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MNDO Study of Nucleophilic Aromatic Substitution

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MNDO calculations were conducted to investigate the S_NAr mechanism. The mechanism is an addition–elimination sequence, as expected. A new charge-transfer complex was discovered that may explain a variety of observations, including weak base catalysis and the greater facility of fluoride to act as a leaving group when compared to other halides.

Introduction

Many aromatic nucleophilic substitutions have been proposed to proceed through an addition-elimination mechanism (S_NAr). This proposal is consistent with the available kinetic data.[1,2] Although little attention has been paid to the theoretical investigation of this reaction, calculations have been done on the suspected intermediate Meisenheimer complex,[3] theories have also been advanced to explain attack-site preferences,[4] and some theoretical work using bond energies has been done.[5] It is the purpose of this investigation to use the MNDO method to study these reactions, with special attention to those factors likely to affect the rates.

The S_N2 reaction of nucleophiles with chloromethane has been studied by using MNDO.[6] The results of this study follow both experiment[7] and more detailed theory[8] closely, thus giving us confidence that MNDO may be usefully applied as in this work.

Procedure

The calculations reported in this work were done by using the MNDO method, as contained in the MOPAC package.[9] The calculations were carried out with the standard MNDO parameters.[10-13] All energy minima were calculated without bond angle or bond length constraints.

Energy minimum geometries and transition states were located approximately by using the reaction coordinate method.[14] The carbon–nucleophile atomic distances were used as the reaction coordinates. These minimum energy reaction pathways (MERPs) were estimated by using mirror symmetry for the arene. The transition state was then refined by using the SADDLE[15] option.

Results

For convenience we divide the results of this work into four reaction classes. Reaction class 1 is the attack of *p*-chloronitrobenzene by the soft nucleophiles chloride, bromide, and thiomethoxide. Reaction class 2 is the attack of *p*-chloronitrobenzene by the hard nucleophiles fluoride and methoxide. Reaction class 3 is the attack of chlorobenzene by the soft nucleophiles chloride, bromide, and thiomethoxide. Reaction class 4 is the attack of chlorobenzene by the hard nucleophiles fluoride and methoxide.

Figure 1 depicts the MERP for these reactions. The abreviations of Figure 1 are explained in the following text. In Table I the energies associated with the MERPs are given.

Reaction Class 1. Depending upon the direction of approach of the nucleophile toward the arene, different types of minimum energy geometries revealed themselves. There were several types of contact ion–arene pairs, which in this paper will be called charge–dipole complexes (CDC). In general, these complexes have quite shallow minima and have little importance. The only important CDC is approximately above the arene ring at the Van der Waals contact distance. It is characterized by a slight shifting of charge distribution in the arene without any acceptance of charge from the nucleophile. Another type of complex that is formed we term a charge-transfer complex (CTC). In the CTC the approaching nucleophile is located on a linear line intersecting the chloro carbon (C4 carbon) and the chlorine atom. The CTC is characterized by a closer than contact distance between the ion and the leaving group substituent on the ring and a transfer of charge from the ion to the ring of the arene. For example, in the CTC formed between the chloride nucleophile and the *p*-chloronitrobenzene arene the charge on the ion is −0.71. This is a new complex, not previously postulated in nucleophilic aromatic substitution.

As the nucleophile approaches the arene, it falls into either the CDC or CTC energy minima. The CDC is situated in relation to the transition state such that movement to the transition state (TS) is easily accomplished, but the CTC is situated such that there is a very high energy barrier for direct movement from the CTC to the TS. The MERP for the nucleophile in the CTC going to the TS is disassociation from the CTC with the arene and then reassociation with the arene to the CDC, which can then go on to the TS.

The Meisenheimer complex (MC) was of the geometry expected from examination of the known geometries of isolated, stable Meisenheimer complexes.[16,17] The transition state for the formation or decomposition of the Meisenheimer complex had only some of the charge on the nucleophile delocalized onto the arene ring. For example, in the TS for the chloride nucleophile attacking the *p*-chloronitrobenzene, the ion has a charge of −0.88. Most of the delocalization of the charge onto the ring occurs in

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[1] Bernasconi, C. F. *Aromatic Compounds*; Zollinger, H., Ed.; Organic Chemistry Series 1; Butterworths; University Park: Baltimore, MD, 1973; Vol. 3, Mill Valley, Chapter 2.

[2] Terrier, F. *Chem. Rev.* **1982**, *82*, 78.

[3] (a) Strauss, M. J. *J. Chem. Rev.* **1970**, *70*, 667. (b) Sekiguchi, S.; Hirai, M.; Ota, E.; Hiratsuka, H.; Mori, Y.; Tanaka, S. *J. Org. Chem.* **1985**, *50*, 5105.

[4] Burdon, J.; Parsons, I. W. *J. Am. Chem. Soc.* **1977**, *99*, 7445.

[5] Miller, J. *J. Am. Chem. Soc.* **1963**, *85*, 1628.

[6] Carrion, F.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 3531.

[7] Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219.

[8] Keil, F.; Ahlrichs, R. *J. Am. Chem. Soc.* **1976**, *98*, 4787.

[9] Stewart, J. P. *QCPE* **1983**, *16*, 455.

[10] Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907.

[11] Dewar, M. J. S.; Rzepa, H. S. *J. Am. Chem. Soc.* **1978**, *100*, 58.

[12] Dewar, M. J. S.; McKee, M. L. *J. Comput. Chem.* **1983**, *4*, 84.

[13] Dewar, M. J. S.; Healy, E. *J. Comput. Chem.* **1984**, *5*, 358.

[14] McIver, J. W., Jr.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625.

[15] Dewar, M. J. S.; Healy, E. F. *J. Am. Chem. Soc.* **1984**, *106*, 7127.

[16] Messmer, G. G.; Palenik, G. *J. Chem. Soc., Chem. Commun.* **1969**, 470.

[17] Ueda, H.; Sakabe, N.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2866.

0022-3263/88/1953-0777$01.50/0

Table I. Energies of Species[a]

nuclphle	A(CTC)	B(CDC)	C(TS)[b]	D(MC)	E(TS)[c]	F(CDC)	G(CTC)	heats of reactn this work	heats of reactn lit.
			Reaction with *p*-Chloronitrobenzene						
F^-	−22.6	−7.6	−5.8	−88.7	−81.6	−83.6	N/A	76.6	
Cl^-	−20.6	−6.2	−2.6	−17.5				0.0	0.0
Br^-	−28.7	−6.0	−4.6	−23.2	−8.3	−12.5	−39.2	−7.0	
CH_3O^-	N/A	−6.0	+5.2	−57.3	−52.4	−50.6	N/A	−46.9	
CH_3S^-	−26.6	−7.4	−5.9	−32.7	−24.0	−34.3	N/A	−19.8	
			Reaction with Chlorobenzene						
F^-	−9.2	−6.2	+8.5	N/A	N/A	−81.4	N/A	−76.3	−34.9
Cl^-	−9.6	−5.5	+11.7	+7.1				0.0	0.0
Br^-	−17.2	−5.4	+8.1	+1.4	+6.2	−11.8	−27.9	−6.8	9.4
CH_3O^-	−21.7	N/A	−9.4	N/A	N/A	−77.2	N/A	−46.6	
CH_3S^-	−14.2	−5.3	+9.3	−6.5	−6.3	−25.8	N/A	−23.4	

[a] kcal/mol relative to separated reactants. [b] Transition between B and D. [c] Transition between D and F. [d] Compiled from ref 25 and 26.

Table II. Charges on Nucleophiles

nuclphle	substrate	CTC	CDC	TS	MC
F^-	*p*-chloronitrobenzene	−0.63	−1.00	−0.88	−0.23
Cl^-	*p*-fluoronitrobenzene		−1.00	−0.87	−0.43
Cl^-	*p*-chloronitrobenzene	−0.71	−1.00	−0.88	−0.32
Br^-	*p*-chloronitrobenzene	−0.66	−1.00	−0.90	−0.27
Cl^-	*p*-bromononitrobenzene	−0.70	−1.00	−0.88	−0.32
CH_3O^-	*p*-chloronitrobenzene		−1.00	−0.29	−0.16
Cl^-	*p*-nitroanisole		−1.00	−0.84	−0.45
CH_3S^-	*p*-chloronitrobenzene	−0.63	−0.99	−1.00	−0.15
Cl^-	*p*-nitrothioanisole		−0.99	−0.84	−0.37
F^-	chlorobenzene	−0.67	−0.99	−0.85	
Cl^-	chlorobenzene	−0.76	−0.99	−0.81	−0.41
Br^-	chlorobenzene	−0.71	−0.99	−0.79	−0.37
Cl^-	bromobenzene	−0.74	−0.99	−0.81	−0.41
CH_3O^-	chlorobenzene	−0.76		−0.80	
Cl^-	anisole		−1.00		
CH_3S^-	chlorobenzene	−0.68	−0.99	−0.84	−0.18
Cl^-	thioanisole		−0.99	−0.70	−0.56

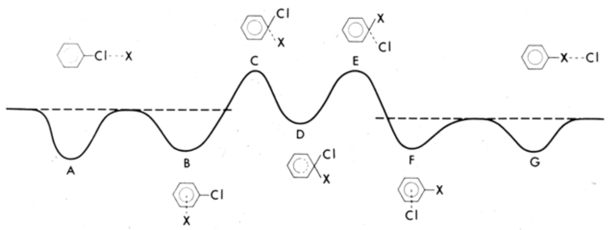

Figure 1. A generalized MERP for attack of chlorobenzene by a nucleophile X. Positions A–G correspond to the species in Table I. Not all of these species were observed in all reactions. The dashed line indicates an alternate pathway.

the MC, where the charge on the former ion is −0.32. When the transition state is allowed to relax on the other side, the resultant energy minimum is always the CDC. The MERP need not include either the initial CTC or the CTC composed of products, but only the charge–dipole complexes.

Reaction Class 2. As either fluoride or methoxide approach the *p*-chloronitrobenzene arene, there are again many possible CDC which may be formed. The primary CDC of interest is directly above the arene ring at the Van der Waals contact distance. Also a CTC may be formed as described for the class 1 reactions. The MERP for these hard nucleophiles is basically the same as the MERP for the soft nucleophiles in class 1 above. The major difference is the very weak CTC exhibited with fluoride, and the complete lack of a CTC observed with methoxide. After decomposition of the MC to products, neither the *p*-fluoronitrobenzene nor the *p*-nitroanisole show any inclination to form the CTC with the liberated chloride ion.

Reaction Class 3. The reaction of the soft nucleophiles chloride, bromide and thiomethoxide with chlorobenzene follow the same MERP as these same nucleophiles do with *p*-chloronitrobenzene described in class 1. The only exceptions are that the CDCs of interest no longer reside over the arene ring but now reside on a line intersecting the para carbon and the chloro carbon on the other side of the ring from the chlorine.

The MC, the CTC, and the TS are all at significantly higher energies relative to the separated reactants when compared to reaction class 1.

Reaction Class 4. The substitution of chlorobenzene by the hard nucleophiles fluoride and methoxide do not procede through an intermediate MC. No Meisenheimer complex is formed in the substitution of chlorobenzene by fluoride or methoxide, even though a Meisenheimer complex is formed for the substitution of *p*-chloronitrobenzene by fluoride and methoxide. The mechanism in this case (and the reverse case of the substitution of fluorobenzene by chloride) is best described as an S_N2 mechanism. The activation energy in the gas phase for substitution of chlorobenzene by fluoride is only about 15 kcal/mol.

In each of the above reaction classes the sequence of attack could be reversed, so that chloride could act as the nucleophile attacking the substituted arene.

The heats of reaction in the gas phase do not closely coincide with those that can be calculated from literature heats of formation (see Table I). The heats of formation for each of the arenes are within 2.0 kcal/mol of the literature values; the discrepancy in the heats of reaction lies in the poor ability of MNDO in calculation of isolated gas-phase ions and should not affect the major conclusions of this paper.

Discussion

In general, the minimum energy pathway for substitution consists of initial formation of a charge–dipole complex (CDC), movement through the transition state (TS) to form the Meisenheimer complex (MC), decomposition of the MC through the other TS and relaxation from the TS to the formation of another CDC which can then dissociate to form the isolated products. If the attacking nucleophile should minimize to the charge-transfer complex (CTC), it finds itself trapped in a situation where the activation energy to go directly to the transition state is very high. Dissociation of the CTC to reactants is the minimum energy pathway to the transition state. Thus, the initial formation of the CTC is an alternate pathway to formation of the MC, and it thus acts to retard the reaction rate.

Leaving Group Ability. The activation energy for the chloride nucleophile attacking a para-substituted nitrobenzene to give the Meisenheimer complex from the charge–dipole complex differs by only about 1.6 kcal/mol if fluoride is the leaving group rather than chloride. In addition, the charge delocalization from the chloride nucleophile to the ring is only 0.007 less when chloride attacks *p*-chloronitrobenzene than when chloride attacks *p*-fluoronitrobenzene. Thus it seems unlikely that fluoride acts as a better leaving group because of its ability to stabilize the addition step for the substitution reaction. If fluoride is the leaving group, no charge-transfer complex with the incoming nucleophile is observed; this fact might be an important factor contributing to the increased ability of fluoride (compared to other halides) to act as a leaving group in nucleophilic aromatic substitution.

Weak Base Catalysis. The CTC may also be responsible for weak base catalysis[1] of chloroarenes. If no base is present in solution, formation of the CTC would retard the reaction rate. However, if a stronger base than the nucleophile is present, then the stronger base would probably form the CTC. An apparent acceleration in rate would result because the alternate pathway for the nucleophile to a CTC would then be blocked.

The Activating Group. The nitro group appears to lower the transition state relative to the CDC. Even though the Meisenheimer complex is more stable with the nitro group present, this lowering of the transition state relative to the CDC (which facilitates the formation of the Meisenheimer complex) is probably responsible for the increased reaction rate with a nitro group present. Nevertheless, this does not appear to be due to large amounts of charge delocalization in the TS. For example, the charge on the attacking ion is −0.81 in the TS for chloride attack of chlorobenzene, and it is −0.88 in the TS for chloride attack of *p*-chloronitrobenzene.

Using a qualitative MO approach, it is observed that the nitro group in *p*-chloronitrobenzene acts to lower the energies of both the HOMO and LUMO by extending the delocalization of these orbitals relative to chlorobenzene. The LUMO provides a path for transfer of charge from the nucleophile to the arene, whereas the HOMO provides a path for transfer of charge from the arene to the nucleophile. As the TS forms, charge is transfered both to and from the nucleophile via the former HOMO and LUMO. The TS for *p*-chloronitrobenzene with a nucleophile is thus lower than the corresponding TS for chlorobenzene due to these MOs, even though total charge on the nucleophile remains about the same.

It was also observed that rotation of the nitro group did not effect the total energy of any species by more than about 2 kcal, a result consistent with recent work.[18]

Solvation Energies. It is expected that in solution the solvation energies (especially for hard, anionic nucleophiles, such as fluoride) will play an important role in the transition states described here.[6,19] Some desolvation of nucleophile must take place on forming the charge–dipole and charge-transfer complexes, as well as in the transition states. An estimation of these energies should be made in order that the importance of the various species in solution be judged. Hydration energies of halide anions in water vary from −110 to −60 kcal/mol for the halides.[19,20] Most solvents will have a solvation energy for anions less than these values. The stabilization energies of the CDC's are all less than 10 kcal/mol and thus probably do not exist in solution. The anions in the TS's and MC's will be affected by the desolvation of approximately half their coordination shells.

The most important consideration relating these calculations to what may actually happen in solution is the degree to which the CTC would desolvate the anion. The anion is sterically more exposed in the CTC than in any other complex described in this work, therefore it is reasonable to assume that only about one-fourth of the solvent sphere need disassociate in order to form the CTC. The CTC probably exists in solutions with weaker anion solvation energies than water. These general observations are consistent with recent relating gas-phase reaction mechanisms to solution-phase reaction mechanisms, which indicates that CDCs are likely to be lost in solution while other features of the MERP are retained.

These calculations support the addition–elimination mechanism for aromatic nucleophilic substitution, except in the case of fluoride and methoxide attack on chlorobenzene. The charge-transfer complex, which has not previously been proposed, may be envolved in the weak base catalysis of chloroarenes and the increased facility of fluoride to act as a leaving group. The activation of nucleophilic substitution by a nitro group is not related to the nitro group stabilization of the transition state via electron withdrawal from the incoming nucleophile.

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Registry No. F^-, 16984-48-8; Cl^-, 16887-00-6; Br^-, 24959-67-9; CH_3O^-, 3315-60-4; CH_3S^-, 17302-63-5; *p*-$ClC_6H_4NO_2$, 100-00-5; C_6H_5Cl, 108-90-7; *p*-$FC_6H_4NO_2$, 350-46-9; *p*-$BrC_6H_4NO_2$, 586-78-7; *p*-$CH_3OC_6H_4NO_2$, 100-17-4; *p*-$CH_3SC_6H_4NO_2$, 701-57-5; C_6H_5Br, 108-86-1; $C_6H_5OCH_3$, 100-66-3; $C_6H_5SCH_3$, 100-68-5; 1,2-$ClFC_6H_4$-4-NO_2^-, 112348-99-9; 1,1-$Cl_2C_6H_4$-4-NO_2^-, 112349-00-5; 1,1-$BrClC_6H_4$-4-NO_2^-, 112349-01-6; 1,1-$ClOCH_3C_6H_4$-4-NO_2^-, 112349-02-7; 1,1-$ClSCH_3C_6H_4$-4-NO_2^-, 112349-03-8; 1,1-$Cl_2C_6H_5^-$, 112349-04-9; 1,1-$BrClC_6H_5^-$, 112349-05-0; 1,1-$ClSCH_3C_6H_5^-$, 112349-06-1.

Supplementary Material Available: All minimum energy configurations with atomic coordinates and charge densities for each atom and Figures 2–6 containing models of the species discussed in this work (32 pages). Ordering information is given on any current masthead page.

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(18) Politzer, P.; Lane, P.; Jayasuriya, K.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1987**, *109*, 1899.

(19) Desmoyers, J. E.; Jolicoeur, C. *Modern Aspects of Electrochemistry*; Bockris, J. O'M., Conway, B. E., Eds.; Plenum: New York, 1969; Vol. 5, Chapter 1.

(20) Porterfield, W. W. *Inorganic Chemistry*; Addison-Wesley: Reading, MA, 1984; p 256.

(21) Jorgensen, W. L.; Buckner, J. K.; Huston, S. E.; Rossky, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 1891.

(22) Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 2974.

(23) Shaik, S. S. *J. Am. Chem. Soc.* **1984**, *106*, 1227.

(24) Gopalakrishnan, G.; Hogg, J. L. *J. Org. Chem.* **1984**, *49*, 1191.

(25) Stull, D. R.; Westrum, E. F., Jr.; Sinke, G. C. *The Chemical Thermodynamics of Organic Compounds*; Wiley: New York, 1969.

(26) *"The NBS Tables of Chemical Thermodynamic Properties". J. Phys. Chem. Ref. Data, Suppl. 2* **1982**, *11*.