancellation of calculation errors. Indeed, the HF 3-21G$^{(*)}$ energy difference for entry 3 minus entry 2 is 3.2 kcal, which may be compared to the difference of 0.4 kcal that was found experimentally. The favored transition state is the one calculated to have lower energy. At higher levels of theory, the energy differences (in kcal) were as follows: HF/3-21G$^{(*)}$ in water (SM8), 6.0; HF/6-31G*, 6.7; HF/6-31G* in water (SM8), 11.4; HF/6-31+G* 5.5; HF/6-31+G* in water (SM8), 10.7;[34] B3LYP/6-31G*, −1.0; B3LYP/6-31G* in water, 7.8. Only one of these methods, B3LYP (vacuum), misses the favored transition state (by about 1 kcal). The other seven methods are successful at identifying the favored transition state.

As shown by the results discussed above, we prefer the HF/3-21G$^{(*)}$ calculations for this system because of their lower cost and adequate accuracy. Calculation of the species in Table 3 at the HF/6-31G* level yielded geometries and energy differences very similar to those of the HF/3-21G$^{(*)}$ level. While the calculations, save one, identify the lower-energy transition state, we do not know the reason that the calculated energy differences of the competitive transition states are typically larger than the experimental values, even at higher levels of theory that provide large valence sets, more polarization, diffuse functions for charges, electron correlation, and solvation.

The favored regiochemistry could also be identified by comparing the energies of the triplet σ-complexes. These (entries 4 and 5) were found to lie 20.8 and 18.3 kcal below the respective transition states (entries 2 and 3). In this case, the energy difference at the HF/3-21G$^{(*)}$ level for entry 5 minus entry 4 is 5.7 kcal. These differences (in kcal) at higher levels of theory were: HF/6-31G*, 6.5; HF/6-31+G*, 2.7; and B3LYP/6-31G*, 5.0. The calculations all identify the favored pathway, and the differences cluster more closely than those for the transition states. The lower-energy pathway is correctly identified by all methods, and they agree with results for the transition states. The agreement supports the view that the mechanism involves electron-paired bond formation within the triplet manifold, since in that case, these transition states and intermediates would be related by an elementary reaction step. The correspondence of their relative energies is a manifestation of the Bell−Evans−Polanyi principle. In view of the agreement of the σ-complex energy differences, calculation of their relative energies may be a more reliable indicator of regioselectivity than calculation of relative transition-state energies.

Several studies[11,12] have suggested that nucleophilic photosubstitution para to the nitro group may occur by a mechanism different from S_N2Ar^*, that being the electron transfer−radical coupling ($S_N(ET)Ar^*$) mechanism. We reported evidence that the para photosubstitutions by amines on 4-nitroanisole may actually involve bond formation by the amine at the meta position followed by a fast sigmatropic rearrangement to the para σ-complex.[35] We also suggested that the results reported in ref 14 could be caused by an analogous rearrangement mechanism. That suggestion now appears unnecessary because the para substitution on 4-nitroanisole by hydroxide ion appears to fit a straightforward S_N2Ar^* model.

The calculations of the triplet transition states for expulsion of nitrite ion or methoxide ion shown as entries 6 and 7, respectively, reveal that they lie 14.4 and 18.6 kcal above the respective triplet σ-complexes. These present large activation energy barriers. They suggest that expulsion of leaving groups from the triplet σ-complexes would be slow, giving the triplet σ-complexes sufficient lifetime to undergo intersystem crossing. The corresponding ground state singlet σ-complex for nitro displacement (entry 8) lies 48.5 kcal below the triplet σ-complex (entry 4), and that for methoxy displacement (entry 9) lies 10.9 kcal below the corresponding triplet σ-complex (entry 5). The former singlet (entry 8), however, reached energy minimization with an impossibly long C−N bond of 3.92 Å. This implies that an energy minimum structure was not found with a normal C−N distance and that the singlet σ-complex is dissociative.[36] It implies that nitrite ion loss from the singlet σ-complex would have no activation energy and would follow intersystem crossing very rapidly. The similarity of the energy gap (67.3 kcal) between entry 8 and the excited reactants, and the spectroscopic triplet energy of 4-nitroanisole (60 kcal)[25] suggests that entry 8 represents the ground singlet state of the products, 4-methoxyphenol and nitrite ion. This view was confirmed by direct calculation of the energy of the singlet hydrogen-bonded complex of 4-methoxyphenol and nitrite ion, which was 68.2 kcal below that of the excited reactants. The methoxide ion expulsion is reasonably formulated as an activated reaction that competes with hydroxide ion expulsion from the singlet σ-complex that lies about 24 kcal below the excited reactants. We conclude that the required intersystem crossing from triplet reactants to singlet products occurs at the σ-complex stage, and that leaving group expulsion occurs from the singlet rather than the triplet σ-complex.

The mechanistic conclusions afforded by the experimental and quantum chemical results of this study agree with those based on element effects[16] for nucleophilic reactions of triplet nitrophenyl ethers. The main features are the following: (1) nucleophilic bond formation occurs adiabatically within the triplet manifold; (2) competitive nucleophilic reactions occur through thermally competitive transition states; and (3) the elementary reactions produce triplet σ-complexes that undergo intersystem crossing to singlet σ-complexes, which dissociate anionic leaving groups to make the products. The relative transition-state energy predictor of regioselectivity in these reactions appears to have a sound basis. We intend to test its application to regioselectivity by quantum chemical methods for other reactions of the S_N2Ar^* type that have been reported.[7]

Experimental Section

Except as noted below, chemicals and solvents were commercial materials of high purity. Ethanol was anhydrous, and attempts to dehydrate it further were not made. Acetonitrile

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(34) The calculation by HF/6-31+G* in water for entry 2 converged only to twice the normal gradient tolerance, which did not permit calculation of the vibrational frequencies. The energy difference is that for the total energies.

(35) Wubbels, G. G.; Johnson, K. M. *Org. Lett.* **2006**, *8*, 1451.

(36) The calculation seeks geometry optimization by stretching the C−N bond that increasingly produces nitrite ion in the gas phase. As its energy goes up, the energy minimum is realized.

was chromatographic grade. 1-Ethoxy-4-nitrobenzene and 4-ethoxyanisole were made by alkylating the corresponding phenol with ethyl iodide in 2-butanone containing K_2CO_3. These substances gave satisfactory ^{1}H NMR spectra and literature melting points.

UV−vis spectra were obtained with a diode-array spectrophotometer with samples in quartz cuvettes. Gc/ms was carried out with a 25 m silicone oil capillary column and an ion trap mass spectrometer.

Photolyses for preparative purposes in ethanolic NaOH were carried out in Pyrex tubes in a Rayonet RPR-208 reactor fitted with eight 300 nm broadband lamps. Workups for chromatographic product analyses were carried out by diluting irradiated samples 5-fold with water, acidifying with H_2SO_4, extracting with CH_2Cl_2 or toluene, concentrating, and diluting to volume with CH_2Cl_2. Products were identified by coinjection with authentic samples as well as by the mass spectra.

Temperature-controlled photolyses were carried out in the Rayonet reactor with seven 350-nm broadband lamps in quartz septum-capped cuvettes suspended in water or water/ice at controlled temperature in a uranium glass filter sleeve within a vacuum-jacketed quartz well. Reaction solutions were purged with argon through syringe needles for 10 min. UV−vis analyses were done directly in the irradiation cuvettes. The extinction coefficients for the quantitative analyses were: 4-nitroanisole: 317 nm (9700); 4-nitrophenoxide ion: 400 nm (18,300), 306 nm (1050); 4-methoxyphenoxide ion: 306 nm (2920).

The quantum calculations were carried out with Spartan '08 software running on a desktop computer with the Windows operating system. The structures were found by convergence to equilibrium geometry at an energy minimum or a saddle point with a gradient tolerance of 4.5×10^{-4} hartree bohr^{-1} and a distance tolerance of 1.8×10^{-3} Å. We calculated the vibrational frequencies for the transition states, and they showed with one exception the imaginary frequency for the transition-state vibration.

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Supporting Information Available: Cartesian coordinates of the structures reported in Table 3, the total energies, the imaginary frequencies of transition states, and chromatogram of photoproducts in ethanolic NaOH. This material is available free of charge via the Internet at http://pubs.acs.org.