Chart III. Differences in Energy of Complexation ΔG (kJ mol^{-1}) between Cavity Compound CP66 and Semiopened Compound V

		in CP66	Diff.	in Cleft V	ΔG
(1)	Diiodomethane	7.5	5.8	1.7	kJ mol^{-1}
(2)	Benzene	10.0	7.3	2.7	
(3)	Di-(4-aminophenyl)-methane	14.5	7.6	6.9	
(4)	" - amine	14.5	8.5	6.0	
(5)	AMP^{2-}	19.3	9.5	9.8	
(6)	(GMP^{2-} *)	(15.9	3.9	12.0)	

*) (GMP^{2-} only partially encapsulated)

and double interaction in fact would require the build up of dipoles of opposite sign in the heterocycles. Complexations of V with nucleotides such as AMP^{2-} and GMP^{2-}, however, could be evaluated with sufficient accuracy (Table V) and give, as we believe for the first time, experimental numbers for the hydrophobic contribution to the binding of nucleotides with a closed cavity compared to a structurally similar semi-open receptor shape (V). The complexation ΔG values between CP66 (Tables I and II) and V (Table V) differ for AMP^{2-} by 9.5 and for GMP^{2-} by 3.5 kJ mol^{-1}. The latter compound is shown by the CIS values (see above) to be encapsulated in the CP66 cavity to a much lesser degree and therefore is less sensitive to the hydrophobic cavity effect. AMP^{2-}, however, with ΔG = 9.5 kJ mol^{-1}, shows within ±1 kJ mol^{-1} the *same* ΔG difference as we observed with four other substrates of totally different nature[14] (Chart III).

Conclusions

We have shown that electrostatic contributions to nucleotide binding can be separated from other effects and are quantified on the basis of constant salt bridge increments. van der Waals contributions show selectivity for adenine in terms of binding constants and binding geometry. The latter is characterized by inclusion of the nucleobase vis-a-vis of positively charged nitrogen and sheds light on DNA intercalation mechanisms. In contrast to predictions from molecular modeling and experiments with benzene compounds, pyrimidine derivatives are not encapsulated. The observed NMR shifts are valuable tools for structural investigations of nucleic acid derivatives in solution. Comparison of binding in structurally related open and closed hosts lends further support to our earlier conclusions[14] that the solvophobic effect of cavity formation on the binding energy of quite different substrates can be tentatively factorized simply by considering the number of hydrogen-disruptions of the intracavity water molecules.

Experimental Details

NMR titrations, evaluation of equilibrium constants and CIS values, and molecular modeling studies were performed as described before.[5b,33] The substrates were used as commercially available without further purification; CP66 was prepared as described earlier.[34]

Bis[4-(trimethylammonio)phenyl]methane (V) was prepared by alkylation of commercially available bis[4-(dimethylamino)phenyl]methane with methyl iodide in methanol.[35]

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Single-Electron Transfer in Aromatic Nucleophilic Substitution on Dinitrobenzonitriles

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Abstract: Reaction of OH^- with 3,5-dinitrobenzonitrile in water or water–DMSO gives a mixture of unproductive 2- and 4-Meisenheimer complexes that equilibriate and eventually form 3,5-dinitrobenzamide and finally the benzoate ion. The corresponding reaction of 2,4-dinitrobenzonitrile gives the 5-Meisenheimer complex and then a mixture of 2,4-dinitrobenzamide and 2,4-dinitrophenoxide ion. The ratio amide:phenoxide ion increases with increasing [OH^-]. These reactions appear to involve formation of charge-transfer complexes of the radical anion of the substrate and $^{\bullet}OH$ which collapse to give Meisenheimer complexes and final products. The rate constants of the various reaction steps can be estimated by simulation based on relaxation theory, which also fits the product mixture from 2,4-dinitrobenzonitrile. This reaction scheme is consistent with observations of exchange of arene hydrogen and of extensive broadening of ^{1}H NMR signals of the substrates during reaction.

Reactions of hydroxide or alkoxide ions with 3,5-dinitrobenzonitrile (**1**) in polar solvents give mixtures of Meisenheimer complexes. The 4-complex forms and then equilibriates with the more stable 2-complex.[2-6] Fyfe and co-workers used flow NMR spectroscopy to show unambiguously that the 2-complex predominates in the equilibrium mixture. This difference in stability is predicted by qualitative models of electronic effects and by molecular orbital calculations.[7]

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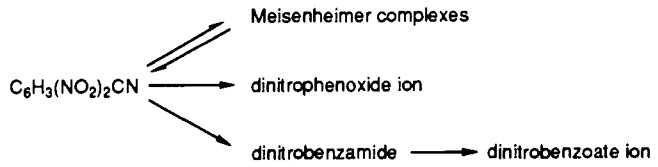
Scheme I



Both forward and reverse steps of formation of Meisenheimer complexes have been followed kinetically with OH^- in aqueous DMSO and with MeO^- in MeOH and in MeOH–DMSO.[2-6,8] These complexes disappear as substitution products gradually form, although there is conflicting evidence on overall reaction products. Fendler and co-workers treated **1** with MeO^- in MeOD–DMSO and observed a product that, on the basis of its ^1H NMR spectrum, appeared to be 1-methoxy-3-cyano-5-nitrobenzene.[6] However, Abe examined the same reaction in MeOH and then acidified the solution and poured it into water. He isolated methyl 3,5-dinitrobenzoate, which he postulated was formed via the alkoxy imide by addition of MeO^- to the cyano group.[8]

Aromatic nucleophilic addition and substitution in polar hydroxylic solvents are generally written as two-electron transfers,[9] although there is compelling evidence for single-electron transfers in less polar media,[10] and the radical anion of 3,5-dinitrobenzonitrile has been identified by ESR spectrometry in solutions of MeO^- in MeOH and in aprotic solvents.[6]

There is evidence that reactions of OH^- with polynitroarenes in H_2O and aqueous DMSO occur by transfer of one electron into the antibonding orbital of the nitroarene to give a short-lived intermediate that can be written as a charge-transfer complex of a radical anion and $^{\bullet}OH$.[11-13] This intermediate may return to reactants, collapse to form a new covalency, or dissociate into free radicals, especially in aprotic solvents. Electron-withdrawing groups strongly stabilize these complexes and appear to be necessary for their observation in polar solvents. If COOR or CN substituents were present, collapse could give not only Meisenheimer complexes but also nucleophilic addition to the COOR or CN group, and collapse of ipso Meisenheimer complexes leads to aromatic substitution. Reactions of OH^- with ethyl 2,4- and 3,5-dinitrobenzoate in aqueous DMSO give Meisenheimer complexes and finally deacylation.[13,14] Kinetic and ^1H NMR spectroscopic evidence suggests that formation of Meisenheimer complexes and tetrahedral intermediates, and eventual deacylation, involves intermediate charge-transfer complexes, formed by single-electron transfer from OH^-. Such complexes of nitriles could collapse to form unproductive or productive (*ipso*) Meisenheimer complexes which give aryloxide ions or amides via hydroxy imides.[6,8]

Nitriles differ from other substrates studied to date in that their reactions with OH^- can give Meisenheimer complexes and dinitrophenoxide ion by nucleophilic aromatic addition and substitution or amides and carboxylate ion by nucleophilic addition to the cyano group. 3,5-Dinitrobenzonitrile gives Meisenheimer complexes rapidly and reversibly,[2-6,8] but 2,4-dinitrobenzonitrile should not form Meisenheimer complexes so readily. Overall reactions are illustrated in Scheme I.

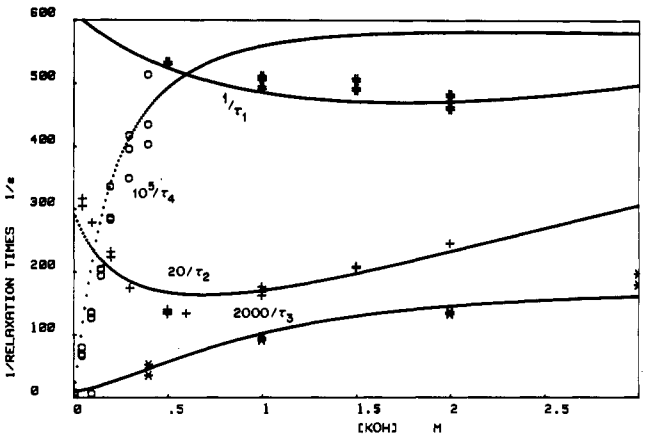


Figure 1. Observed and predicted values of τ^{-1} for reaction of 3,5-dinitrobenzonitrile, 10^{-4} M, in aqueous OH^-.

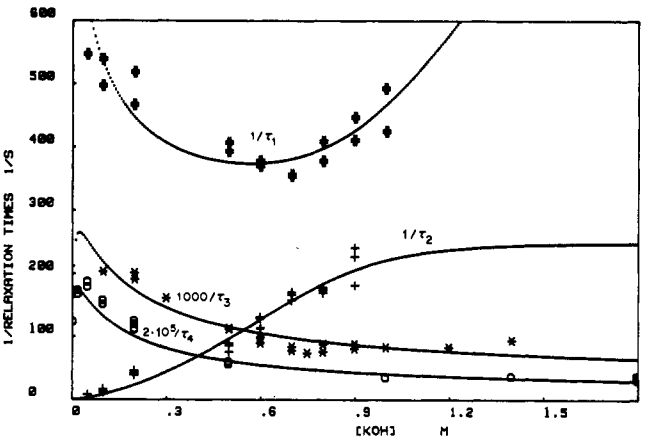


Figure 2. Observed and predicted values of τ^{-1} for reaction of 3,5-dinitrobenzonitrile, 10^{-5} M, with OH^- in DMSO–H_2O 1:1 v/v.

Nucleophilic addition to 3,5-dinitrobenzonitrile is well-studied, but there is little work on the reaction of OH^- with 2,4-dinitrobenzonitrile, although both 2,4-dinitrophenoxide ion and 2,4-dinitrobenzamide, or the benzoate ion, are probable final products. For example, reactions of OH^- with *N*-alkyl-4-cyanopyridinium ions give amide and also pyridone by loss of CN^-.[15]

Molecular orbital calculations, based on AM1 parameters, predict that formation of charge transfer and Meisenheimer complexes from OH^- and dinitrobenzonitriles should be enthalpically favorable in aprotic solvent.[7] Equilibriation of 3,5-dinitrobenzonitrile and its Meisenheimer complexes with OD^- in DMSO–D_2O is accompanied by exchange of arene hydrogen, which probably involves a charge-transfer complex.[11] Reactions of OD^- with activated arenes in DMSO–D_2O are often accompanied by NMR line broadening of ^1H signals of unreacted substrate, which suggests the presence of radicaloid species.[11,16]

We therefore examined kinetics and products of reactions of OH^- with 2,4- and 3,5-dinitrobenzonitrile and used NMR spectrometry to study hydrogen exchange and line broadening during the reaction.

Results

Kinetics. 3,5-Dinitrobenzonitrile (1). Reaction with OH^- rapidly and reversibly generates 4- and 2-Meisenheimer complexes,

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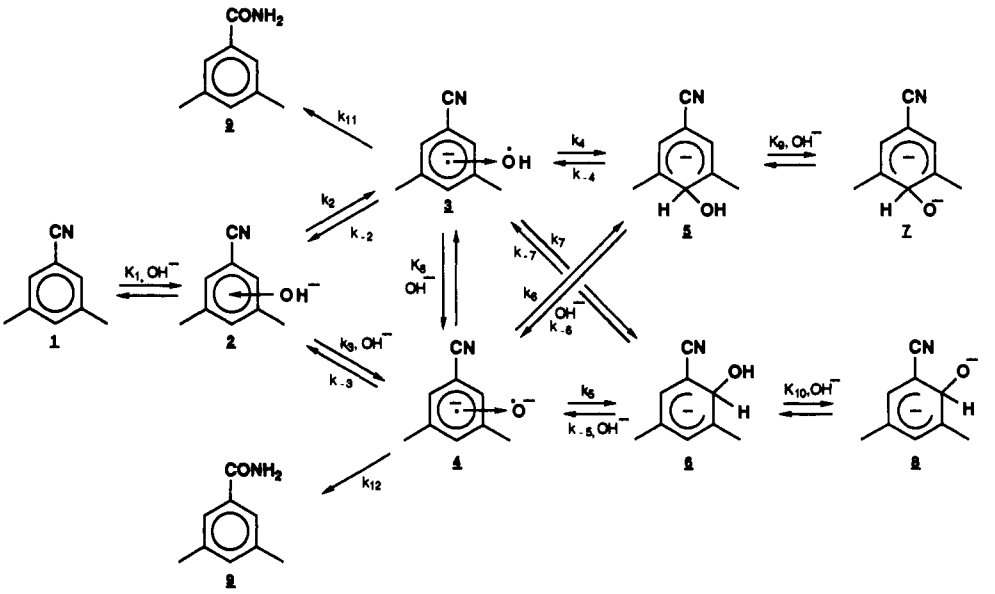
Table I. Reciprocal Relaxation Times for Reaction of 3,5-Dinitrobenzonitrile in Water[a]

	τ_1^{-1}, s^{-1}		τ_2^{-1}, s^{-1}			$10^2\tau_3^{-1}$, s^{-1}		$10^3\tau_4^{-1}$, s^{-1}		
[OH$^-$], M	500[b]	360[b]	500[c]	360[c]	257[b]	500[b]	350[c]	500[b]	367[b]	350[b]
0.01								0.10	0.08	0.09
0.05			15.2	15.8				0.82	0.69	0.72
0.10			13.9					1.29	1.37	1.38
0.15								2.06	2.07	1.96
0.20			11.6	11.1				3.38	2.85	2.87
0.30			8.66					4.20	3.98	3.50
0.40						1.74	2.60	5.16	4.37	4.05
0.50	531	531	6.75	6.93	6.6					
0.60			6.64							
1.00	507	492	8.58	8.35	8.07	4.52	4.69			
1.50	490	505	10.3	10.3	10.4					
2.00	460	490	12.2			6.58	6.73			
3.00						8.90	9.78			

[a] At 25.0 °C, with 10^{-4} M **1**; wavelengths in nm. [b] Decrease in absorbance. [c] Increase in absorbance.

Scheme II[a]



[a] — denotes NO_2.

but amide is formed by addition to the cyano group (cf. refs 6 and 8) and gradually forms 3,5-dinitrobenzoate ion. We followed several relaxations with first-order kinetics in both water and DMSO–H_2O 1:1 v/v. The kinetic behavior is very similar to that seen earlier in reactions of trinitrobenzene and its chloro or sulfonate derivatives.[12]

We saw four relaxations in water. The fastest, τ_1, followed as an absorbance decrease at 500 and 360 nm, is ascribed to formation of a charge-transfer complex. The second relaxation, τ_2, was followed as an absorbance increase at 500 and 360 nm and a decrease at 257 nm, characteristic of formation of 2- and 4-Meisenheimer complexes, cf. refs 2–6. The third relaxation, τ_3, followed at 500 and 350 nm, is assigned to equilibriation of Meisenheimer complexes.[4] The fourth relaxation, τ_4, followed as a decrease of absorbance at 500 and 350–367 nm, gives the amide, which in turn gives 3,5-dinitrobenzoate ion as the final product (Experimental Section). We saw no evidence for formation of a phenoxide ion.[8] We did not follow the kinetics of this final step quantitatively. Values of τ^{-1} are given in Table I and Figure 1.

We also saw four relaxations for the reaction in DMSO–H_2O 1:1 v/v under our usual operating conditions. Our assignments are as for reaction in water, and values of τ^{-1} are given in Table II and Figure 2. The dependences of τ^{-1} upon [OH$^-$] for the slower relaxations differ in water and DMSO–H_2O (Figures 1 and 2). The overall reaction (Scheme II) is based on analogies with deacylation of ethyl 3,5-dinitrobenzoate,[16] and we used it to analyze the kinetic data.

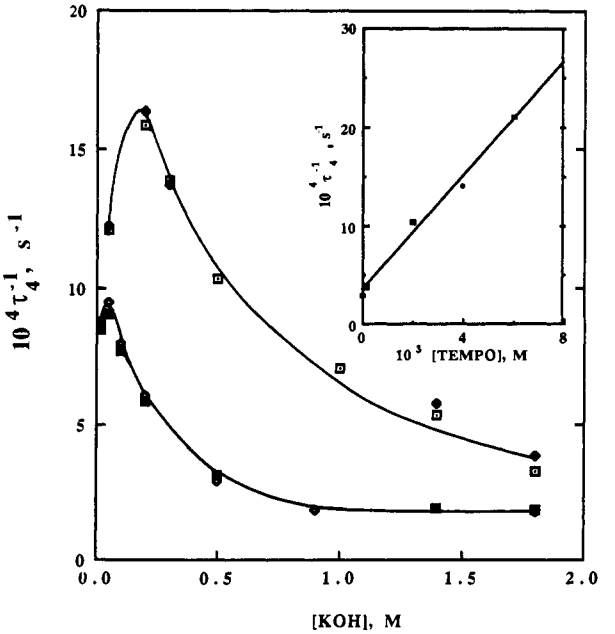


Figure 3. Trapping by 2×10^{-3} M 4-hydroxy-TEMPO (**10**) in the reaction of 3,5-dinitrobenzonitrile. The lower curve is for reaction in the absence of **10**. Insert shows the effect of varying of [**10**] with 0.5 M KOH. Open and solid points, followed at 380 and 500 nm, respectively.

Table II. Reciprocal Relaxation Times for Reaction of 3,5-Dinitrobenzonitrile in DMSO–H_2O[a]

	τ_1^{-1}, s^{-1}		τ_2^{-1}, s^{-1}			τ_3^{-1}, s^{-1}		$10^4\tau_4^{-1}$, s^{-1}	
[OH^-], M	500[b]	360[b]	510[c]	360[c]	250[b]	500[b]	360[c]	500[b]	380[b]
0.005								6.30	
0.02								8.46	8.77
0.05	546		6.66					9.04	9.45
0.10	496	538	10.8	11.8	15.7	0.20		7.68	8.00
0.20	466	518	38.2	42.2	45.4	0.20	0.19	5.86	6.03
0.30							0.16		
0.50	392	406	88.1	84.8	74.5	0.11	0.11	3.11	2.90
0.60	369	377	112	128	130	0.098	0.089		
0.70	353	355	165	157	170	0.083	0.074		
0.75						0.073			
0.80	377	408	176	173	168	0.075	0.087		
0.90	446	410	181	240	226	0.080	0.087		1.85
1.00	424	492				0.082			
1.20						0.090			
1.40						0.093		1.95	
1.80								1.87	1.76
2.00								1.89	1.67

[a] At 25 °C, in DMSO–H_2O 1:1 v/v, with 10^{-5} M **1**; wavelength in nm. [b] Decrease in absorbance. [c] Increase in absorbance.

We used nitroxide trapping as evidence for the intermediacy of species with radicaloid character. Picrate ion forms when O_2 is bubbled into a solution of 1,3,5-trinitrobenzene and OH^-, probably by trapping of a charge-transfer complex with dioxygen.[17] We therefore examined the effect of a scavenger, the 4-hydroxy-2,2,6,6-tetramethylpiperidineoxy free radical, 4-hydroxy-TEMPO (**10**),[18] upon τ_4^{-1} (Figure 3).

Kinetic Simulation. Variations of values of τ^{-1} with [OH^-] for the various relaxations can be fitted by a computer simulation based on relaxation theory[19,20] and the overall reactions of 3,5-dinitrobenzonitrile (Scheme II). As in previous work we assume that a π or encounter complex (**2**) of substrate and OH^- is formed in a very rapid equilibrium step which is too fast to be followed at 25 °C. This reaction step was postulated by Caldin and co-workers.[21] This complex rapidly generates charge-transfer complexes **3** and **4** in acid–base equilibrium, and they give unproductive 2- and 4-Meisenheimer complexes[2-6] **5** and **6** and collapse to amide **9** via hydroxy imide.[8] The Meisenheimer complexes equilibriate[4] via the charge-transfer complexes, and in the fourth relaxation they form amide, again via the charge-transfer complexes. In fitting the data we have to include dianionic Meisenheimer complexes **7** and **8**. We write their formation as deprotonations because they appear to be very fast, and we see no evidence for dihydroxy Meisenheimer complexes, although we cannot exclude their existence (cf. refs 12, 22, and 23). The fit to the data is reasonably good, both in water and in DMSO–H_2O 1:1 v/v, although, as in any simulation procedure, we cannot guarantee that we have a uniquely correct set of rate and equilibrium constants.[20] Dependence of τ^{-1} upon [OH^-] in the two solvents fits the simulations (Figures 1 and 2).

Rate and equilibrium constants for the various steps are given in Table III.

2,4-Dinitrobenzonitrile (11). There is little information regarding reaction of 2,4-dinitrobenzonitrile (**11**), but it forms Meisenheimer complex(es) less readily than does the 3,5-isomer. In 0.1 M OH^- (DMSO–H_2O 1:1 v/v) absorbance of a Meisenheimer complex at 500–510 nm is weak, but there are well-defined absorbance maxima of 2,4-dinitrophenoxide at 360 and 410 nm which appear as the Meisenheimer complex disappears. The final products are 2,4-dinitrophenoxide ion and 2,4-dinitrobenzamide plus benzoate ion. The concentration of 2,4-dinitrophenoxide ion decreases markedly with an increase of [OH^-].

In 2 M OH^- there is a stronger absorbance of Meisenheimer complex at ca. 500 nm within 2 s of mixing, and then the absorbance at 400–410 nm increases as that of the Meisenheimer complex decreases. However, the final absorbance of 2,4-di-

Table III. Individual Rate and Equilibrium Constants for Reaction of Dinitrobenzonitriles[a]

	2,4-$(NO_2)_2C_6H_3CN$	3,5-$(NO_2)_2C_6H_3CN$
k_2, s^{-1}	347	1550 (577)
k_{-2}, s^{-1}	379	77.2 (561)
k_3, M^{-1} s^{-1}	576	2740 (161)
k_{-3}, s^{-1}	165	36.7 (206)
k_4, s^{-1}	15.9	678 (53.5)
k_{-4}, s^{-1}	2.39	2.65 (16.4)
k_5, s^{-1}		3.51 (0.80)
k_{-5}, M^{-1} s^{-1}		0.08 (0.025)
k_6, s^{-1}	8.20	231 (29.5)
k_{-6}, M^{-1} s^{-1}	4.70	9.48 (6.86)
k_7, s^{-1}		57.4 (0.13)
k_{-7}, s^{-1}		0.13 (0.0054)
k_{11}, s^{-1}	0.022	0.75 (0.43)
k_{12}, s^{-1}	0.38	0.032 (0.40)
k_{13}, s^{-1}	0.74	
k_{14}, s^{-1}	0.039	
K_1, M^{-1}	0.21	0.93 (0.06)
K_8, M^{-1}	1.00	10.5 (0.76)
K_9, M^{-1}	9.87	5.07 (3.35)
K_{10}, M^{-1}		6.84 (1.31)

[a] In DMSO–H_2O 1:1 v/v at 25.0 °C unless specified; values in parentheses are for reaction in water.

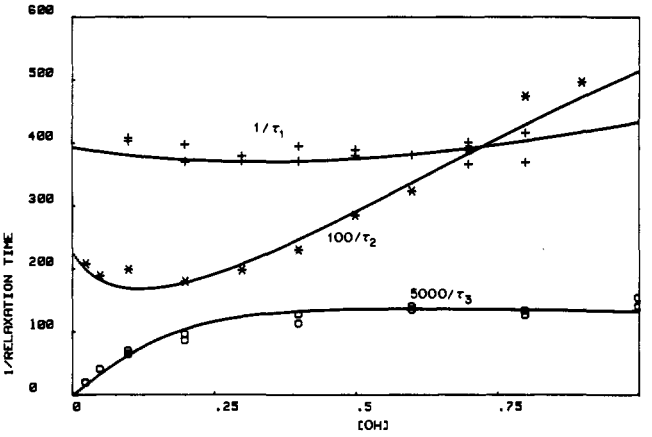


Figure 4. Observed and predicted values of τ^{-1} for reaction of 2,4-dinitrobenzonitrile with OH^- in DMSO–H_2O 1:1 v/v.

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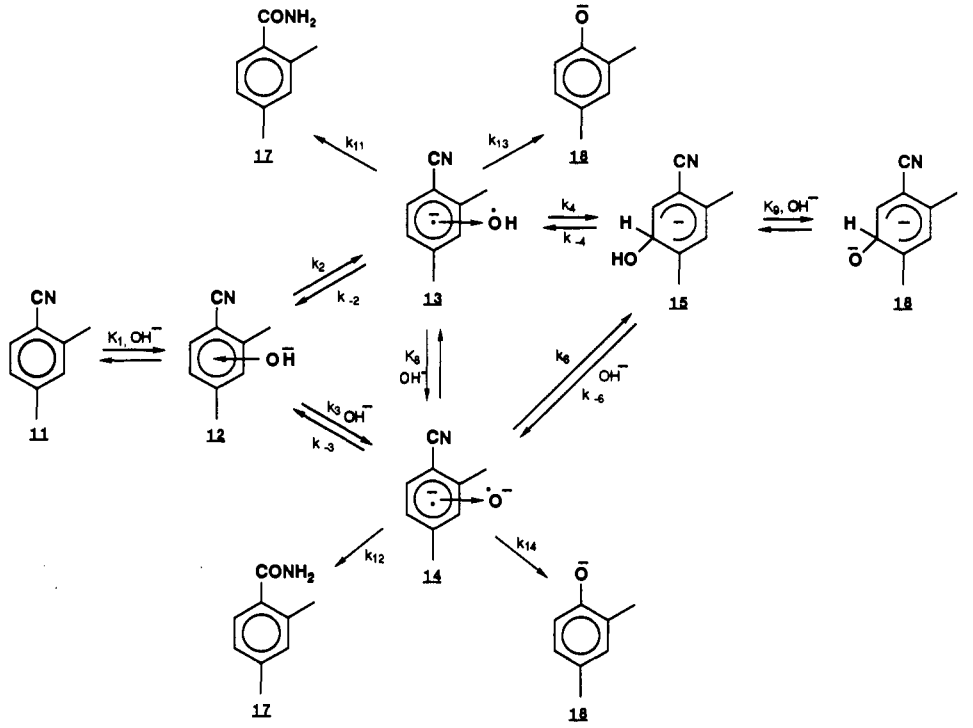
Scheme III[a]



[a] — denotes NO_2.

Table IV. Reciprocal Relaxation Times for Reaction of 2,4-Dinitrobenzonitrile in DMSO–H_2O[a]

$[OH^-]$, M	τ_1^{-1}, s^{-1}		τ_2^{-1}, s^{-1}	$10^3\tau_3^{-1}$, s^{-1}	
	500[b]	260[c]	500[c]	500[b]	400[c]
0.025			2.07	4.27	4.48
0.05			1.88	8.56	8.56
0.1	407	402	1.98	13.4	14.5
0.2	397	365	1.79	19.7	17.7
0.3	378	370	1.97		
0.4	397	370	2.29	23.1	26.0
0.5	378	388	2.87		
0.6	380		3.27	27.5	28.5
0.7	365	400	3.88		
0.8	368	415	4.73	25.8	27.2
0.9			4.95		

[a] At 25.0 °C, in DMSO–H_2O 1:1 v/v, with 4×10^{-5} M **10**; wavelengths in nm. [b] Decrease in absorbance. [c] Increase in absorbance.

nitrophenoxide ion is weaker than it had been in 0.1 M OH^-, because more amide is formed.

We followed three relaxations in the reaction of 2,4-dinitrobenzonitrile (Figure 4 and Table IV). A slow fourth relaxation generates 2,4-dinitrobenzoate ion from the amide, but we do not include it in our quantitative treatment. The first relaxation, τ_1, followed as a decrease of absorbance at 500 nm and an increase at 260 nm, is assigned to buildup of charge-transfer complexes, as in reactions of similar substrates.[12,13,16] A second relaxation, τ_2, assigned to formation of a Meisenheimer complex, was followed as an increase of absorbance at 500 nm. It had a lower amplitude than that of the corresponding relaxation with the 3,5-isomer **1**. The third relaxation, τ_3, followed as an increase of absorbance at 400 nm and decrease at 500 nm, corresponds to formation of phenoxide ion and amide. Values of τ^{-1} for the three relaxations were measured at various wavelengths (Table IV).

Kinetic Simulation. We fitted variations of τ^{-1} with $[OH^-]$ in terms of the reactions shown in Scheme III, which is similar to Scheme II for reactions of 3,5-dinitrobenzonitrile (**1**) and schemes for reactions of dinitrobenzoate esters.[16] We assume rapid formation of the very short-lived complex[21] **12** which gives charge-transfer complexes **13** and **14**, which then give 5-Meisenheimer complex **15** and dianion **16** or collapse irreversibly either to amide **17** via a hydroxy imide[8] or to phenoxide ion **18** via a transient *ipso*-Meisenheimer complex.

Table V. Product Composition from Reaction of 2,4-Dinitrobenzonitrile[a]

		$[OH^-]$, M				
		0.01	0.6	1.0	1.6	2.0
ArO^-, mol %	obsd	82	75	66	57	54
ArO^-, mol %	calcd	92	75	66	56	51

[a] At 25 °C, in DMSO–H_2O 1:1 v/v.

The kinetic simulation has to accommodate variations of τ^{-1} and the dependence of products **17** and **18** on $[OH^-]$ (Tables IV and V). Amide **17** and phenoxide ion **18** form in a common relaxation, so we first fitted variations of τ^{-1} with $[OH^-]$ without considering product composition. We next estimated relative values of the rate constants of the product-forming steps by numerical integration based on the ratio of phenoxide ion to amide (Table V), and we then resimulated the kinetic and product data together. We tested the fit by estimating the ratio of phenoxide to amide on the basis of the already-derived rate and equilibrium constants. The fit is satisfactory (Table V). Rate and equilibrium constants for the individual reactions (Scheme III) are given in Table III.

Our Scheme III includes only the long-lived 5-Meisenheimer complex **15** and the dianionic speciees **16** derived from it. We did not see a relaxation corresponding to equilibriation of Meisenheimer complexes, although 3- and 5-complexes are seen in the reaction of OH^- with 2,4-dinitrochlorobenzene[24,25] but not with ethyl 2,4-dinitrobenzoate.[16] We do not include dihydroxy Meisenheimer complexes in our scheme because we saw no relaxation corresponding to their formation and destruction. We cannot exclude their rapid formation because it would have the same kinetic form as interconversion of **15** and **16** (Scheme III).

We write the products as being formed directly from mono- and dianionic charge-transfer complexes **13** and **14** (Scheme III), although this model may be too simple. Collapse of charge-

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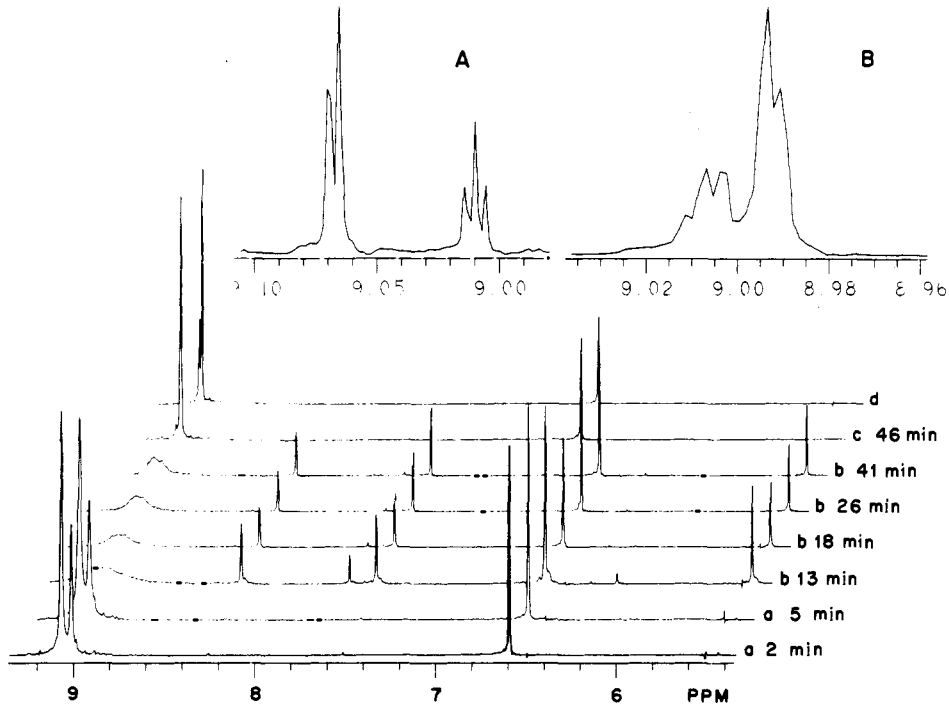

Figure 5. ^{1}H NMR spectra (500 MHz) of 3,5-dinitrobenzonitrile (0.072 M) in DMSO-d_6–D_2O 4:1 v/v at 25 °C. Inserts A and B show spectra before (25 °C) and after (45 °C) complete reaction, respectively. Spectra at time (min) indicated after initial addition of KOD: (a) with 0.011 M KOD; (b) with 0.03 M KOD; (c) after 0.08 M DCl quench (25 °C); and (d) at 45 °C.

transfer complexes should give anions of the hydroxy imide,[8] and they should very rapidly give amide by fast proton transfer which may be concerted with collapse. Collapse to mono- or dianionic *ipso*-Meisenheimer complexes gives phenoxide ion by loss of CN^-. However, CN^- is a poor leaving group, and cyanohydrin chemistry suggests that CN^- will be lost from the dianionic *ipso* complex or by a base-catalyzed decomposition of the *ipso* complex. The strong inductive effect of the cyano group should make the *ipso* complex sufficiently acidic for it to be at least partially deprotonated at high pH, so it will be a transient steady-state species. Hydroxy imides and *ipso*-Meisenheimer complexes should be too short-lived to appear directly in the observed relaxations (Schemes II and III). Molecular orbital calculations predict that the *ipso*-Meisenheimer complex is much less stable than is the 5-complex **15**.[7]

The classical mechanism of single-step formation of an *ipso*-Meisenheimer complex predicts that the ratio of phenoxide:amide should be independent of $[OH^-]$ or should increase with added OH^- if it catalyzes decomposition of the *ipso* complex by deprotonation. We observe the opposite effect (Table V), consistent with Scheme III.

NMR Spectroscopy. 3,5-Dinitrobenzonitrile (1). These experiments were made with higher [DMSO] than that used in the kinetic work because we needed a sufficiently high substrate concentration to obtain spectra within a short time of mixing. The NMR spectrum of the system had been examined in DMSO-d_6–D_2O, where substrate was largely converted into Meisenheimer complex(es).[4,11] As others have done with other nitroarenes,[11,16,25] we took substrate in excess over $[OD^-]$ so that reactions were not inconveniently fast, and we hoped to see signals of Meisenheimer complexes during reaction[4] and of products and unreacted substrate at the end of reaction. We used mesitoate ion as a reference.[11] All chemical shifts (ppm) are relative to that of DMSO at 2.490 ppm. In DMSO-d_6–D_2O 4:1 v/v under N_2, 3,5-dinitrobenzonitrile (0.072 M) has ^{1}H signals at 9.067 ppm (H2,6) and 9.009 ppm (H4) (Figure 5), based on their peak areas (2:1) and coupling constants, which are H4, t, J = 2 Hz and H2,6, d, J = 2 Hz. The relative positions of these signals are medium-dependent and are affected by addition of electrolytes, e.g., DCl (Experimental Section). Addition of KOD at 25 °C markedly changed the spectrum (Figure 5). Within 2 min of addition of 0.011 M KOD (the time required for mixing and signal acquisition) substrate signals broadened slightly and the fine structure disappeared, but signals of H2,6 and H4 were still seen and very weak signals of 2-Meisenheimer complex appeared at 8.275 ppm (H4, d, J = 1.5 Hz), 7.528 ppm (H6, d, J = 2 Hz), and 5.570 ppm (H2, s), but signals of the 4-Meisenheimer complex were too weak to be seen. After 5 min broadening increased. At 11 min after the initial mixing, we added a further 0.03 M KOD, and 2 min later the substrate signal had broadened considerably with $\nu_{1/2} \approx 500$ Hz. Signals of the 2-Meisenheimer complex were much stronger, and those of the 4-Meinsenheimer complex were at 7.677 ppm (H2,6, s) and 6.200 ppm (H4, s). Based on the areas of these signals the ratio of the 2- to the 4-Meisenheimer complex was ca. 4:1. Signals of the 4-Meisenheimer complex gradually disappeared and after 41 min were very weak. There was isotopic hydrogen exchange of the 2-Meisenheimer complex at H4, which increased to ca. 22% after 41 min, based on comparison with the signal of H2. This estimate is probably a little low because there is some exchange at H6 (and H2) of the 2-Meisenheimer complex.[11]

After 41 min the signal of unreacted substrate sharpened slightly and a new signal appeared, superimposed on the original signal at 9.014 ppm, due to formation of 3,5-dinitrobenzamide, which has signals at 8.943 ppm (H4) and 8.950 ppm (H2,6) in DMSO–D_2O 4:1 v/v in the absence of KOD. Deconvolution of the broad signal (GEMCAP program) gave a ratio of nitrile:amide of 10:1. The signal of the 2-Meisenheimer complex persisted, and after 30 min its concentration was ca. 40% of the total (based on the H2 signal). After 46 min we added 0.8 M DCl to stop the reaction and convert Meisenheimer complex back into substrate (Figure 5). There was a merged signal at 9.010 ppm with a shoulder at 9.007 ppm due to nitrile plus amide, and it separated at 45 °C to give signals at 9.006 ppm (H4, t, J = 2 Hz) and an asymmetric doublet at 8.992 ppm (H2,6, d, J = 1.5 Hz). (The amide signal was very small.) Comparison of signal areas of mesitoate ion and nitrile plus amide showed that there was less than 10% hydrogen exchange of recovered nitrile after acidification. There were small signals probably due to formation of 3,5-dinitrobenzoate ion.

Another experiment was made under similar conditions ($DMSO_{d6}$–D_2O 4:1 v/v, 0.031 M KOD and 0.077 M 3,5-dinitrobenzonitrile, 25 °C), and within 2 min of mixing we saw signals of the 2- and 4-Meisenheimer complexes in a ratio of 6:1,

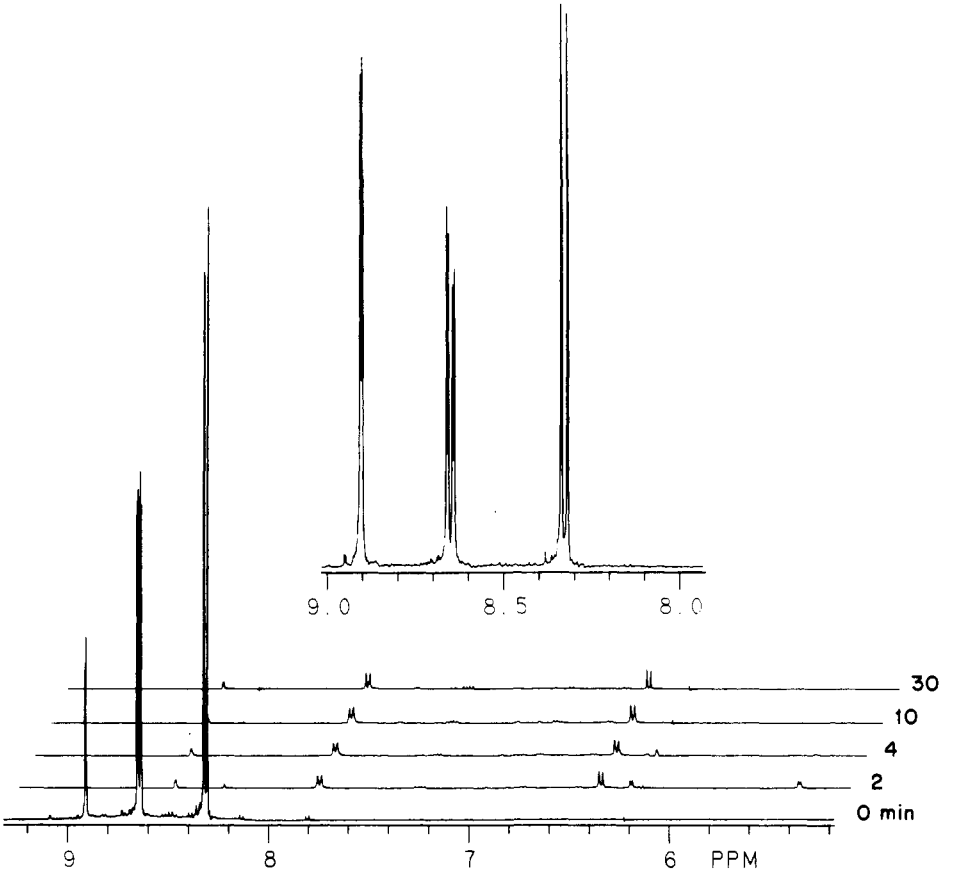

Figure 6. ^{1}H NMR spectra (500 MHz) of 2,4-dinitrobenzonitrile (0.072 M) in DMSO-d_6–D_2O 4:1 v/v at 25 °C before (0 min) and after addition (time indicated, min) of 0.031 M KOD with an interpulse delay of 1.5 s. Insert shows the spectrum of **11** before KOD addition with an interpulse delay of 30 s.

which increased to ca. 12:1 after 10 min. Under these conditions signals of the unreacted nitrile were very broad, but signals of Meisenheimer complexes were always sharp, as were signals after addition of DCl. 3,5-Dinitrobenzamide gradually forms a 2-Meisenheimer complex with OD^- in DMSO-d_6–D_2O and which has signals at 8.350 ppm (H4), 7.773 ppm (H6), and 6.826 ppm (H2). The signal at H4 was weaker than the others, probably due to isotopic exchange, but we did not investigate this system in detail.

2,4-Dinitrobenzonitrile (11). Meisenheimer complex **15** forms with **11** and OH^- in aqueous DMSO, but the equilibrium constant is much lower than it is for **1**. In dilute OH^- (OD^-), 2,4-dinitrophenoxide ion (**18**) is the major product, with more amide **17** at higher [OH^-]. In our initial NMR experiment with dilute OD^-, we had no complications from formation of Meisenheimer complex or amide.

In DMSO-d_6–D_2O 4:1 v/v the nitrile has ^{1}H signals at 8.903 ppm (H3, d, J = 2.5 Hz), 8.650 ppm (H5, dd, J = 8.5 Hz, ^3J = 2.5 Hz), and 8.327 ppm (H6, d, J = 8.5 Hz) related to the ^{1}H signal of DMSO at 2.490 ppm. We had to use long delays (>30 s) to obtain reasonable peak areas of H3 relative to H5 and H6 (Experimental Section), and the first spectrum was taken with a 30-s delay (Figure 6). This delay time is inconveniently long for following the spectrum during reaction, so a second spectrum was taken with a 1.5-s delay, resulting in a decrease, but not suppression, of the H3 signal (Figure 6). We used this delay time during the experiment, but the final spectrum, after addition of excess DCl, was taken with a 30-s delay so that areas of the substrate peaks taken before and after reaction can be compared with the peak area of the signal of the reference mesitoic acid.

Within 2 min of addition of 0.031 M KOD, substrate signals disappeared due to very extensive line broadening (Figures 6 and 7), and new signals of 2,4-dinitrophenoxide ion appeared at 8.548 ppm (H3, d, J = 3 Hz), 7.818 ppm (H5, d, J = 10 Hz), and 6.415 ppm (H6, d, J = 10 Hz). There were also signals of 5-Meisenheimer complex at 8.298 ppm (H3, s), 6.270 ppm (H6, d, J = 6 Hz), and 5.431 ppm (H5, d, J = 5.5 Hz) (Figure 7a). Signals of the complex disappeared after 4 min, and we saw no signals of a 3-Meisenheimer complex. Initially we saw no signals of 2,4-dinitrobenzamide, probably because they are broad in DMSO-d_6–D_2O plus KOD. However, this broadening gradually decreased, and after 45 min we saw weak signals of amide at 8.718 ppm (H3, d, J = 2 Hz), 8.519 ppm (H5, dd, J = 8 Hz, ^3J = 2 Hz), and 7.798 ppm (H6, d, J = 8.5 Hz) (Figure 7b). Some minor signals, which change with time, are probably due to the benzoate ion and Meisenheimer complexes of the amide (Experimental Section). Signals sharpen with time, and after 3 h peak areas of the phenoxide ion and amide signals were similar (Figure 7c). Signals of unreacted substrate reappeared, although they were still broad, and the area of the signal of H3 was small due to extensive exchange and the short interpulse delay time of 1.5 s. At this time approximate peak area ratios (excluding H3) corresponded to nitrile:phenoxide ion:amide 9:1.5:1.

A second experiment was made with reactant concentrations as above, and excess DCl was added after 60 min. All the substrate signals reappeared, although that of H3 was weak, due to isotopic exchange, even with 30-s delay between scans. Comparison of the sum of the signals of unreacted substrate, phenol, and amide with that of mesitoic acid showed that exchange was only at H3. We note that at high pH some of the signals of substrate and products are at similar chemical shifts and their observation depends on the obscuring of substrate signals by line broadening.

Extents of isotopic exchange at position 3 were determined under various conditions with relatively long NMR delay times (30 s) (Table VI). We did not measure the exchange of the amide because its H3 signal is close to that of the nitrile.

Trapping by a Nitroxide Radical. The value of τ_4^{-1} for disappearance of a Meisenheimer complex of 3,5-dinitrobenzonitrile in DMSO–H_2O 1:1 v/v is increased by addition of 4-hydroxy-

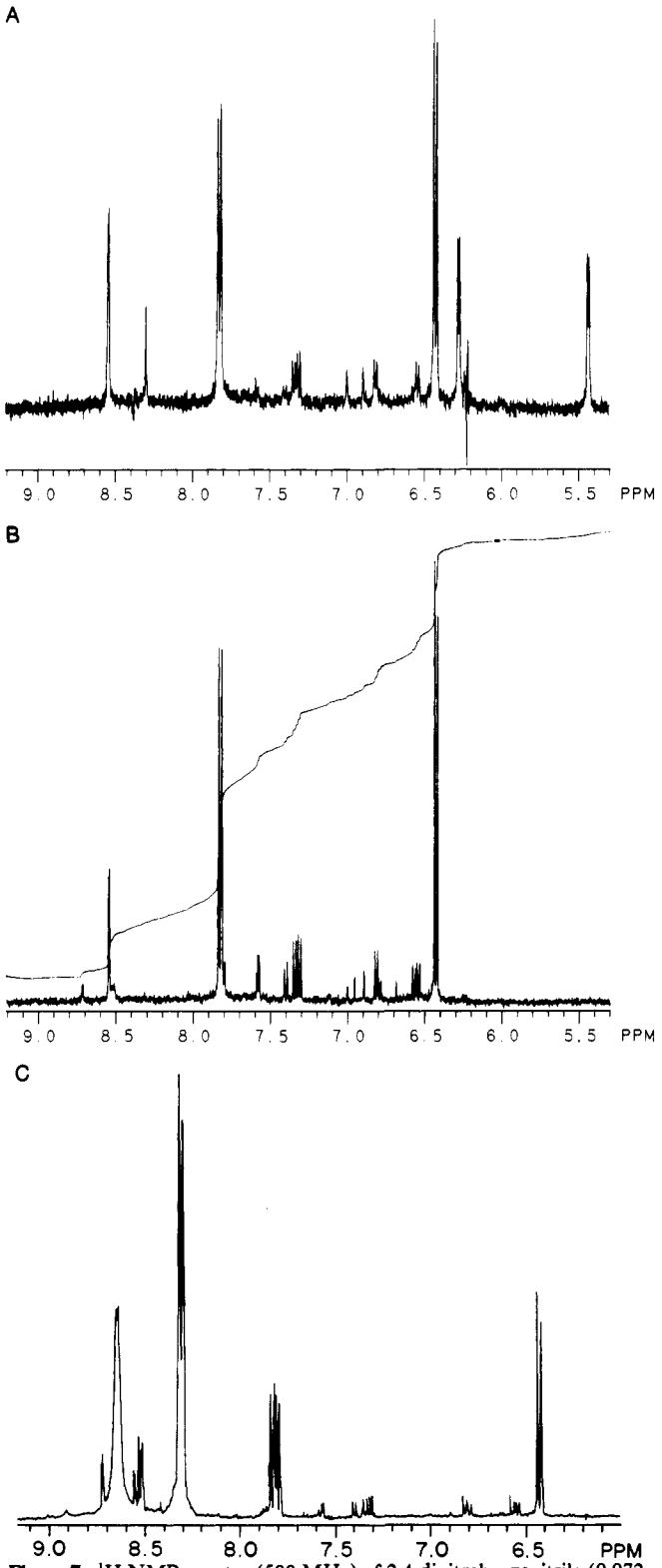

Figure 7. ^{1}H NMR spectra (500 MHz) of 2,4-dinitrobenzonitrile (0.072 M) in DMSO-d_6–D_2O 4:1 v/v. A, 2 min after addition of 0.031 M KOD; B, after 45 min of reaction; and C, after 3 h of reaction.

TEMPO (**10**) (Figure 3) under conditions in which this complex is the dominant species. The rate of this disappearance depends on a reversible return to charge-transfer complex, and hence to final products (Scheme II) and will increase if a radical traps a charge-transfer complex such as **3** or **4**. The value of τ_4^{-1} depends on the concentration of nitroxide radical (Figure 3), so it is not trapping all the charge transfer complex.

Line Broadening with *p*-*tert*-Butylnitrobenzene. Here, and elsewhere,[11,16,25] we suggest that broadening of ^{1}H signals of nitroarene substrates involves their interactions with transient charge-transfer complexes that have radicaloid character. Consistently we never saw line broadening of signals of anions, e.g., of Meisenheimer complexes or aryloxide ions, or of added mesitoate ion. Signals of nitrobenzene do not broaden in DMSO–D_2O–OD^-, but they broaden on addition of *m*-dinitrobenzene which readily generates a charge transfer complex.[11]

Interaction between two species, which permits electron exchange, should be sterically inhibited, e.g., by a *tert*-butyl group, so that the ^{1}H NMR signal of a *tert*-butylnitrobenzene in DMSO–D_2O–OD^- should not broaden on addition of *m*-dinitrobenzene. The original experiments with nitrobenzene and *m*-dinitrobenzene were made in 77% DMSO-d_6,[11] and in 80% DMSO-d_6 signals of *p*-*tert*-butylnitrobenzene (0.07 M) did not broaden on addition of 0.1 M KOD or on subsequent addition of 0.1 M *m*-dinitrobenzene, whose signal broadened as reported earlier.[11]

Results were different in a high [DMSO] solvent. In 98% DMSO-d_6–D_2O with 0.1 M *p*-*tert*-butylnitrobenzene and 0.2 M OD^- there was no initial line broadening of the ^{1}H signal of *p*-*tert*-butylnitrobenzene. However, signals slowly broadened over a period of 10–60 min, and in these conditions signals of nitrobenzene (0.1 M) broadened significantly in 20 min and almost disappeared within 100 min. Addition of 0.1 M *m*-dinitrobenzene to solutions of either nitrobenzene or *p*-*tert*-butylnitrobenzene after ca. 1.5 h sharpened signals of the mononitrobenzenes, and those of *m*-dinitrobenzene broadened and disappeared within 4 min of mixing. These results suggest that a radicaloid species of *m*-dinitrobenzene formed rapidly with a depletion of radicaloid species of the nitrobenzenes and then was converted into a Meisenheimer complex. Sharp signals of this complex of *m*-dinitrobenzene gradually appeared, as they have in the absence of either of the mononitrobenzenes.[11]

Table VI. Hydrogen Isotopic Exchange of 2,4-Dinitrobenzonitrile[a]

$[2,4\text{-}C_6H_3(NO_2)_2CN]$, M	$[OD^-]$, M	time, min	exchange, % 11	15	18
0.077	0.031	180	98		80
0.077	0.031	10[b]	89		
0.073	0.019	4	*c*	70	60
0.073	0.019	30	*c*		66
0.073	0.019	60[b]	78		75

[a] Exchange of H3 at 25.0 °C, in DMSO-d_6–H_2O 4:1 v/v. [b] After addition of DCl. [c] Signals of unreacted substrate could not be followed because of extensive line broadening.

Discussion

Classical mechanisms for reactions of nucleophiles with dinitrobenzoate esters and benzonitriles involve the assumption that formation of Meisenheimer complexes and nucleophilic attack on carbalkoxy and cyano groups follow completely different reaction paths. Our model postulates that both reactions involve common intermediates, the charge-transfer complex and its anion, because charge is delocalized into electron-withdrawing groups, e.g., NO_2, CO_2Et, or CN. This model fits kinetic and exchange data and ^{1}H NMR line broadening of the substrate and also predicts that there will be little or no exchange of anionic species.

Hydrogen Exchange. We postulate exchange on charge-transfer complexes which may go forward to either Meisenheimer complex or final product or revert to substrate.[11,16,17,25] For some nucleophilic aromatic substitutions, product is exchanged more than unreacted substrate,[11] so exchange must involve a species on the reaction path to final products. The situation is more complex when large amounts of unproductive Meisenheimer complexes, e.g., **5** and **6** (Scheme II) or **15** (Scheme III), build up and disappear during reaction. For experimental reasons we carried out exchange experiments with substrate in excess over OD^- (Table VI). With dinitrobenzonitriles, charge-transfer complexes go to Meisenheimer complexes or revert to substrate much more rapidly than they go to final amide or phenolic products (Table III and Schemes II and III). The Meisenheimer complexes may become deuterated during interconversion with charge-transfer complexes

and substrate.[11] As [OD⁻] decreases, Meisenheimer complexes gradually revert to substrate, via charge-transfer complexes, so that the exchange data in Table VI and ref 11 give too much weight to exchange of unreacted substrate relative to product. The problem would be the same if we took OD⁻ in excess over substrate and stopped the reaction by quenching with acid, because Meisenheimer complexes then very rapidly revert to substrate. Reactions are too fast for us to follow conventional NMR spectra under conditions such that the solutions contain similar amounts of unreacted substrate and product. Exchange of arene hydrogens at positions 2 and 6 of the 2-Meisenheimer complex of 3,5-dinitrobenzonitrile had been followed by ^{1}H NMR spectrometry as a function of [OD⁻] in DMSO-d_6–D_2O 50 and 70 wt % DMSO.[11] Under these conditions most of the material is present as the 2-Meisenheimer complex in which 2- and 6-positions are not identical, although exchange rates are identical at these positions. Therefore exchange is not directly on the Meisenheimer complex but on a symmetrical species derived from it. Exchange is faster by a factor of ca. 5 at the 4-position, ortho to the two nitro groups, than at the 2- or 6-position, despite statistical preferences in the charge-transfer complex or substrate (Scheme II). This behavior seems to be general.[11]

If exchange occurs via the charge-transfer complexes **3** and **4**, the rate of exchange depends upon the rate of return of the 2-Meisenheimer complex **6** to charge-transfer complex, which will largely follow reaction step k_{-7} (Scheme II) as shown by the relative values of k_{-7} and k_{-5}[OH⁻] (Table III), with allowance for the equilibrium between mono- and dianionic Meisenheimer complexes **6** and **8**. Therefore OD⁻ will decrease return of **6** to charge-transfer complexes. We do not know the relative rates of exchange of mono- and dianionic charge-transfer complexes **3** and **4** although our speculation is that exchange occurs intramolecularly in the latter[25] and therefore depends upon the equilibrium constant, K_8, [OD⁻], and the lifetimes of the charge-transfer complexes, which depend on the reaction steps k_5 and k_7, which are independent of [OD⁻]. These considerations suggest that the rate of exchange at the *charge-transfer complexes* will be less than first order in [OD⁻], and the rate of exchange observed on a Meisenheimer complex will depend upon its return to charge-transfer complexes and the acid–base equilibrium between them (Scheme II). This model is consistent with the modest initial increase of the rate constants of exchange with increasing [OD⁻] and the rate maxima for exchange at positions 2 (or 6) and 4 of the 2-Meisenheimer complex **6** (Table II, ref 11). For a given [OD⁻], exchange slows with increasing [DMSO-d_6][11] because this solvent change slows return of Meisenheimer to charge-transfer complex, cf. the behavior of trinitrobenzene.[12] We cannot compare these exchange results directly with the present kinetic data because, for experimental reasons, we made up exchange solutions by weight and used high [substrate], but rate constants of exchange should be lower than those for return of 2-Meisenheimer complex **6** to charge-transfer complexes **3** and **4** (Scheme II). Return is largely to the monoanionic complex **3** (step k_{-7}), but we also include return to **4** (step k_{-5}[OD⁻]). The first-order rate constant for return, k_r, is given by

$$k_r = \frac{k_{-7} + k_{-5}[OD^-]}{1 + k_{10}[OD^-]} \quad (1)$$

which allows a qualitative test of the model. We neglect solvent isotope effects and solvent differences, but values of k_r are greater than the sum of the rate constants of exchange (Table II, ref 11) by approximately 1 order of magnitude. This comparison shows that exchange of the charge-transfer complexes of **1** is slower than their formation, consistent with the relatively slow exchange of the 2-Meisenheimer complex of 3,5-dinitrobenzonitrile and the small amount of exchange observed during conversion of the nitrile into Meisenheimer complex (Results).

When 2,4-dinitrobenzonitrile (**11**) reacts with insufficient KOD, there is extensive exchange at position 3 in unreacted nitrile and phenoxide ion product. We cannot follow exchange of the substrate during reaction because its ^{1}H signals become too broad to be seen, so we are forced to obtain data under conditions in which OD⁻ has disappeared due to reaction with substrate or neutralization with DCl (Table VI).

Most hydrogen exchange occurs during reaction with OD⁻ when charge-transfer complexes do not go rapidly or extensively to Meisenheimer complexes,[11] as shown by extents of hydrogen exchange at position 3 in 2,4-dinitrochlorobenzene,[11,25] 2,4-dinitrobenzonitrile (**11**), and ethyl 2,4-dinitrobenzoate.[16] Exchange of 2,4-dinitrochlorobenzene at position 3 is essentially complete in reaction with OD⁻ in DMSO-d_6–D_2O, but exchange is incomplete in reactions of the other substrates. This result argues against exchange by substrate deprotonation, because electron withdrawal by *m*-CN (or *m*-CO_2R), which favors deprotonation, is greater than that by *m*-Cl.[26] It is consistent with exchange of charge-transfer complexes because with the ester and the nitrile they go readily to Meisenheimer complexes and to intermediates that give final products, thus the charge-transfer complexes do not survive long enough to give complete exchange. With 2,4-dinitrochlorobenzene, conversion of charge-transfer into Meisenheimer complexes should be slower than with the other substrates, allowing time for exchange. Substrates such as 3,5-dinitrobenzonitrile[4] go rapidly to Meisenheimer complexes with much less exchange during reaction than do the corresponding 2,4-dinitro compounds.

There is extensive line broadening of ^{1}H NMR signals of both benzonitriles. With 2,4-dinitrobenzonitrile, signals almost disappear on initial addition of OD⁻ but reappear when reaction is largely complete or is stopped by addition of DCl. The signal of H3 is then relatively weak because of exchange. Signals of 3,5-dinitrobenzonitrile do not disappear on addition of OD⁻ because hydrogen exchange is much less than with the 2,4-substrate. However, these signals broaden ($\nu_{1/2} \approx 500$ Hz), as they do with several substrates, under conditions which initially give Meisenheimer complexes and then overall nucleophilic displacement or addition to cyano or carbethoxy groups. These observations are inconsistent with the classical mechanism of single-step nucleophilic addition to generate productive or unproductive Meisenheimer complexes. One could argue that exchange and line broadening involve species that are not on the reaction path but are formed, for example, from Meisenheimer complexes. We think this hypothesis is unlikely for several reasons. (i) It does not explain extensive ^{1}H exchange during reaction and greater exchange of product over unreacted substrate.[11] (ii) We see no line broadening of signals of Meisenheimer complexes, so their conversion into radicaloid species is slow on the NMR time scale. (iii) There is extensive exchange of 2,4-dinitro derivatives that form only small amounts of Meisenheimer complexes (Table VI and refs 16 and 25). (iv) William of Occam argues against the imposition of unnecessary hypotheses.

The decrease of ^{1}H line broadening of nitrobenzene on introduction of a bulky *tert*-butyl group (Results) fits the hypothesis that there is interaction between a nitroarene and a charge-transfer complex. These experiments were made in ca. 80 vol % DMSO-d_6 and an increase in the DMSO content of the solvent leads to extensive line broadening, probably by dissociation of charge-transfer complexes. Consistently there is extensive formation of a Meisenheimer complex of 1,3,5-trinitrobenzene and *n*-butylamine in acetonitrile.[27] Reaction probably involves initial electron transfer, and, after mixing, ^{1}H signals of the amine disappear and those of trinitrobenzene become very broad. After several days sharp signals of a Meisenheimer complex appear, and after 30 days all signals are again sharp, including those of aliphatic ^{1}H and N–^{1}H.

It is important to note that in all our experiments we do not observe paramagnetic line broadening of noninteracting solutes, e.g., mesitoate ion. The situation was similar for experiments with *n*-butylamine in acetonitrile,[27] because TMS was used as an internal reference, and its line broadening was not mentioned. In all these systems line broadening seems to be due to electron

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transfers involving radicaloid species within association complexes rather than to extensive formation of free radicals or radical ions, except in very dry solvents.

Kinetic Schemes. 3,5-Dinitrobenzonitrile behaves like 1,3,5-trinitrobenzene in rapidly forming Meisenheimer complexes,[2-6,12,13] except that there is no evidence of dihydroxy Meisenheimer complexes, although they form readily with trinitrobenzene and OH^-.[12,23] There is no evidence for formation of an *ipso*-Meisenheimer complex of 3,5-dinitrobenzonitrile,[8] although such complexes are transient intermediates in aromatic nucleophilic substitutions. Equilibrium formation constants are similar for the substrates, but are generally slightly larger for trinitrobenzene.[12] In Schemes II and III we show the mono- and dianionic complexes **3** and **4** (Scheme II) or **13** and **14** (Scheme III) as being formed directly, but the mono- and dianionic complexes are in acid–base equilibria, so the kinetics can be fitted equally well by direct formation of **3** or **13** or **4** or **14** and subsequent rapid interconversion (Schemes II and III).

Equilibrium constants (in the forward direction) are generally larger for 3,5-dinitrobenzonitrile than for ethyl 3,5-dinitrobenzoate.[16] Equilibrium constants for formation of Meisenheimer complexes are sometimes estimated from formation rate constants as a function of $[OH^-]$ or $[OR^-]$ on the assumption that forward and reverse reactions are second and first order, respectively. This assumption may be reasonable in dilute OH^- or OR^-, but not at higher concentrations. The two dinitrobenzonitriles differ markedly as regards formation of Meisenheimer complexes (Table III), as do ethyl dinitrobenzoates.[16] This is expected from qualitative considerations of electronic effects[26] and MO calculations with AM1 parameters that predict that Meisenheimer complexes of 1,3,5-derivatives are more stable than those of 1,2,4-derivatives.[7]

The forms of the slower relaxations for reactions of 3,5-dinitrobenzonitrile change markedly in going from water to DMSO–H_2O (Figures 1 and 2). Similar solvent effects had been seen earlier in reactions of trinitrobenzene and its derivatives with OH^- and are to be expected for multistep reactions in which individual reaction steps have different solvent dependencies.[12] It is difficult to understand such kinetic solvent effects in terms of single-step reactions. We did not follow relaxations of 2,4-dinitrobenzonitrile in water, where very little Meisenheimer complex is formed, but variations of τ^{-1} with $[OH^-]$ for the slower relaxations are similar for both substrates in DMSO–H_2O and differ markedly from those for relaxations of 3,5-dinitrobenzonitrile in water.

Schemes II and III for reactions of benzonitriles are similar to those postulated for reactions of ethyl dinitrobenzoates,[16] but there are differences. An *ipso*-Meisenheimer complex is an intermediate in formation of phenoxide ion from 2,4-dinitrobenzonitrile (Scheme III), and conversion of charge-transfer complexes into tetrahedral intermediates of the esters[16] is faster than conversion of charge-transfer complexes into amides (Table I and ref 16). Relative rates of productive collapse of the charge transfer complexes are consistent with the low overall reactivities of nitriles toward nucleophilic anions. Collapse to Meisenheimer complexes is much faster with nitriles than with esters, and equilibria are more favorable (ref 16 and Table III).

Competitive formation of phenoxide ion and amide in the reaction of 2,4-dinitrobenzonitrile with OH^- is analogous to formation of pyridone and amide in reactions of *N*-alkyl-4-cyanopyridinium ions with OH^-. However, in these reactions there is no evidence for common intermediates in the formation of the two products.[15]

Molecular Orbital Calculations. Our kinetic data are consistent with calculations of reaction enthalpies of intermediates in reactions of OH^- with the dinitrobenzonitriles.[7] Calculations were based on AM1 parameters, and in the charge-transfer complexes $^{\bullet}OH$ was located 2.2 Å above the plane of the phenyl group. The prediction was that, without solvent effects, charge-transfer complexes would be formed exothermically from the dinitrobenzonitriles and would have lower enthalpies than would the related radical anions plus $^{\bullet}OH$. Conversion of charge-transfer complexes into Meisenheimer complexes would be enthalpically favorable, and predicted formation enthalpies of Meisenheimer complexes agree with experiment.[2-6] Formation of the transient *ipso*-Meisenheimer complex of 2,4-dinitrobenzonitrile[7] is predicted, consistent with formation of 2,4-dinitrophenoxide ion in the reaction with OH^-. Reaction of 3,5-dinitrobenzonitrile gives no phenoxide ion (Scheme II and ref 8) and the *ipso*-Meisenheimer complex has a predicted higher enthalpy than the 2- and 4-complexes.

General Conclusions

Schemes II and III fit observations of several relaxations in the conversion of 2,4- and 3,5-dinitrobenzonitriles into Meisenheimer complexes and then into final substitution or addition products. Trends in rate and equilibrium constants (Table III) are similar to those seen in reactions of 1,3,5-trinitrobenzene[12] and ethyl 2,4- and 3,5-dinitrobenzoate[16] as are solvent effects upon these parameters.

There is line broadening of ^1H NMR signals of unreacted nitriles, but all other signals are sharp. We believe that line broadening involves interactions of anionic charge-transfer complexes with nonionic substrate.[11] Interaction with anionic species, e.g., phenoxide ion, Meisenheimer complex, or mesitoate ion (Experimental Section), is coulombically unfavorable. The exchange of arene hydrogen during reaction is strong evidence for existence of species not on the classical reaction paths. There is no evidence that free radical anions are on the reaction path in our conditions, although a free radical anion of 3,5-dinitrobenzonitrile was observed with MeO^- in nonaqueous media.[6] It could form by dissociation of a charge transfer complex, which will be favored over formation of Meisenheimer complex or hydroxy imide (amide), in low polarity, nonaqueous solvents.

Physical identification of charge-transfer complexes (**3**, **4** and **13**, **14**) or their counterparts in other reactions is possible only when strongly electron-withdrawing groups are present. Nitro groups are particularly effective in this regard because of their strong electronic effect, and they bring electronic spectral absorbances into experimentally convenient regions. Molecular orbital calculations predict that polynitroarenes will interact strongly with nucleophiles even if no new covalencies form.[7,28] Qualitative descriptions of electronic effects lead to similar conclusions, particularly as regards formation of Meisenheimer complexes.

If strongly electron-withdrawing groups are absent, species such as charge-transfer complexes will probably not be observable. However, our general mechanistic description should still be applicable in that a nucleophile transfers a single electron to the substrate, and species such as **3**, **4**, or **13**, **14** will be steady-state intermediates or transition states. This description has been applied to a variety of nucleophilic (and electrophilic) reactions[29] and fits correlations between nucleophilicity and ionization or oxidation potentials.[30]

Many nucleophilic reactions, especially those of organometallic compounds in apolar solvents, could be written as two-electron transfers, but there is now considerable evidence for single-electron transfers.[10,29-31] The situation is similar for electrophilic reactions,[29c,32] and general models that involve transfer of a single electron from a nucleophile to an electrophile appear to fit the evidence.

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Experimental Section

Materials. 3,5-Dinitrobenzonitrile (Aldrich, mp 128–129 °C) and 3,5-dinitrobenzamide (Lancaster, mp 183–185 °C) were commercial samples, 2,4-dinitrobenzonitrile (mp 103–104 °C) was prepared from the aniline by a modified Sandmeyer reaction,[33] and 2,4-dinitrobenzamide (mp 184–186 °C) was prepared from the acid chloride and NH_3 in dry $CHCl_3$. Samples were recrystallized, and the NMR spectra were fitted to the structures. Dimethyl sulfoxide (DMSO) (Aldrich) was freshly distilled.

Kinetics. Rate measurements were made under first-order conditions at 25.0 °C with a Durrum stopped-flow spectrophotometer for the faster reactions, and with Hewlett-Packard diode array spectrophotometers for the slower reactions. First-order rate constants were calculated by using nonlinear or log-linear least squares programs. Values of τ^{-1} from stopped-flow kinetics were means from three to five runs, and where possible more than one wavelength was used (Tables I, II, and IV). Wavelengths were chosen so as to allow reasonable changes in absorbance in the course of the relaxation and, in some cases, to avoid interference by other relaxations. They do not necessarily correspond to absorbance maxima, which is not a problem provided that Beer's law and first-order kinetics are obeyed. Relaxations that involve interconversions of Meisenheimer complexes, e.g., τ_3 (Tables I and II), give small absorbance changes and could not be followed over the whole range of [OH^-]. Absorbance changes are also small for τ_1 in dilute OH^-. For reasons of solubility we had to take [KOH] < 1 M for reactions in DMSO–H_2O followed on the stopped-flow spectrophotometer. Substrate concentrations were from 10^{-5} to 2×10^{-5} M for relaxations involving Meisenheimer complexes of **1** in DMSO–H_2O 1:1 v/v, and we used 10^{-4} M **1** in water. The concentration of 2,4-dinitrobenzonitrile was 4×10^{-5} M. 2,4- and 3,5-dinitrobenzamide form Meisenheimer complexes and carboxylate ions with OH^- in DMSO–H_2O, and these reactions interfered with measurement of τ_3^{-1} of **11** at high [OH^-]. We therefore followed this relaxation with [OH^-] < 1 M. The problem was less serious for reactions of **1**.

NMR Spectra. Spectra were recorded on a GN-500 spectrometer (500 MHz). Formation of Meisenheimer complexes was so fast that we generally took substrate in excess over OD^-. We used less aqueous solvents than we had used for the kinetic work in order to use relatively high [substrate] to avoid excessively long accumulation times. We sometimes added mesitoate ion as an inert marker to the reaction solutions.

We had to use long delays (ca. 30 s) in quantitative measurements of peak areas for 2,4-dinitrobenzonitrile because the relaxation of H3 is slow (T_1 = 25.4 ± 1.2 s) relative to H5 and H6 (T_1 = 4.70 ± 0.01 s). Therefore we measured peak areas in the reaction mixture under conditions in which reaction had been stopped, e.g., by addition of DCl. We used shorter delay times when we followed NMR signals during reaction and simply needed to identify signals by their chemical shifts and coupling constants. With a delay time of 1.5 s the peak area of the signal of H3 was ca. 50% of the correct value. There was no problem with 3,5-dinitrobenzonitrile where both 4- and 2,6-hydrogens have similar values of T_1 (18.4 ± 0.7 s), and delay times were in the usual range of 1.5 s. We saw unidentified, but relatively weak, signals in the NMR spectra of 2,4-dinitrobenzonitrile. Some of the signals appear during reaction and could be due to formation of small amounts of 2,4-dinitrobenzoate ion and Meisenheimer complexes of the amide.

It is difficult to separate the signals of H4 and H2,6 of 3,5-dinitrobenzonitrile because their chemical shifts are very similar and medium-dependent. When we dissolved the substrate in DMSO-d_6–D_2O 4:1 v/v we saw a doublet at 9.067 ppm, J = 2 Hz and a triplet at 9.009 ppm, J = 2 Hz with areas 2:1. After partial reaction, when KOD was neutralized by added DCl, relative positions of the signals changed and were centered on 9.005 ppm (t, H4) and 8.992 ppm (d, H2,6) relative to $(CHD_2)CD_3SO$ at 2.490 ppm, measured at 45 °C to improve signal separation. Coupling constants did not change (Figure 5).

The line broadening experiments that probed steric effects and compared the behavior of nitrobenzene and *p-tert*-butylnitrobenzene were carried out in ca. 80 vol % DMSO-d_6, and the low solubility of the *tert*-butyl compound limited its usable concentration. We also had planned to use 2,4,6-tri-*tert*-butylnitrobenzene, but it is too insoluble to be useful even in 98 vol % DMSO-d_6.

Kinetic Simulations. Simulations were made with a Hewlett-Packard 310 microcomputer as described earlier.[20] The procedure simultaneously minimizes the sum of absolute errors in τ^{-1} for all the relaxations[34] and is explained in detail in refs 20 and 12 (supplementary material). The error of each simulation is the sum of the differences between predicted and observed values of τ^{-1} divided by the predicted values of τ^{-1} and divided by the number of data points (Tables I and II). The values of the errors are as follows: for 3,5-dinitrobenzonitrile, 11 and 12% in H_2O and DMSO–H_2O, respectively, and for 2,4-dinitrobenzonitrile, 7%. As noted earlier,[12,13,16,20] this procedure does not guarantee a uniquely correct set of numerical values of individual rate and equilibrium constants, but where relaxations can be isolated this treatment agrees with results of simpler methods.[12,20] For example, variations of τ_1^{-1} with OH^- (Figure 1) calculated considering only **1**, **2**, **3**, and **4** (Scheme II) agree with values predicted by our complete simulation. This simple test is feasible only when relaxations are well separated[19,20] and cannot be applied to the data in Figure 2. As noted earlier, procedures give equal weight to all values of τ^{-1}, although the accuracies of measurements are lower in some conditions than in others, especially in dilute OH^- and for interconversion of Meisenheimer complexes where absorbance changes are small, and some relaxations were followed over a wider range of [OH^-] than others (Figures 1, 2, and 4).

3,5-Dinitrobenzonitrile. The UV–vis spectra of the two Meisenheimer complexes were known.[2-6,8] In water we saw four relaxations, but in DMSO–H_2O we saw an additional relaxation as an increase of absorbance at 510 nm, intermediate in rate between τ_2 and τ_3. It had a very low amplitude, and we saw it only with 5×10^{-4} M substrate. The other relaxations were followed with 10^{-5} M substrate, so this additional relaxation made an insignificant contribution to the overall reaction, and we do not include it in the simulation. It probably involved a Meisenheimer complex based on the wavelength, possibly an *ipso* complex, although we saw no phenoxide ion in the final product (cf. ref 8). It also might have been a dihydroxy Meisenheimer complex present in low concentration.

2,4-Dinitrobenzonitrile. Relaxations were followed only in DMSO–H_2O 1:1 v/v, and we used 4×10^{-5} M substrate because much less Meisenheimer complex is formed here than is formed with 3,5-dinitrobenzonitrile. We saw no 3-Meisenheimer complex, although a 3-complex is formed in low concentration in the reaction of OH^- with 2,4-dinitrochlorobenzene.[24,25] A fourth reaction, slower than τ_3 and involving reactions of 2,4-dinitrobenzamide, was not included in the simulation.

Reaction Products. Reaction of 2,4-dinitrobenzonitrile with OH^- gives a mixture of 2,4-dinitrophenoxide ion and amide which is analyzed spectrophotometrically from absorbances at 365 and 404 nm, where the phenoxide absorbs strongly and amide is transparent. The product composition was calculated by using extinction coefficients of 2,4-dinitrophenoxide ion measured under the reaction conditions. Both 2,4- and 3,5-dinitrobenzamide react with OH^- to give the corresponding benzoate ions isolated as acids at the end of reaction.

Both amides form Meisenheimer complexes with OH^- in DMSO–H_2O 1:1 v/v, based on absorbances at ca. 500 nm. The signals appear and gradually disappear, but to see them we used concentrations higher than those used for kinetic studies on the nitriles. We therefore conclude that decomposition of the amides is not complicating kinetic studies on the nitriles.

Absorbance Spectra. We used a diode-array spectrometer to confirm formation and disappearance of Meisenheimer complexes of 2,4-dinitrobenzonitrile during overall reactions. Examples of these spectra are in Figures S1 and S2 (supplementary material), and they show how formation of Meisenheimer complex and 2,4-dinitrophenoxide ion depends upon [OH^-]. Figure S3 shows the relatively slow buildup of the Meisenheimer complex of 2,4-dinitrobenzamide.

Trapping by a Nitroxide Radical. The effect of nitroxide radical **10** upon τ_4^{-1}, which represents disappearance of 2-Meisenheimer complex **6** (Scheme II), was followed at 380 and 500 nm in DMSO–H_2O 1:1 v/v under N_2.

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Supplementary Material Available: Figure S1, absorbance spectra for reaction of 2,4-dinitrobenzonitrile with 0.1 M KOH, Figure S2, absorbance spectra for reaction of 2,4-dinitrobenzonitrile with 2 M KOH in DMSO–H_2O 1:1 v/v, and Figure S3, absorbance spectra for reaction of 2,4-dinitrobenzamide with 2 M KOH in DMSO–H_2O 1:1 v/v (3 pages). Ordering information is given on any current masthead page.

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