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Rate and Equilibrium Studies in Jackson–Meisenheimer Complexes

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François Terrier was born in Gisors, France. He obtained his Ph.D. in 1968 from the University of Paris and did postdoctoral work with Professor Claude F. Bernasconi at the University of California, Santa Cruz. He became Professor of Chemistry at the University of Rouen in 1974 while keeping the responsibility of a research group at the Ecole Nationale Supérieure de Chimie de Paris (L.A. CNRS 161). In addition to kinetics, catalysis, and areas described in this article, he is currently interested in proton transfer processes involving carbon acids and in solvent effects on reaction rates and acid–base equilibria.

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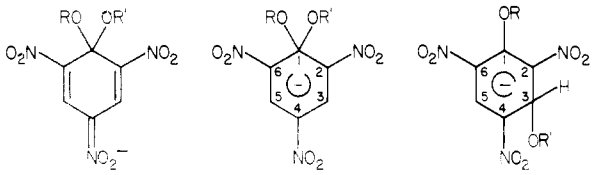
I. Introduction

A. History and Scope

Anionic σ complexes form as stable or transient species from covalent addition of nucleophiles to a substituted or unsubstituted ring carbon atom of electron-deficient aromatic and heteroaromatic substrates. They have been known since 1900 when Jackson and Gazzolo[1] proposed structure 1 for the red-colored



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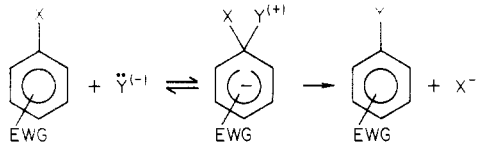
species resulting from reaction of picryl ethers with potassium alkoxides. Since the first chemical evidence for this structure was obtained in 1902 by Meisenheimer,[2] compounds of this type are now commonly referred to as "Jackson-Meisenheimer" or "Meisenheimer" complexes. In the fifties, research in the area was strongly stimulated by Bunnett's proposal[3,4] that most nucleophilic aromatic substitution (S_NAr) reactions involving activated substrates and good leaving groups should proceed by the two-step mechanism shown below where the intermediate 4 is formally



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analogous to 1 (EWG = electron-withdrawing groups). Following this suggestion, many investigations were devoted to the structural characterization of σ complexes. NMR spectroscopy and crystal structure determinations have played a central role in these studies.[5-14] In contrast, if one excepts the pioneering work of Caldin et al. on the reaction of ethoxide ion with some trinitrobenzene derivatives in ethanol[15,16] and related data on a few similar systems,[6-11,13,14] it was not until 1968 that systematic quantitative studies on Meisenheimer complex stability were made or that the kinetics of formation of such complexes were investigated in detail.[9,11,14,17-19] Two main reasons for this late interest are undoubtedly the low stability of most of the complexes known at that time in commonly used protic solvents and the high rates associated with most of the reactions. During the past 12 years, as fast reaction techniques have become widely used[20] and as protic-dipolar aprotic cosolvent systems like water-dimethyl sulfoxide (Me_2SO) or alcohol-Me_2SO mixtures have proven very adequate media to enhance complex stability,[5-14] the number of reports of kinetic and thermodynamic studies has greatly increased. These studies have provided a better understanding of factors influencing formation and decomposition of Meisenheimer complexes and, therefore, of the mechanism of S_NAr reactions.[3-14,21,22]

With the exception of discussion related to nitrogen-bonded complexes which have been the subject of short reviews,[17-19] details of the thermodynamic and kinetic aspects of Meisenheimer complex chemistry are notably absent in published reports.[5-14] An attempt is made here to summarize all the important work which has been done through April 1981. Structural characteristics of the complexes have been extensively reviewed[5-14] and will be referred to only when necessary for understanding mechanistic interpretation. In order to keep the review within reasonable bounds, it will be limited solely to a discussion of anionic σ complexes. In particular, pseudobase formation from covalent addition of hydroxide ion to heterocyclic cations will not be covered. Recently, there has been an excellent review on this subject.[23] The discussion is arranged into sections and, when needed, into subsections on the basis of the nature of the attacking nucleophile and the structure of the aromatics, respectively. Both of these factors are responsible for primary changes in mechanism and reactivity. This also allows rapid location of the various reactions described. Important features related to solvent and salt effects will be considered in special sections at the end of the review. General remarks on complex stability precede the detailed discussion. This provides an introduction and facilitates presentation of the results.

B. General Remarks and Nomenclature

The stability of the adducts depends on the nature and the number of substituents bonded to the anionic ring. Typically, two or three electron-withdrawing groups located ortho and/or para to the site of nucleophilic attack are required to detect anionic σ-complex formation. With polynitro compounds as a point of reference, the replacement of one of the nitro groups by a less electron-withdrawing group has the expected effect of decreasing complex stability. In the case of picryl adducts, crystal-structure determinations[24,25] and molecular orbital calculations[26,27] fully support the quinoid structure 1 where the negative charge is essentially associated with the p-NO_2 group. However, this representation is no longer suitable for benzene or arene complexes lacking a NO_2 group para to the sp^3 carbon. In this review, we will use the more general structure 2, where the negative charge is shown to be delocalized through the ring and any electron-withdrawing substituents. Similar delocalized structures are used for most heteroaromatic complexes.

Conventional nomenclature is generally employed to indicate the position of substituents in the reacting substrates. Exceptions will be indicated. Classical abbreviations are used for some common aromatics, e.g., TNB = 1,3,5-trinitrobenzene, TNA = 2,4,6-trinitroanisole, TNT = 2,4,6-trinitrotoluene, etc. The complexes will, in all cases, be referred to by number to avoid nomenclature problems. When the position of some substituents in the ring must be indicated, for example, to distinguish between isomers, the numbering of the parents is used. The alkoxide adducts 2 and 3 are thus designated as 1,1- and 1,3-dialkoxy complexes, respectively. The complexes formed from addition of 1, 2, or 3 equiv of nucleophile on the same substrate are also referred to as mono or 1:1 adducts, di- or 1:2 adducts, tri- or 1:3 adducts. In accord with previous usage, the terms cyclohexadienylide and cyclopropenide are employed to name the anionic moieties of benzene mono- and diadducts.

Dipolar aprotic solvents greatly enhance the stability of numerous complexes relative to hydroxylic solvents. A great number of kinetic and thermodynamic studies have thus been carried out in water–Me_2SO and methanol–Me_2SO mixtures. Water–dioxane and water–dimethylformamide (DMF) mixtures have also been used in some instances. The composition of such media is indicated by volume percentages or, more simply, by the volume percentage of the dipolar aprotic component.

C. Methods of Investigation

Nucleophilic addition at a ring carbon of an aromatic substrate disrupts the aromaticity, leading to significant changes in electronic conjugation and therefore in the UV–visible absorption of the system.[5-14] Since intense colors are often produced upon complex formation, visible spectroscopy has been a primary tool in kinetic and thermodynamic studies of complex-forming reactions.[9,11,17-19] Typically used substrate concentrations are in the range 10^{-5}–10^{-4} M. Equilibrium constants have been determined either directly, by using well-known procedures such as the Benesi–Hildebrand treatment[28] or acidity function methods,[29-31] or indirectly, from kinetic experiments. The latter are usually conducted under pseudo-first-order conditions with the base or buffer reagents as the excess component; where this is not the case, it will be stated explicitly. Stopped-flow (SF) and temperature-jump (TJ) techniques have been frequently employed.[20] Calorimetric studies,[32-39] radioactive exchange,[40-42] and high-pressure stopped-flow experiments[43,44] have also been used to study complexation.

II. Oxygen-Bonded σ Complexes

More than half of the kinetic and equilibrium studies of Meisenheimer complex formation deal with intermolecular and intramolecular additions of oxygen bases. The basic mechanisms and rate laws encountered in these two types of processes are first considered. The typical mechanisms will be discussed when relevant to the system at hand.

A. Basic Mechanisms

1. Intermolecular Additions

Equation 1 describes the most simple mechanism for intermolecular addition of an oxygen base (R = H, alkyl, aryl) to an aromatic S to give a 1:1 complex, C. On the basis of eq 1, the equilibrium constant K_1 is defined by eq 2 and the observed first-order rate constant k_{obsd} for the equilibrium attainment is given by eq 3. The linear

$$S + RO^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \quad (1)$$

$$K_1 = \frac{[C]}{[S][RO^-]} = \frac{k_1}{k_{-1}} \quad (2)$$

$$k_{obsd} = k_{-1} + k_1[RO^-] \quad (3)$$

dependence of k_{obsd} on $[RO^-]$ has often allowed a facile determination of the rate constants k_1 and k_{-1} for the formation and decomposition of C, respectively.[45]

When RO^- is the lyate ion of the solvent, an alternative way to express equilibrium 1 is the Brønsted-like formulation of eq 4 which emphasizes the acid–base

$$S + ROH \underset{k^{H^+}}{\overset{k^{ROH}}{\rightleftharpoons}} C + H^+ \quad (4)$$

character of the reaction with the pK_a value denoting the pH at which C is half-formed.[46] The equilibrium constant K_a (eq 5) is simply related to K_1 through the

$$K_a = \frac{[C][H^+]}{[S]} \quad (5)$$

$$K_a = K_1K_s \quad (6)$$

ionic product K_s of the solvent by eq 6. Equation 4 also points out that the H^+-catalyzed decomposition of C, a process which has received much attention, is the microscopic reverse of the formation of this complex through nucleophilic attack by the solvent molecules on S. Although this latter pathway is often negligible, examples are known where both solvent molecules and lyate ions compete to form C.[46-48] In these cases, a rigorous analysis of the kinetic data includes a simultaneous consideration of eq 1 and 4.

Such a coupling is illustrated by the equilibrium of 1,3,5-tris(trifluoromethylsulfonyl)benzene (**8**) (S) with its methoxyl complex **9** (C) in methanol.[48] Figure 1 shows the pH–rate profile of the observed first-order rate constant k_{obsd} for this process together with those of the individual first-order rate constants k_f and k_d for formation and decomposition of **9**, respectively. Provided pK_a is known from equilibrium studies, both k_f and k_d can easily be calculated from k_{obsd} at each pH.[46-48] The k_{obsd}–, k_f–, and k_d–pH dependences are consistent with eq 7, 8, and 9, respectively. In the

$$k_{obsd} = k_f + k_d \quad (7)$$

$$k_f = k^{ROH} + k_1[RO^-] \quad (8)$$

$$k_d = k_{-1} + k^{H^+}[H^+] \quad (9)$$

chosen example, k^{ROH} and k_1 refer to attack of **8** by methanol and MeO^- ion, respectively, while k^{H^+} and k_{-1} refer to H^+-catalyzed and spontaneous decompositions of **9**, respectively. Clearly, these rate constants are easily accessible from the two linear portions of each of the k_f and k_d pH–rate profiles. These intersect at pH = pK_a. Of interest is that a comparison of the k_{obsd}–pH profile with those for k_f and k_d immediately reveals the significance of the minimum values of k_{obsd}. Here, k_{obsd} is identical with k_d and k_f at low and high pH, respectively, but close to k_f around pH 9. It is thus apparent that formation of C from solvent attack on S is an important pathway. Such an analysis is so informative that it has been frequently used in studies of cation–pseudobase equilibrations.[23] In fact, it is quite useful in analysis of any system investigated over a large pH range.[49]

Concurrent attack of an oxygen base at two different positions of an aromatic S with formation of two isomeric complexes C_1 and C_2 (eq 10) is frequently ob-

$$S + RO^- \begin{matrix} \overset{k_2}{\rightleftharpoons} C_2 \\ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \end{matrix} \quad (10)$$

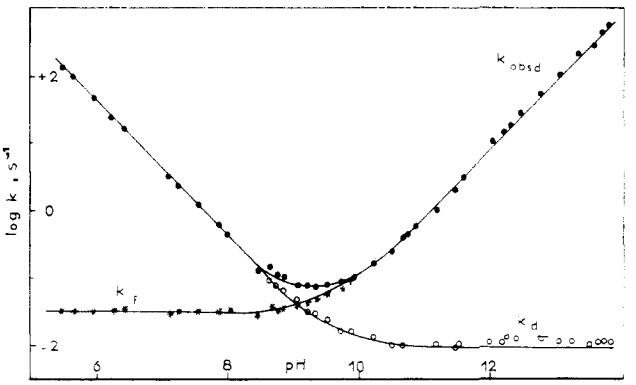


Figure 1. pH dependence of k_{obsd}, k_f, and k_d for the formation and decomposition of the trifluoromethylsulfonyl complex 9 in methanol.[48] I = 0.01 M, t = 20 °C.

served.[50-60] In general, experimental conditions can be found where the interaction occurs in two well-separated steps with one of the two complexes, for example C_2, being formed faster than the other. In such an instance, the first step is the direct equilibration between S and C_2, as described in eq 1-3. The second step is the slower equilibrium formation of C_1 (often thermodynamically much more stable than C_2), from S considered to be in instantaneous equilibrium with C_2. The first-order rate constant k_{obsd} associated with this process is given by eq 11, which predicts a curvilinear

$$k_{obsd} = k_{-1} + \frac{k_1[RO^-]}{1 + K_2[RO^-]} \quad (11)$$

dependence of k_{obsd} on $[RO^-]$ with attainment of a plateau at the base concentrations where there is complete initial formation of C_2.[53,56] Depending upon the system under study, treatment of the data according to eq 3 and 11 and using inversion plots according to

$$\frac{1}{k_{obsd} - k_{-1}} = \frac{1}{k_1[RO^-]} + \frac{K_2}{k_1} \quad (12)$$

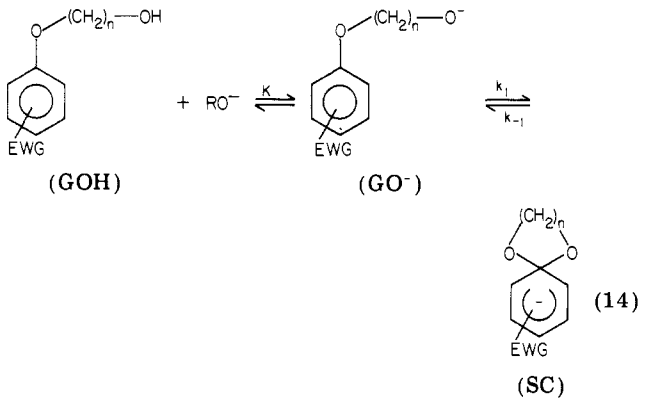
eq 12 lead to a complete or partial determination of the rate and equilibrium parameters. When C_2 isomerizes completely to C_1, the maximum value of k_{obsd} (eq 13) may be used as a reference for its lifetime: $t_{1/2} = 0.693/k_{obsd}^{max}$.[53,56]

$$k_{obsd}^{max} = \frac{k_1}{K_2} = k_{-1}\frac{K_1}{K_2} \quad (13)$$

Regarding eq 10, one should note that the question of whether the actual conversion of C_2 to C_1 takes place by the direct route $C_2 \rightarrow C_1$ rather than by the $C_2 \rightarrow S \rightarrow C_1$ route has been raised.[11,58,61] Although this is a question that kinetic experiments cannot answer, it is generally considered to be unlikely.

2. Intramolecular Additions

The usual mechanism for intramolecular addition of an oxygen base is described by eq 14.[62-68] It involves a rapid proton transfer from the alcohol side chain to base (OH^-, MeO^-) followed by a slower internal cyclization of the formed anion GO^- to give the spiro complex SC. The stoichiometric equilibrium constant K_c associated with the conversion of GOH to SC is defined by eq 16, from which eq 17 is deduced. K_c is generally evaluated from spectrophotometric measurements by



(14)

$$GOH \underset{k_{H^+}}{\rightleftharpoons} SC + H^+ \quad (15)$$

$$K_c = \frac{[SC]}{([GOH] + [GO^-])[RO^-]} \quad (16)$$

$$K_c = \frac{KK_1}{1 + K[RO^-]} \quad (17)$$

$$K_c = KK_1 \quad (18)$$

$$K_a = K_cK_s \quad (19)$$

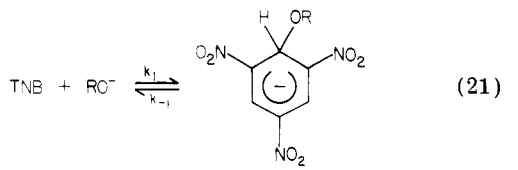
$$k_{obsd} = k_{-1} + \frac{Kk_1[RO^-]}{1 + K[RO^-]} \quad (20)$$

assuming that GO^- anions have extinction coefficients similar to those of the parent GOH. In most cases, the product $K[RO^-]$ is << 1 so that eq 17 reduces to eq 18 and then relation 19 holds between K_c and the equilibrium constant K_a associated with the Brønsted-like formulation of eq 14, i.e., eq 15. Based on eq 14, the observed rate constant k_{obsd} for equilibrium attainment between GOH and SC is given by eq 20. Plots of k_{obsd} vs. $[RO^-]$ are usually linear, in accord with $K[RO^-]$ << 1. The H^+-catalyzed decomposition of SC via the k^{H^+} pathway has been studied in several cases.[68,69]

B. Hydroxy and Alkoxy Complexes

1. Activated 1,3,5-Trisubstituted Benzenes

a. 1,3,5-Trinitrobenzene (TNB). The orange-colored 1:1 complexes **5** formed by the attack of lyate ions



(21)

5a-g

R = (a) H; (b) Me; (c) Et; (d) Pr; (e) i-Pr; (f) *n*-Bu; (g) *i*-Bu; (h) *t*-Bu

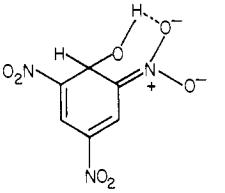
of water and alcohols on TNB in the respective solvents are among the most thoroughly studied Meisenheimer complexes. Reaction 21 is, in fact, a usual reference for any system involving complex formation from RO^- addition to an unsubstituted carbon. Kinetic and thermodynamic data for complexes **5** are listed in Table I,

together with those for complexes derived from other 1,3,5-trisubstituted benzenes.

i. Hydroxy, Methoxy, and Ethoxy 1:1 Complexes (**5a**, **5b**, **5c**). There is satisfactory agreement between the different sets of rate and equilibrium constants measured for formation and decomposition of **5a** and **5b** in aqueous and methanolic solutions, respectively: K_1 ranges from 1.5 to 6.7 L mol^{-1} for **5a**[44,70–79] and from 12.5 to 23.1 L mol^{-1} for **5b**[78,79,84–88] at 20–28 °C. The reaction of ethoxide ion with TNB to give **5c** in ethanol was the first kinetic study ever made of such reaction systems.[15,16] However, the kinetic and thermodynamic parameters derived in this study for formation and decomposition of **5c** do not agree very well with those recently determined.[78,79,90,91] TJ experiments have shown, in particular, that the formation of **5c** is exothermic[78] and not endothermic as initially reported.[15] The reasons for the discrepancies are difficult to assess, since the reaction was studied in media of quite different ionic strengths and at quite different temperatures (in the range −50, −80 °C on the one hand,[15] 10–25 °C on the other[78]). Ion-pairing effects might account for part of the differences (vide infra).

The reversible formation of **5a**, **5b**, and **5c** has been studied in two highly aqueous mixed solvents, namely 22.5% MeOH–77.5% H_2O (v/v) and 19% EtOH–81% H_2O (v/v), which approximate a "common" solvent for the three equilibrium reactions concerned.[81] Going from MeOH and EtOH to these solvents has only a 3- to 4-fold retarding effect on the rate of nucleophilic attack by MeO^- and EtO^- and does not appreciably affect the rates of leaving group departure. Thus, the k_1, k_{-1}, and K_1 reactivity sequences found for **5a**, **5b**, **5c** in the pure solvents are not fundamentally modified. Since steric effects are not important in the addition of OH^-, MeO^-, and EtO^- to TNB, comparison of these parameters is of interest with respect to the relative reactivities of the three bases toward an aromatic carbon. The relative k_1^{RO} values are in the ratio 1:188:918 for **5a**, **5b**, and **5c**, respectively;[78] i.e., they do not correlate at all with the relative Brønsted basicities of OH^-, MeO^-, and EtO^- which are in the ratio 1:0.62:1.80 in water[92] and 1:0.3:1.3 in 2-propanol (*i*-PrOH),[93] respectively. However, this result is in agreement with the general pattern found in other nucleophilic reactions and is attributed to the greater solvation of OH^- compared to MeO^- and EtO^-.[7,94] The higher entropy of activation $\Delta S_1^{\ddagger}$ for k_1^{OH} than for k_1^{MeO} and k_1^{EtO} [78] as well as the observation of a positive volume of activation ($\Delta V_1^{\ddagger}$ = 1.1 cm^3 mol^{-1}) for the formation of **5a**[44] favor this interpretation.

On the basis of the pK_a value of the respective solvents, a reactivity order $k_{-1}^{OH} >> k_{-1}^{MeO} > k_{-1}^{EtO}$ is expected for the k_{-1} values. Instead, these rate constants are in the ratio $k_{-1}^{OH}:k_{-1}^{MeO}:k_{-1}^{EtO}$ = 1:31:2.9, implying an abnormally low k_{-1}^{OH} value. The very high negative entropy of activation ($\Delta S_{-1}^{\ddagger}$ = −122.9 J mol^{-1} K^{-1}) for k_{-1}^{OH} compared to k_{-1}^{MeO} and k_{-1}^{EtO} has been taken as evidence for the existence of intramolecular hydrogen bonding in **5a**, as shown in **6**.[78] This would explain the slow rate of departure of OH in **5a**. In addition, it evidently affects the K_1 sequence which measures the thermodynamic affinity of the three bases for the aromatic carbon of TNB. The K_1 values are in the ratio 1:6.2:324.[78]



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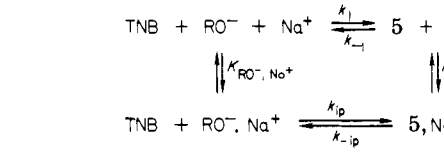
Addition of Me_2SO or DMF to aqueous and methanolic solutions causes the stability of **5a** and **5b** to increase.[82,83,95] K_1 for **5a** is about 10^3-fold greater in 50% H_2O–50% Me_2SO[82] and 40% H_2O–60% DMF[83] than in water while K_1 for **5b** is estimated to be 10^8 times greater in Me_2SO than in methanol.[95] As evidenced by the kinetic results (Table I), this reflects both an increase in k_1 and a decrease in k_{-1}. Going from water to *tert*-butyl alcohol (*t*-BuOH) causes similar changes in the parameters for **5a**.[96] In DMF–D_2O mixtures containing NaOD, the increase in the ease of formation of **5** (R = D) with increasing DMF concentration is paralleled by a decrease in the rate of aromatic proton exchange in TNB.[97]

Decomposition of **5a**, **5b**, and **5c** in acidic medium is very fast. Data for this process have been obtained at low temperatures for **5c** in EtOH.[16] From the values measured for the H^+-catalyzed rate constant k^{H^+} between −50 and −80 °C, a k^{H^+} value of $\sim 10^{10}$ L mol^{-1} s^{-1} is obtained at 25 °C, i.e., close to the diffusion-controlled limit. The reaction was found to be general acid catalyzed with a Brønsted coefficient α of 0.67.[16]

ii. Other alkoxy 1:1 Complexes (**5d**–**5h**). An extensive kinetic study of the reactions of TNB with sodium propoxide in PrOH and sodium isopropoxide in *i*-PrOH has been made.[59,60] The results cannot be interpreted in terms of eq 1. Instead, the scheme (eq 22) where

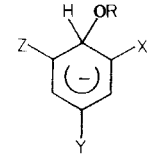


(22)

both the free PrO^- or *i*-PrO^- ions and the sodium propoxide or isopropoxide ion pairs (PrO^-, Na^+; *i*-PrO^-, Na^+) contribute to the formation of **5d** or **5e** is more appropriate. From experiments carried out in the presence of 18-crown-6-polyether or tetramethylammonium propoxide or isopropoxide on the one hand or in the presence of sodium perchlorate or tetraphenylborate on the other, values of the rate constants k_1 and k_{ip} for attack on TNB by free ions and ion pairs, respectively, have been determined.

The reactivities of PrO^- and *i*-PrO^- ions are clearly reduced by ion pairing: the ratio k_1/k_{ip} is equal to 6.5 and 2.15 for *i*-PrO^- and PrO^-, respectively. No difference exists between the rate coefficients k_{-1} and k_{-ip} for decomposition of the unassociated and associated forms of **5d** while, due to its high thermodynamic stability, reliable k_{-1} and k_{-ip} values could not be obtained for **5e**.[59] Although it was not checked, the influence of such ion-pairing effects on the formation of **5c** in EtOH cannot be excluded at relatively high ionic strengths. Indeed, the rate of ethoxide ion attack at the unsubstituted 3-position of 2,4,6-trinitrophenetole to give **3** (R = R′ = Et)[57] is decreased by ion pairing of NaOEt at I = 0.057 M (section IIB2d).

TABLE I. Thermodynamic and Kinetic Parameters for Hydroxy and Alkoxy 1:1 Complexes of 1,3,5-Trisubstituted Benzenes



Cpx	X	Y	Z	R[a]	solvent	t, °C	k_f,[b] L mol^{-1} s^{-1}	k_d,[b] s^{-1}	K,[b] L mol^{-1}	activation and thermodynamic parameters,[c] conditions and comments[d]	ref
5a	NO_2	NO_2	NO_2	H	H_2O	25			3.6, 6.7	isnc	70
						20			6.5	isnc	75
						20			1.5	isnc	72,73
						25			2.7	isnc	74
						28			2.7	isnc	76
						20	27	10.5	2.57	isnc	77
						25	37.5	9.8	3.73	1M NaCl; $\Delta H_f^{\ddagger} = 65.2$; $\Delta S_f^{\ddagger} = 4.6$; $\Delta H_d^{\ddagger} = 30.5$; $\Delta S_d^{\ddagger} = -123$; $\Delta H^{\circ} = 34.7$; $\Delta S^{\circ} = 127.6$	78
						25	25.3	13.4	1.88	0.25 M NaCl	79
						25	33.9	8	4.21	3 M NaCl	81
						25	37.4	9.8	3.8	0.1–0.5 M [OH^-]; $\Delta V_f^{\ddagger} = 1.1$; $\Delta V_d^{\ddagger} = -8.9$; $\Delta V = 10$	44
					H_2O–dioxane						
					90:10	25	49	9.8	5	0.5 M NaCl	80
						25	70	6.5	11.8	0.5 M Me_4NCl	80
					H_2O–MeOH						
					77.5:22.5	25	17.1	10.5	1.63	0.5 M NaCl	81
						25	8.8	8.5	1.03	3 M NaCl	81
					H_2O–EtOH						
					81:19	25	70.2	6.8	10.3	0.5 M NaCl	81
					H_2O–tBuOH						
					80:20	30	140	5	28	isnc	96
					10.1:89.9	30	1.9×10^4			isnc	96
					H_2O–DMF						
					40:60	25			10^3	[TNB] > [OH^-]	83
					H_2O–Me_2SO						
					60:40	20	174	0.5	348	isnc	82
					50:50	20	547	0.145	3770	isnc	82
5b	NO_2	NO_2	NO_2	Me	MeOH	20			16.2	isnc	84
						28			15.4	isnc	85
						25			12.5	isnc	86
						25			13.6	isnc	87
						25			17	isnc	88
						25	7050	305	23.1	0.2 M $NaClO_4$, $\Delta H_f^{\ddagger} = 42.6$; $\Delta S_f^{\ddagger} = -28$; $\Delta H_d^{\ddagger} = 38.5$; $\Delta S_d^{\ddagger} = -68$; $\Delta H^{\circ} = 4.1$; $\Delta S^{\circ} = 40$	78
						25	7700	357	21.6	isnc	79
						25				cd; $\Delta H^{\circ} = 9$; $\Delta S^{\circ} = 52.6$	33
					H_2O–MeOH						
					77.5:22.5	25	2425	254	9.55	0.5 M NaCl	81
						25	2460	134	18.3	3 M NaCl	81
					MeOH–Me_2SO						
					60:40	20			$\approx 1.5 \times 10^4$	isnc	95

5c	NO_2	NO_2	NO_2	Et	EtOH	−80	1.1	4.6×10^{-4}	2390	isnc; $k^{H^+} = 2 \times 10^6$ [e]	15
						20	27500	11.4	2400	isnc; $k^{H^+} \sim 10^{10}$ [e]; $\Delta H_f^{\ddagger} = 46.4$; $\Delta S_f^{\ddagger} = 9$; $\Delta H_d^{\ddagger} = 45$; $\Delta S_d^{\ddagger} = -60$; $\Delta H^{\circ} = 1.4$; $\Delta S^{\circ} = 69$	16
						25	33400	27.5	1210	|TNB| > |EtO^-|; $\Delta H_f^{\ddagger} = 36.4$; $\Delta S_f^{\ddagger} = -36$; $\Delta H_d^{\ddagger} = 43.5$; $\Delta S_d^{\ddagger} = -70.6$; $\Delta H^{\circ} = -7$; $\Delta S^{\circ} = 34.6$	78
						20			1600	isnc	89
						25			2070	unspecified	6
						25	49500	15.4	3100	isnc	79
						25	37000	11.9	3100	isnc	90
						25	49500	15.4	3100	TNB-d_3 + EtO^-; isnc	79
					EtOD	25	95000	37	2570	isnc	79
					H_2O–EtOH 81:19	25	7700	32	241	0.5 M NaCl	81
5d	NO_2	NO_2	NO_2	Pr	PrOH	25	92600	11.9	7800	isnc; $\Delta H_f^{\ddagger} = 30.5$; $\Delta S_f^{\ddagger} = -27$; $\Delta H_d^{\ddagger} = 43$; $\Delta S_d^{\ddagger} = -59$; $\Delta H^{\circ} = -12.5$; $\Delta S^{\circ} = 32$	79
						25	86000	10	8600	$k_{ip} = 40000$; $k_{-ip} = 10$; $K_{ip} = 4000$ [f]	60
5e	NO_2	NO_2	NO_2	iPr	iPrOH	25	96700	1.7	2.04×10^5	isnc; $\Delta H_f^{\ddagger} = 24$; $\Delta S_f^{\ddagger} = -49$; $\Delta H_d^{\ddagger} = 67$; $\Delta S_d^{\ddagger} = -8$; $\Delta H^{\circ} = -43$; $\Delta S^{\circ} = -41$	79
						25	2.6×10^5	≤1	$>3 \times 10^5$	$k_{ip} = 4 \times 10^4$ [f]	59
5f	NO_2	NO_2	NO_2	*n*-Bu	*n*-BuOH	25	94700	5.3	17900	isnc; $\Delta H_f^{\ddagger} = 30$; $\Delta S_f^{\ddagger} = -27$; $\Delta H_d^{\ddagger} = 37.5$; $\Delta S_d^{\ddagger} = -83$; $\Delta H^{\circ} = -7.5$; $\Delta S^{\circ} = 56$	79
5g	NO_2	NO_2	NO_2	*i*-Bu	*i*-BuOH	25	1.26×10^5	1.7	7.4×10^4	isnc; $\Delta H_f^{\ddagger} = 33.4$; $\Delta S_f^{\ddagger} = -16$; $\Delta H_d^{\ddagger} = 46$; $\Delta S_d^{\ddagger} = -70$; $\Delta H^{\circ} = -12;5$; $\Delta S^{\circ} = 54$	79
5h	NO_2	NO_2	NO_2	*t*-Bu	*t*-BuOH	25	38000	<1	>38000	isnc; $\Delta H_f^{\ddagger} = 27$; $\Delta S_f^{\ddagger} = -48$	79
9	SO_2CF_3	SO_2CF_3	SO_2CF_3	Me	MeOH	20	3.9×10^5	0.011	3.54×10^7	$pK_a^{MeOH} = 9.12$; $k^{MeOH} = 3.02 \times 10^{-2}$; $k^{H+} = 2.88 \times 10^7$ [e]	48
11a′	CN	NO_2	NO_2	H	H_2O–Me_2SO 60:40	20	21.8	1.14	19.5	isnc	102
					50:50	20	112	0.3	372	isnc	102
						25	134	0.372	360	isnc; $\Delta H_f^{\ddagger} = 54$; $\Delta S_f^{\ddagger} = -21$; $\Delta H_d^{\ddagger} = 66$; $\Delta S_d^{\ddagger} = -31$; $\Delta H^{\circ} = -12$; $\Delta S^{\circ} = 10$	102
11a	CN	NO_2	NO_2	Me	MeOH	25			1.9	isnc	104
						25			1	af	88
					$MeOH$–Me_2SO 70:30	25			75	isnc	104
					50:50	20	3660	47	78	isnc	102
10a′	NO_2	CN	NO_2	H	H_2O–Me_2SO 50:50	20	19300	4.5	4300	isnc	102
						25	325	9.25	35	isnc; $\Delta H_f^{\ddagger} = 54$; $\Delta S_f^{\ddagger} = -14.5$; $\Delta H_d^{\ddagger} = 56$; $\Delta S_d^{\ddagger} = -35.5$; $\Delta H^{\circ} = -2$; $\Delta S^{\circ} = 21$	102
					40:60	20	600	1.62	370	isnc	102
10a	NO_2	CN	NO_2	Me	$MeOH$–Me_2SO 50:50	20	40000	118	340	isnc	102
11b	CF_3	NO_2	NO_2	H	H_2O–Me_2SO 40:60	20	24.6	0.46	53.5	isnc	102
					30:70	20	126	0.086	1460	isnc	102
					20:80	20	740	<0.01	$>7 \times 10^4$	isnc	102
11b	CF_3	NO_2	NO_2	Me	MeOH	25			0.012	af	88
					$MeOH$–Me_2SO 50:50	20	1180	48	23.6	isnc	102
					40:60	20	4300	13	330	isnc	102
					30:70	20	10000	4.6	2180	isnc	102

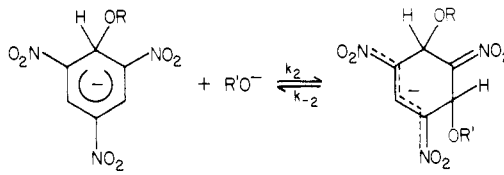
TABLE I (*Continued*)

Cpx	X	Y	Z	R[a]	solvent	t_1, °C	k_f,[b] L mol^{-1} s^{-1}	k_f,[b] s^{-1}	k_d,[b] s^{-1}	K,[b] L mol^{-1}	activation and thermodynamic parameters,[c] conditions and comments[d]	ref
10b′	NO_2	CF_3	NO_2	H	H_2O-Me_2SO							
					40:60	20	60	19		3.1	isnc	102
					30:70	20	375	6		94	isnc	102
					20:80	20	2340	0.6		3900	isnc	102
10b	NO_2	CF_3	NO_2	Me	MeOH-Me_2SO							
					30:70	20	36000	150		240	isnc	102
11c	SO_2Me	NO_2	NO_2	Me	MeOH	25				0.50	af	88
11d	COOMe	NO_2	NO_2	Me	MeOH	25				6×10^{-3}	af	88
11e	I	NO_2	NO_2	Me	MeOH	25				8.9×10^{-4}	af	88
11f	$CONEt_2$	NO_2	NO_2	Me	MeOH	25				1.1×10^{-4}	af	88
11g	SMe	NO_2	NO_2	Me	MeOH	25				3.9×10^{-5}	af	88
11h	SO_3^-	NO_2	NO_2	Me	MeOH	25				10^{-4}-10^{-5}	af	88
11i	H	NO_2	NO_2	Me	MeOH	25				10^{-6}	af	88
					MeOH	25				5×10^{-7}	af	9
					MeOH-Me_2SO							
					10:90	20	1625	20.5		79	isnc	108

[a] Sodium or potassium hydroxide or alkoxides. [b] k_f, k_d, and K represent k_1, k_{-1}, K_1 or k_2, k_{-2}, K_2 as defined by eq 1, eq 21, and 25. [c] Enthalpies in kJ mol^{-1}, entropies in J mol^{-1} K^{-1}; activation and reaction volumes in cm^3 mol^{-1}. [d] Abbreviations: isnc = ionic strength not constant; af = acidity function method; cd = calorimetric determination. [e] k^{H^+} in L mol^{-1} s^{-1}; k^{MeOH} in s^{-1}; as defined by eq 4. [f] k_{ip1}, k_{-ip}, and K_{ip} are the rate and equilibrium constants defined by eq 22.

Equilibrium and kinetic data are available for attack of lyate ions of *n*-butyl, isobutyl and *tert*-butyl alcohol on TNB.[79] Surprisingly, ion-pairing effects were not reported to affect the course of the reactions, and the data have been worked out in terms of eq 1. The lower rate coefficient for *t*-BuO^- attack on TNB as compared with those for PrO^-, *i*-PrO^-, *n*-BuO^-, and *i*-BuO^- probably reflects steric hindrance to approach of the large *t*-BuO^- ion (F strain).

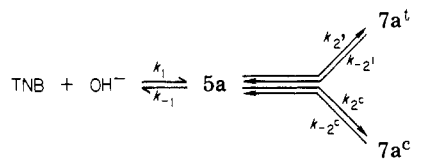
iii. 1:2 Complexes. As the base concentration is increased, conversion of the monoadducts into the diadducts **7** may occur according to eq 23. The kinetics



(23)

5a	R = R′ = H	7a
5b	R = R′ = Me	7b
5c	R = R′ = Et	7c
	R = H; R′ = Me	7d
	R = H; R′ = Et	7e

of formation of the dihydroxy complex **7a** was thoroughly studied in water and, together with those of **7b** or **7c**, in 22.5% MeOH-77.5% H_2O (v/v) and 19% EtOH-81% H_2O (v/v).[98] Since each 1:2 complex may form as a mixture of cis and trans isomers, three relaxation effects were in principle expected for the conversion of TNB into **7a** according to eq 24 where the



(24)

superscripts "c" and "t" refer to cis and trans. Instead, only two relaxation times were observed, suggesting that one of the two isomers does not form. By applying the principles of normal coordinates to chemical reactions,[20] it was shown that in the not unlikely event where the cis and trans isomers dissociate with similar rates, i.e., $k_{-2}^c = k_{-2}^t$, one of the relaxation times would not be observable in a SF experiment. On this basis, it was concluded that cis-trans isomerism in **7a** cannot be ruled out. However, ^1H NMR evidence for such isomerism has not been obtained so far.

Due to the competition between OH^- and RO^- ions, three 1:2 complexes, namely **7a**, **7b** (or **7c**), and **7d** (or **7e**), can form in mixed solvents. This should give rise to three relaxation effects in addition to those for 1:1 complex formation. Instead, only two, which have been attributed to **7a** and **7b** (or **7c**), were observed by SF. A normal coordinate analysis of the systems[20,98] again shows that detection of the missing relaxation effect is not possible if two of the diadducts; i.e., **7b** and **7d** or **7c** and **7e**, decompose with similar rates. Just as for **7a**, experiments have failed to provide evidence for cis-trans isomerism in **7b** and **7c**.

As for the 1:1 complexes, the stabilities and the rates of formation of the diadducts **7** are in the order EtO^- > MeO^- >> OH^- (Table II). On the other hand, diadduct formation is very much slower than that of the adducts **5** with all three bases. This result, which has

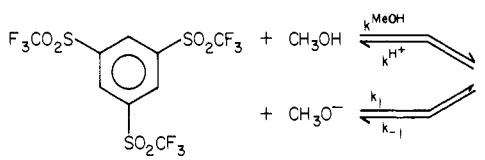
TABLE II. Rate and Equilibrium Constants for Hydroxy and Alkoxy 1:2 Complexes 7 of TNB (t = 25 °C)[a]

	R, R' =	solvent	k_2, L mol^{-1} s^{-1}	k_{-2}, s^{-1}	K_2, L mol^{-1}	ionic strength (NaCl)
7a	H	H_2O	0.022	0.082	0.27	2 M
			0.057	0.068	0.84	3 M
		H_2O-MeOH 77.5:22.5		0.11		3 M
		H_2O-EtOH 81:19		0.07		3 M
7b	Me	H_2O-MeOH 77.5:22.5	7.5	0.20	37	3 M
7c	Et	H_2O-EtOH 81:19	45	0.20	225	3 M

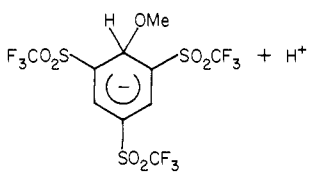
[a] Reference 98. [b] k_2, k_{-2}, and K_2 as defined by eq 23.

been observed for other diadducts (section III), arises from a transition-state effect, which can be seen by a comparison of the rate parameters for **5c** and **7c** in 19% EtOH–81% H_2O (v/v) at I = 3 M. The equilibrium constants K_1 and K_2 are about the same, while the ratios k_1/k_2 and k_{-1}/k_{-2} are quite different: k_1/k_2 = 171; k_{-1}/k_{-2} = 214. The marked dependence of the parameters on the ionic strength I, as expected for the charge type of reaction 23, should also be noted. The transient formation of **5a** is not observed in the acid decomposition at **7a**,[99] but this does not necessarily suggest that the reaction takes place other than via **7a** → **5a** → TNB.

b. 1,3,5-Tris(trifluoromethylsulfonyl)benzene. The aromatic 8 has just recently been synthesized and its conversion into **9** studied.[48] The results are remarkable in that, in contrast to its trinitro analogue **5b**, **9** forms at an appreciable extent in MeOH even in the absence of any added methoxide. The pK_a^{MeOH} for formation of **9** is 9.12 as compared with a pK_a^{MeOH} of 15.51 for **5b** (at 20 °C). The kinetics of formation and decomposition of **9** were investigated over a large pH range (Figure 1), and we have used the data to illustrate the coupling of eq 1 and 4 (section IIA). Formation of **9** from methanol attack on **8** is an important pathway between pH 9 and 10: k^{MeOH} = 3.02 × 10^{-2} s^{-1}. There are no other reports (in benzene series) of such rapid MeOH attack at an unsubstituted carbon to give a methoxy σ complex. The very strong electron-withdrawing character of the SO_2CF_3 group[100] is responsible for the unique reactivity of **8**. Another noteworthy result is the high susceptibility of **9** to H^+-catalyzed decomposition: k^{H^+} = 2.88 × 10^7 L mol^{-1} s^{-1} (at 20 °C). This suggests k^{H^+} values close to the diffusion-controlled limit for less stable complexes like **5b**.

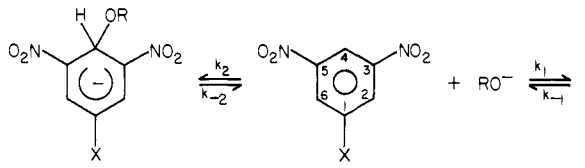


8

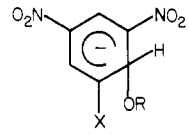


9

c. 1-X-3,5-dinitrobenzenes (1-X-3,5-DNB). Due to the nonequivalence of the 2- and 4-positions, there is the possibility of isomeric addition of RO^- to 1-X-3,5-DNB with formation of the complexes **10** and **11**.



10 1-X-3,5-DNB



(25)

11

R = Me, X = (a) CN; (b) CF_3; (c) SO_2Me; (d) COOMe; (e) I; (f) $CONEt_2$; (g) SMe; (h) SO_3^-; (i) H
R = H, X = (a') CN; (b') CF_3; (i') H

Both types of adducts have been characterized by visible spectroscopy in the reactions of OH^- and MeO^- with a number of such substrates in Me_2SO.[88,101-104] Initial addition of the base preferentially occurs at C-4 to give **10**, which subsequently rearranges to the thermodynamically favored complex **11**. In some cases (X = SO_2Me, $CONEt_2$, SO_3^-, SMe, H) conversion of **10** to **11** is complete or nearly so.[88] However, the proportion of **10** present at final equilibrium is in the range 5–10% when X = CF_3, CN[101,102] and 27% when X = COOMe.[88] ^1H NMR experiments have confirmed the structure of both **10** and **11** for X = CN, CF_3, COOMe, and COOEt.[61,101,104]

Equilibrium formation of **11** (R = Me) was studied by visible spectroscopy in MeOH and MeOH–Me_2SO mixtures containing 0.098 M NaOMe.[88] The results allowed the simultaneous determination of the thermodynamic values of the equilibrium constant K_1, referred to pure MeOH as solvent, and the J_M acidity function for these media.[88] The order of stabilities parallels the electron-withdrawing power of X.

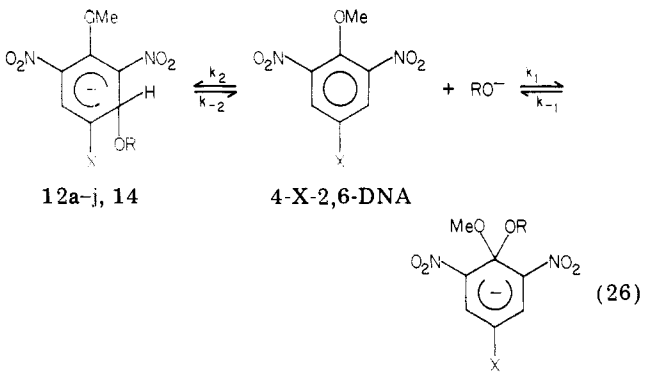
The kinetics of the interaction of OH^- and MeO^- with 3,5-dinitrobenzonitrile and benzotrifluoride (X = CN, CF_3) were studied by SF in H_2O–Me_2SO and MeOH–Me_2SO mixtures.[101,102] Increasing the amount of Me_2SO in the mixtures enhances the stability of both adducts **10** and **11** to about the same extent. MeO^- and OH^- attack C-4 to give **10a**, **10b** and **10a'**, **10b'** only 2–3 times faster than they attack C-2 to give **11a**, **11b** and **11a'**, **11b'**, but these latter complexes decompose at much lower rates than their isomers: the ratios k_{-2}/k_{-1} are equal to about 25 and 50 for X = CN and CF_3, respectively. The parameters (Table I) have been derived from experiments conducted at base concentrations where the relative rates of formation of **10** and **11** are mainly governed by the ratio k_{-2}/k_{-1}. Then the interaction consists of two sufficiently well-separated steps for an analysis of the data in terms of eq 10. In flow-NMR experiments where such conditions are not fulfilled, the reactions initially yield a mixture of **10** and **11** in a ratio close to the k_2/k_1 values.[61] The lower stability of **10** relative to **11** is attributed to the effect of the NO_2 group located in the position para to the sp^3 carbon of **11**.[88,101,102] Due to its greater ability to delocalize electrons by resonance,[26,27] a p-NO_2 group generally exerts a very strong stabilizing effect on Meis-

enheimer complexes and is a factor of overwhelming importance in determining their relative stabilities (section VII). Interestingly, the activation and thermodynamic parameters determined in 50% H_2O-50% Me_2SO for **10a'** and **11a'** are all very similar, with the exception of $\Delta H^{\ddagger}$ for their decomposition.[102] The higher enthalpy of activation for the decomposition of **11a'** as compared with that of **10a'** ($\delta\Delta H^{\ddagger}$ = 9.6 kJ mol^{-1}) must essentially reflect the stabilizing effect of the *p*-NO_2 group on **11a'**.

The kinetics of the reaction of 1,3-dinitrobenzene (X = H) with MeO^- was investigated in 90% Me_2SO-10% MeOH.[108] No evidence for the transient formation of **10i** was found in this solvent, and only k_1, k_{-1}, and K_1 for **11i** were determined. Evidence for **10i'** and **10i** was obtained in 98% Me_2SO-2% H_2O (MeOH) by means of a rapid scan spectrophotometer.[105-107]

2. *Activated 2,4,6-Trisubstituted 1-Alkoxybenzenes*

a. 4-X-2,6-Dinitroanisoles (4-X-2,6-DNA). Methoxide addition to substituted 4-X-2,6-DNA in MeOH-Me_2SO mixtures has been the subject of many investigations (see ref 30–33, 37, 38, 40, 41, 43, 44, 50–53, 56, 108–124). In all cases, addition to the unsubstituted C-3 to give the 1,3-dimethoxy complexes **12** is kinetically favored, but rearrangement occurs to give the 1,1-dimethoxy complexes **13**. For most substituents X (NO_2, SO_2CF_3, CN, SO_2Me, CHO, COOMe), complexes **13** are thermodynamically much more stable products so that their detection in a given solvent requires much lower base concentrations than that of their 1,3-isomers **12**. This allows the formation of these complexes to be studied either directly according to eq 1 or indirectly as the second step of eq 10. Reactions of TNA with OH^- and EtO^- resemble reaction with MeO^- and result in initial formation of **14a** and **14b**.[67,136,137] Addition of OH^- to C-1 is about 10-fold slower than at C-3 but is followed by nucleophilic displacement of OMe to give picrate anion[136] (**15a** is undetected). There is also nucleophilic displacement of OMe by OH^- within **14a**.[136] **14b** is rapidly converted into the most stable 1,1-complex **15b** in EtOH.[137] Table III gives the most representative kinetic and thermodynamic data obtained for complexes **12**, **13**, **14**, and **15**.



12, 13, R = Me; X = (a) NO_2; (b) SO_2CF_3; (c) CN; (d) SO_2Me; (e) CHO; (f) COOMe; (g) CF_3; (h) Cl; (i) F; (j) H

14, 15, (a) R = H, X = NO_2; (b) R = Et; X = NO_2

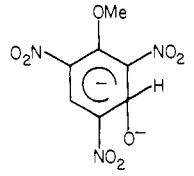
i. 1,1 Complexes. Direct equilibration between TNA and **13a** was studied by different authors in MeOH, but notable differences exist between the values reported for the k_1, k_{-1}, and K_1 rate and equilibrium constants associated with the reaction (see ref 43, 44, 52, 109, 110, 113, 114, 121, 124). The main reason for this discrepancy lies in the unfavorably high stability of **13a** which is completely formed in a 5×10^{-3} M NaOMe solution. Since carbon dioxide may interfere at lower MeO^- concentrations, the results obtained by Fendler et al. in the 10^{-3}–10^{-2} M range are considered to be the most reliable.[113] The linear response of k_{obsd} (eq 3) on [MeO^-] confirms that **12a** does not form prior to **13a** in such experimental conditions. Interestingly, the k_{-1}, $\Delta H_{-1}^{\ddagger}$, and $\Delta S_{-1}^{\ddagger}$ values obtained in this work agree extremely well with those determined by carbon-14 exchange techniques[40,41] while the k_1 value is close to the one recently determined from high-pressure SF experiments.[43,44] The observation by Crampton[119,123] that the 1,1-complexes **13** have a particular tendency to associate with cations like K^+ or Na^+ in MeOH may also account for part of the differences in k_1, k_{-1}, and K_1 for **13a**. A detailed discussion of this phenomenon which does not concern complexes like **5b** or **12** arising from MeO^- attack at an unsubstituted carbon is made in section IX together with the analysis of salt and micellar effects on the decomposition of **13a**.[125-128] Direct equilibration between TNA and **13a** was thoroughly investigated in MeOH-Me_2SO mixtures.[37,38] In addition to the k_1, k_{-1}, and K_1 values, the heats of reaction as well as the heats of transfer for both the reactants and this complex were measured.[37,38] These data are of primary importance to discuss the effect of Me_2SO on complex formation (see section VIII). At low MeOH contents in water-MeOH mixtures, k_1 is not significantly changed but there is a decrease in k_{-1} and therefore a concomitant increase in the stability of **13a**.[129] The formation of the ethoxide complex **15a** was investigated in the temperature range of -20, +10 °C in EtOH.[137]

Replacing the 4-NO_2 group of TNA by a SO_2CF_3 group causes a 60-fold increase in the stability of the 1,1 complex.[56] Formation of **13b** is complete at [MeO^-] = 5×10^{-4} M so that buffer solutions must be used to study the reaction. The pK_a^{MeOH} for formation of **13b** is 10.68 at 20 °C. Analysis of the data by coupling eq 1 and 4 is necessary because methanol attack on the parent ether contributes for about 10–15% of the formation of **13b** between pH 10 and 11.[56] In contrast, replacing the 4-NO_2 group by a less electron-withdrawing function has the expected effect of decreasing the stability of **13**.[31,56,119-123] The stability order is SO_2CF_3 > NO_2 > CN, SO_2Me > CHO > COOMe > CF_3 > Cl > F, H.

ii. 1,3 Complexes. The 1,3-complex **12a** was first detected by Servis[111] in Me_2SO where its conversion into **13a** is complete within a few minutes. Addition of MeOH strongly catalyzes the isomerization and the observation of **12a** is no longer possible by NMR in 50% Me_2SO-50% MeOH. In MeOH, the fast transient formation of **12a** was detected only at [MeO^-] ≥ 0.05 M and kinetically studied at different temperatures in a SFTJ apparatus.[52] The reaction is endothermic (ΔH_2° = 6.18 kJ mol^{-1}) and not exothermic as reported in a calorimetric study of the system.[33] The 1,3-complex **12b** is 12-fold more stable than **12a**, in agreement with the greater electron-withdrawing effect of an *o*-SO_2CF_3 group relative to an *o*-NO_2 group.[56] Other complexes

are less stable than **12a** and were detected only in the presence of Me_2SO cosolvent.[50,51,56,113,118,122] In the case of X = H, the 1,3-complex **12j** was observed by SF in 98% Me_2SO-2% MeOH.[51]

At high [OH^-] in water, ionization of the hydroxy group of the 1,3-complex **14a** occurs to give the dianion **16**. The solvent deuterium isotope effect on the rate



16

constant k_{-2} for hydroxide ion departure from **14a** is $k_{-2}^{H_2O}/k_{-2}^{D_2O} = 1.72$.[67] The formation of **14b** has been studied at very low temperatures (-80, -60 °C).[137]

iii. Mechanism of 1,3 vs. 1,1 Addition. A clear picture of the mechanism emerges from Table III. On the one hand, the 1,3 complexes which arise from base addition at the unsubstituted 3-carbon have high rate coefficients but a relatively low thermodynamic stability. Kinetic and thermodynamic parameters for the 1,3-dimethoxy complexes **12** compare well with those for the methoxy complexes **11** (R = Me) of 1-X-3,5-DNB. Similarly, the parameters for the hydroxy complex **14a** are similar to those obtained for the TNB complex **5a**. On the other hand, the 1,1 complexes form and decompose much more slowly, but they have in most cases a greater stability than their 1,3 isomers. The energy diagram of Figure 2 illustrates the interaction in the case of the reaction of MeO^- with TNA. The most striking feature in this diagram is the much higher enthalpy of activation $\Delta H^{\ddagger}$ for the decomposition of **13a** relative to that for **12a**.

The TNA-MeO^- system has been the most discussed (see ref 9, 11, 14, 17, 52, 57, 78, 85, 113, 130, 131). The greater stability of **13a** relative to **12a** was attributed to the release of steric strain from the molecule and to the stabilizing influence of the two methoxyl groups at the sp^3 carbon.[9,11,52,78,109] To account for the slower attack of MeO^- ions at C-1 than at C-3, it was first suggested that **13a** is less strained than TNA but the transition state leading to it is sterically more strained than TNA.[109,130] In contrast, steric effects should be unimportant in the transition state leading to **12a**. This explanation has been criticized since it is difficult to visualize why steric strain should maximize in the transition state.[78] Thus, a recent interpretation in terms of steric hindrance of approach of the reagent (F strain) has been proposed.[57,131] According to Bernasconi,[17,52,78] the main factor may be the stabilization, through a resonance interaction of the OMe group and nitro aromatic ring, of TNA and **12a**, and thus also of the transition state leading to this complex (structures **17a**, **17b** and **18a**, **18b**). Such stabilization is not possible in **13a** and thus probably very little in the corresponding transition state. This effect could reduce the rate of its formation relative to **12a**. Isomeric addition of OH^- and EtO^- on TNA may be interpreted along similar lines.

Since all 4-X-2,6-DNA present the same steric strain around C_1,[117,132] it is clear that the nature of X is an additional factor of major importance in determining

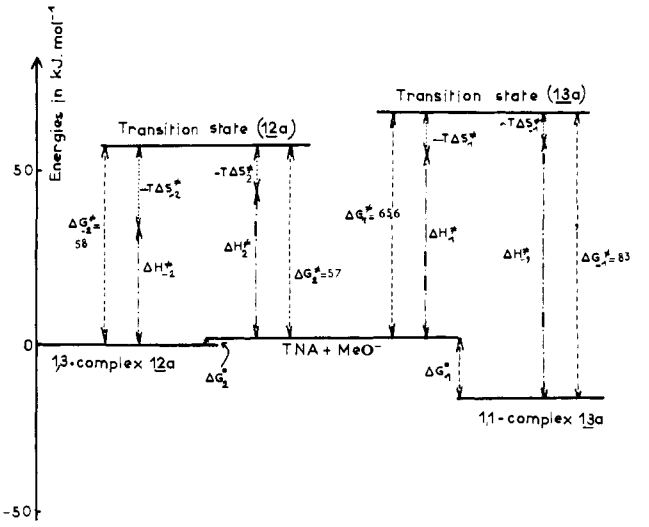
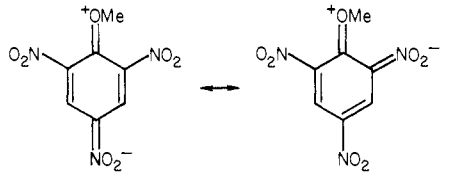
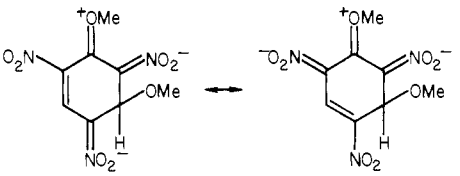


Figure 2. Energy diagram for the reaction of TNA with methoxide ion to give the 1,3 and 1,1 complexes **12a** and **13a** in methanol.



17a 17b

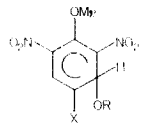


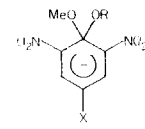
18a 18b

the relative stabilities as well as the relative rates of formation and decomposition of **12** and **13**.[53,56] This is clearly shown in Table IV. It can be noted that the ratio k_2/k_1 increases from X = SO_2CF_3 to X = F, i.e., as the electron-withdrawing ability of X which is para to C-1 but ortho to C-3 decreases. The value of k_2/k_1 for X = NO_2 is, however, abnormally high with respect to the series. On the other hand, the ratio k_{-2}/k_{-1} decreases from X = NO_2, SO_2CF_3 to X = F. As a result, going from X = SO_2CF_3 to X = F causes a much larger decrease in K_1 for 1,1-complex formation than in K_2 for 1,3-complex formation. The ratios $K_1^{SO_2CF_3}/K_1^{F}$ and $K_2^{SO_2CF_3}/K_2^{F} = 1.6 \times 10^{10}$ and 1.5×10^5, respectively.[56] The greater stability of the fluoro 1,3-complex **12i** relative to the 1,1-analogue **13i**[51] clearly emphasizes the importance of these structural changes, the general observation being that complex stability is more sensitive to changes in the substituent para to the site of nucleophilic attack than ortho to it.[133] The abnormal value of k_2/k_1 for X = NO_2 probably reflects the fact that resonance stabilization as described in **17** and **18**[52,78] should be much more important in the TNA system than in the other anisoles systems due to the greater electron-delocalizing ability of a *p*-NO_2 group relative to other substituents.

Figure 3 shows that approximately parallel straight lines are obtained on plotting log k_1, log k_2 as well as log k_{-1}, log k_{-2} vs. the mole fraction of Me_2SO. While the existence of such correlations is probably fortui-

TABLE III. Kinetic and Thermodynamic Parameters for 1,1- and 1,3-Complexes of 4-X-2,6-Dinitroanisoles





X	R[a]	solvent	t, °C	Cpx	k_2,[b] L mol^{-1} s^{-1}	k_{-2},[b] s^{-1}	K_2,[b] L mol^{-1}	Cpx	k_1,[b] L mol^{-1} s^{-1}	k_{-1},[b] s^{-1}	K_1,[b] L mol^{-1}	activation and thermodynamic parameters;[c] conditions and comments[d]	ref
NO_2	Me	MeOH	25	12a				13a	~4	5×10^{-4}	7700	isnc	109
			25						4.55	2.01×10^{-3}	2260	isnc	110
			25							5×10^{-4}		^{14}C exchange; $\Delta H_{-1}^{\ddagger} = 78.6$; $\Delta S_{-1}^{\ddagger} = -3.7$	40, 41
			20						10.33	5×10^{-4}	20600	isnc	114
			25		950	350	2.71					0.5 M $NaClO_4$; $\Delta H_2^{\ddagger} = 43.5$; $\Delta S_2^{\ddagger} = -45$ $\Delta H_{-2}^{\ddagger} = 34$; $\Delta S_{-2}^{\ddagger} = -80.5$; $\Delta H_2^{\circ} = 9.5$; $\Delta S_2^{\circ} = 35.5$	52
			25									cd; $\Delta H_2^{\circ} = -6$; $\Delta H_1^{\circ} = -20$; $\Delta S_1^{\circ} = 12.5$	33
			25						17.3	1.04×10^{-3}	17000	isnc; $\Delta H_1^{\ddagger} = 54$; $\Delta S_1^{\ddagger} = -39$; $\Delta H_{-1}^{\ddagger} = 77$; $\Delta S_{-1}^{\ddagger} = -20$; $\Delta H_1^{\circ} = -23$; $\Delta S_1^{\circ} = -19$	113
			25						15.4			HPSF; $\Delta V_1^{\ddagger} = -7.2$; $\Delta V < 0$	43, 44
			25						14			isnc; $\Delta H_1^{\ddagger} = 44.7$; $\Delta S_1^{\ddagger} = -53.5$	197
			25						13.9	1.10×10^{-3}	12600	isnc; $\Delta H_1^{\ddagger} = 38$	124
		MeOH–Me_2SO											38
		90:10	25						39.3	4.25×10^{-4}	92600	isnc; cd; $\Delta H_1^{\circ} = -27$; $\Delta S_1^{\circ} = 5$	38
		80:20	25						48	2.60×10^{-4}	1.85×10^5	isnc; cd; $\Delta H_1^{\circ} = -29$; $\Delta S_1^{\circ} = 3$	38
			25		2450	95	33		44			isnc	135
		70:30	25						88.3	1.90×10^{-4}	4.65×10^5	isnc; cd; $\Delta H_1^{\circ} = -35.5$; $\Delta S_1^{\circ} = -10$	38
		MeOH–H_2O											
		3.17:96.83	25						18	5.5×10^{-4}	3.3×10^4	isnc; $\Delta H_1^{\ddagger} = 52$; $\Delta S_1^{\ddagger} = -46$; $\Delta H_{-1}^{\ddagger} = 73$ $\Delta S_{-1}^{\ddagger} = -62$; $\Delta H_1^{\circ} = -21$; $\Delta S_1^{\circ} = 16$	129, 138
NO_2	H	H_2O	25	14a	12	8.3	1.4	15a	1.4			2 M NaCl	136
			25		12	8.4	1.4					1 M NaCl	136
			25		7.37	8.90	0.83					isnc	67
			20		8.3	7	1.18					isnc	77
	D	D_2O	25			5.18						isnc; $k_{-2}^{H_2O}/k_{-2}^{D_2O} = 1.72$	67
NO_2	Et	EtOH	−60	14b	1.03	1.96×10^{-2}	52	15b				isnc; $k_2^{H^+} = 2.65 \times 10^6$ at −70° [e,f]	137
			25		3690	472	7.3		20.2			isnc; $k_1^{H^+} = 6 \times 10^6$ at +10 °C;[e] $\Delta H_1^{\ddagger} = 52$; $\Delta S_1^{\ddagger} = -35$; $\Delta H_{-1}^{\ddagger} = 73$ to 83; $\Delta H_1^{\circ} = -20$ to −30; $\Delta H_2^{\ddagger} = 41$; $\Delta S_2^{\ddagger} = -39$; $\Delta H_{-2}^{\ddagger} = 55$; $\Delta S_{-2}^{\ddagger} = -9$ $\Delta H_2^{\circ} = -14$; $\Delta S_2^{\circ} = -30$	137
SO_2CF_3	Me	MeOH	20	12b	750	25	30	13b	141	1.17×10^{-4}	1.2×10^6	0.01 M buffer salts; $k_1^{MeOH} = 5 \times 10^{-5}$ [i] $k_1^{H^+} = 1.66 \times 10^6$ [e]	56
		MeOH–Me_2SO											
		80:20	20		2300	3.7	620		450			isnc	56
CN	Me	MeOH	25	12c				13c	6.1	0.022	280	isnc; $\Delta H_1^{\ddagger} = 55.5$; $\Delta S_1^{\ddagger} = -43$; $\Delta H_{-1}^{\ddagger} = 38$; $\Delta S_{-1}^{\ddagger} = -133$; $\Delta H_1^{\circ} = 17.5$; $\Delta S_1^{\circ} = 90$	113
			43								2.46	LiOMe	115
			20		60[g]	420[g]	0.14[h]		2.82	0.017	168	isnc	118
		MeOH–Me_2SO											
		80:20	20		190	128	1.48		7.07	6.5×10^{-3}	1090	isnc	118
		50:50	20		2460	11	224		60	8.5×10^{-4}	70500	isnc	118
		30:70	20		14800	1.85	8000		251			isnc	118

SO_2Me	Me	MeOH	20	12d	35[g]	440[g]	0.08[h]	13d	1.75	0.017	101	isnc	56
		$MeOH–Me_2SO$											
		80:20	20						5.8	8×10^{-3}	720	isnc	56
		60:40	20		362	30	12		17	1.36×10^{-3}	12500	isnc	56
		40:60	20		3160	5.5	575		117			isnc	56
CHO	Me	MeOH	25	12e				13e			210	isnc; LiOMe	122
COOMe	Me	MeOH	25	12f				13f	0.36	0.06	6	isnc	119
											5.5	isnc; n-Bu_4NOMe	120
CF_3	Me	MeOH	20	12g	2.5[g]	1400[g]	1.8×10^{-3} [h]	13g			5	isnc	56
			20								2	af	30
			25								2	isnc	119
			25								1.2	NaOMe with crown ether	123
		$MeOH–Me_2SO$											
		20:80	20		5500	2.75	2000		152	0.013	11700	isnc	51
		15:85	20		10000	1.18	8500					isnc	51
Cl	Me	MeOH	20	12h	2[g]	2000[g]	0.001[h]	13h	0.012[g]	5[g]	2.5×10^{-3} [h]		56
			25								4.3×10^{-3}	af	31
		$MeOH–Me_2SO$											
		25:75	20		725[g]	5.95[g]	120		4.65	0.011	420	isnc	51
		20:80	20		1260	2.80	440		10	6.85×10^{-3}	1460	isnc	51
		10:90	20		5250	0.74	7100		30	1.44×10^{-3}	20800	isnc	51
F	Me	MeOH	20	12i	1[g]	5000[g]	2×10^{-4} [h]	13i	2.5×10^{-3} [g]	30[g]	8.5×10^{-5} [h]		56
		$MeOH–Me_2SO$											
		15:85	20		1260	4.67	270		3.47	0.021	165	isnc	51
		10:90	20		2820	2.24	1260					isnc	51
H	Me	MeOH	20	12j				13j	1.5×10^{-3} [g]	20[g]	7.5×10^{-5} [h]		56
			20								3.63×10^{-4}	af	30
			25								9×10^{-5}	af	31
		$MeOH–Me_2SO$											
		10:90	20						4.17	6.2×10^{-3}	675	isnc	134

[a] Sodium or potassium hydroxides or alkoxides unless indicated otherwise. [b] Rate and equilibrium constants as defined by eq 26. [c] Enthalpies in kJ mol^{-1}; entropies in J mol^{-1} K^{-1}; activation and reaction volumes in cm^3 mol^{-1}. [d] Abbreviations: HPSF = high-pressure stopped-flow experiments; see Table I for others. [e] $k_1^{H^+}$, $k_2^{H^+}$ in L mol^{-1} s^{-1}, are defined by eq 4 and refer to the H^+-catalyzed decomposition of the 1,1 and 1,3 complexes, respectively; see Table V for other k^{H^+} values in H_2O. [f] Rate constants for catalysis by other acids, in L mol^{-1} s^{-1} at −70 °C: 2,2-dimethylpropionic acid = 0.54; acetic acid = 1; 3-chloropropionic acid = 1.97; chloroacetic acid = 9.5. [g] Values estimated from the influence of Me_2SO on the rate constants k_1, k_2, and k_{-1}, k_{-2} (see section VIII). [h] K_1 $(K_2) = k_1$ $(k_2)/k_{-1}(k_{-2})$. [i] k^{MeOH}, in s^{-1}, as defined by eq 4 with R = Me.

TABLE IV. Influence of the X Substituent on the Rate and Equilibrium Constants for Formation and Decomposition of 1,3- and 1,1-Complexes 12 and 13

	SO_2CF_3[a]	NO_2[a]	aza[a,c]	SO_2Me[b]	CN[b]	CF_3[b]	Cl[b]	H[b]
k_2/k_1	5.32	55	16.6	22	26	36	130	360
k_{-2}/k_{-1}	2.13×10^5	3.5×10^5	4.35×10^3	2.2×10^4	1.5×10^4	200	430	225
K_2/K_1	2.5×10^{-5}	1.6×10^{-4}	3.80×10^{-3}	10^{-3}	1.75×10^{-3}	0.18	0.3	1.6

[a] Values in MeOH. [b] Average values in MeOH–Me_2SO mixtures (see Table III). [c] Reference 53; see section IIB5a.

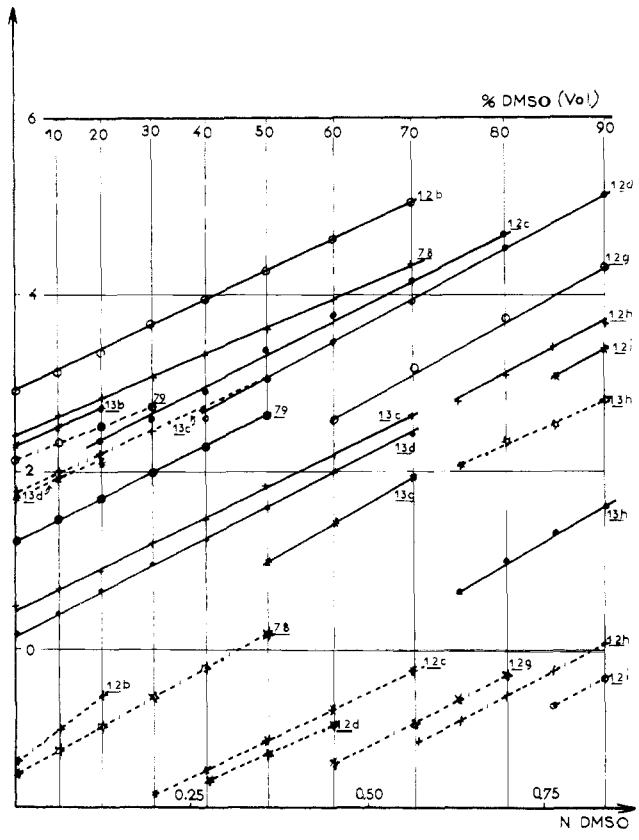


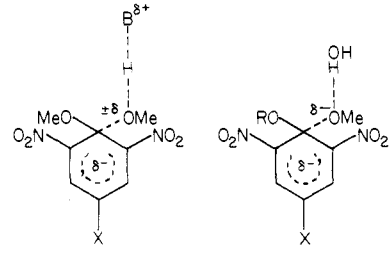
Figure 3. Effect of Me_2SO concentration on the rate constants for the formation (k_1, k_2) and decomposition (k_{-1}, k_{-2}) of the 1,1 and 1,3 complexes of 4-X-2,6-dinitroanisoles. (—) Log k_1 (k_2); (- - -) -log k_{-1} (k_{-2}).

tous,[56,133] they indicate that Me_2SO affects the rates for formation and decomposition of **12** and **13** to about the same extent. Therefore, the relative thermodynamic stability of 1,1 and 1,3 complexes is not markedly altered by a change in the Me_2SO concentration. This observation is of considerable importance with respect to the rate of conversion of **12** into **13**. The k_{obsd}^{max} value of the rate constant for this process (eq 13) may be used as a measure of the lifetime of **12** when this latter completely isomerizes into **13**.[53,56] Owing to the independence of the ratio K_1/K_2 on the Me_2SO concentration, the variation of k_{obsd}^{max} parallels that of k_{-1}. Increasing the Me_2SO content therefore results in a strong decrease in k_{obsd}^{max} and a concomitant increase in the lifetime of **12**. Thus, the $t_{1/2}$ of **12b** is ~0.14 s in MeOH but 10 000 s in 90% Me_2SO, i.e., 10^5-fold greater than in the absence of Me_2SO cosolvent.[56] Similarly, the $t_{1/2}$ of a less stable complex like **12d** changes from 0.5 s in 40% Me_2SO to 250 s in 90% Me_2SO.[56] These results show why NMR observation of such transient species can be made in Me_2SO.[111,113,117]

iv. Buffer Catalysis. Methoxide ion departure from 1,1-complexes **13** (X = NO_2, SO_2CF_3, CN, SO_2Me, CF_3) is general acid catalyzed in aqueous solution.[144,145] Buffer catalysis is appreciable with pyridinium ions but hardly detectable with neutral (carboxylic) or anionic ($H_2PO_4^-$) acids. In all cases, the observed rate constant obeys the equation

$$k_{obsd} = k_{-1} + k^{BH^+}[BH^+] + k^{H^+}[H^+] \qquad (27)$$

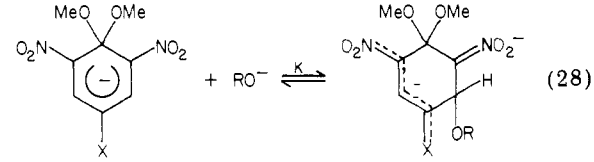
The Brønsted α values range from 0.55 for X = CF_3 to 0.63 for X = SO_2CF_3; i.e., α slightly increases as X becomes more electron withdrawing (Table V). This trend has been rationalized, as has the trend in α values associated with the decomposition of a number of 1,1-dialkoxy-2,4,6-trinitrocyclohexadienylides (section IIB2d), with the help of More O'Ferrall–Jencks energy diagrams.[149-151] The results are fully consistent with a concerted mechanism and a transition state like **19**.[144]



19 **20**

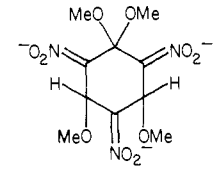
Such a mechanism must also operate in the general acid catalyzed decomposition of the TNB complex **5c**[16] and the 1,3-complex **14b**[137] in EtOH. (α = 0.67 and 0.56, respectively). The uncatalyzed decomposition of the complexes **13**[138,139,144] involves a simple alkoxide ion departure, assisted by water solvation, as shown in **20**, but without a proton transfer taking place in the rate-determining step.[144] Failure to observe general catalysis in earlier studies of the decomposition of **13a**,[138,146,147] **15b**,[137] or other 1,1 complexes[138,148] was probably due to the use of very low buffer concentrations and/or inefficient catalysts.[144]

v. 1:2 Complexes. At high base concentrations in methanolic and aqueous solutions, the 1,1-complexes **13** are converted into the diadducts **21** and **21′**, respectively[30,74,140-143] (eq 28). The triadduct **22** has also



(28)

13 R = Me **21**
R = H **21′**



22

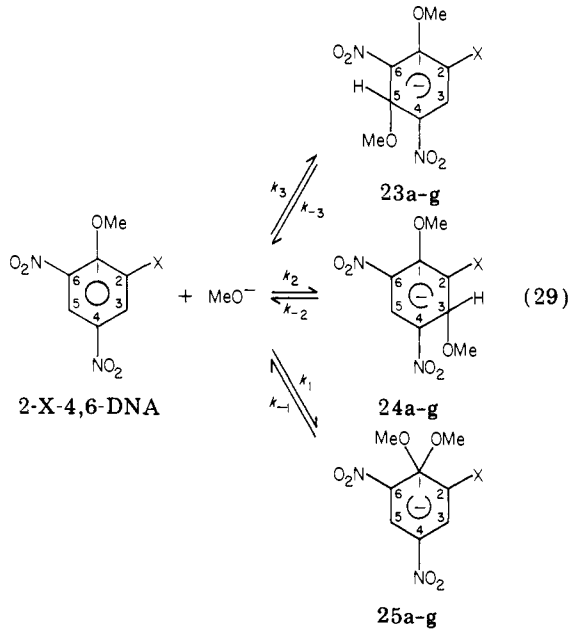
been observed.[30,140] By use of the acidity functions H_M[29,30,141] and J_M[29,30,140] values of the equilibrium constant K for **21a** (X = NO_2) and **21j** (X = H) have been estimated in MeOH (Table VII). Interestingly, the conversion of **13** into **21** requires quite different NaOMe and KOMe concentrations, giving evidence for great differences in ion association.[30] The rate of decomposition of the diadduct **21a′** (X = NO_2) in aqueous solution has been reported to depend on the nature of the cation.[142]

b. 2-X-4,6-Dinitroanisoles[152] (2-X-4,6-DNA). Due to the nonequivalence of the 3- and 5-positions, 2-X-4,6-dinitroanisoles may react with MeO^- to give the complexes **23**, **24**, and **25** (eq 29) which are designated as 1,5, 1,3, and 1,1 complexes, respectively.[54,102,112,153-155] Under conditions where they can be observed, **23** and **24** which both result from MeO^- addition to an un-

TABLE V. Rate Constants and Brønsted α Values for the Decomposition of 1,1-Complexes 13 in Water at 25 °C[a,b]

	X (σ^-)				
	CF_3, 13g (0.74)	CN, 13c (1.00)	SO_2Me, 13d (1.05)	NO_2, 13a (1.27)	SO_2CF_3, 13b (1.65)
k_{-1},[c] s^{-1}	0.134	1.30×10^{-2}	1.06×10^{-2}	4.96×10^{-4} 5.51×10^{-4} [d,e]	2.56×10^{-4}
k^{BH^+}, L mol^{-1} s^{-1}					
γ-picoline-H^+ (6.23)f	7.44	0.85	0.65	3.22×10^{-2}	2.44×10^{-2}
pyridine-H^+ (5.36)f	17.4	1.98	1.72	8.30×10^{-2}	6.51×10^{-2}
nicotinamide-H^+ (3.40)f		28	29.6	1.25	0.9
k^{H^+}, L mol^{-1} s^{-1} (−1.74)f	2.4×10^5	4.7×10^4	4.2×10^4	3.4×10^3	3.3×10^3
α	0.55	0.58	0.59	0.61	0.63

[a] References 144, 145. [b] I = 0.2 M KCl. [c] Rate constants as defined by eq 27. [d] Reference 138. [e] $\Delta H_{-1}^{\ddagger}$ = 82 kJ mol^{-1}; ref 139. [f] $pK_a^{BH^+}$.



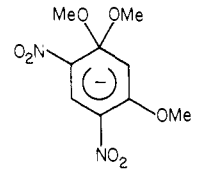
(29)

X = (a) SO_2CF_3; (b) CN; (c) CF_3; (d) COOMe; (e) Cl; (f) F; (g) H

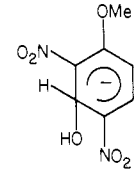
substituted carbon, are formed under kinetic control. In all cases, these undergo a *complete* conversion into the thermodynamically more stable 1,1-complexes **25**. NMR measurements have unambiguously confirmed the structure of the transient complexes where X = CN and CF_3.[153] Kinetic and thermodynamic data are summarized in Table VI.

i. 1,1 Complexes. Formation of the 1,1-complexes **25** could be directly investigated in MeOH under conditions in which eq 1 applies, i.e., where **23** and **24** do not form (ref 26, 30, 31, 102, 113, 154–156). The stability sequence is essentially the same as that for the 4-X-2,6-DNA series, i.e., SO_2CF_3 > NO_2 > CN > CF_3 > COOMe > Cl > F > H. Because these adducts benefit from the stabilizing effect of a *p*-NO_2 group, all are isolable as potassium or sodium crystalline salts.[113,153,155,157] In fact, with the exception of **25a** and **25g**, they are more stable than their isomers **13**. The SO_2CF_3 complex **25a** is 6-fold more stable than the trinitro analogue **13a** but less stable than its isomer **13b**.[134] This shows that a *p*-SO_2CF_3 has more effect than an *o*-SO_2CF_3 group on complex stability.[56,100] This behavior is similar to that observed for a NO_2 group[11,53,113] and suggests greater electron-delocalizing ability for a para than for an ortho SO_2CF_3 group.[56,158] The hydrogen complex **25g** is two times less stable than **13j** because its formation involves much less release of steric strain.[31] Ion-pairing effects have in some cases a marked influence on the K_1 values[119–121,123] (section IX).

An interesting related 1,1 complex is **26**, which forms from 1,3-dimethoxy-4,6-dinitrobenzene.[31] Although it



26

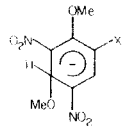
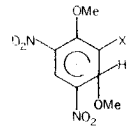
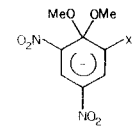


27

should be favored on statistical grounds, **26** (K_1 = 3.8 × 10^{-6} L mol^{-1})[31] is about 10-fold less stable than **25g** at 25 °C (K_1 = 5 × 10^{-5} L mol^{-1}).[30,31,156] Since steric effects at the position of addition are similar, the lower stability of **26** has been attributed to a greater stabilization of the parent through resonance structures involving the two OMe groups (as shown for TNA in **17a**, **17b**). In addition, steric interactions between the OMe group at C-5 and the NO_2 group at C-4 may also be important. This latter factor would reduce the ability of the NO_2 group to delocalize the negative charge of **26**.[31]

Kinetic data have been obtained for the formation of **25a** between pH 4 and 13 in MeOH.[134] Contrary to the observation with **13b**, methanol attack does not significantly contribute to the formation of **25a**. Formation and decomposition of the cyano and hydrogen complexes **25b** and **25g** have been investigated in MeOH and MeOD.[113,156] The solvent deuterium isotope effects on the equilibrium and rate constants are similar: K_1^H/K_1^D, k_1^H/k_1^D, k_{-1}^H/k_{-1}^D are equal, respectively, to 0.38, 0.51, and 1.34 for **25g**;[156] 0.45, 0.6, and 1.36 for **25b**.[113] They have been interpreted as secondary solvent isotope effects[156] and their magnitudes regarded to be typical for relevant S_NAr reactions.[113] Comparison of the activation parameters for **25b**[113] and **25g**[156] with those for **13a**[113] is of interest. The activation enthalpies for formation of these adducts increase in the order **13a** << **25g** < **25b** while the corresponding rate constants k_1 for **13a** and **25b** are similar and about 2500-fold greater than that for **25g**. This supports the idea that entropy changes may also be important in determining the relative rates of formation of such complexes. This is also true for the rates of decomposition. The formation of **25g** is rate determining in the symmetrical methoxyl exchange reaction for 2,4-dinitroanisole (methyl-^{14}C) in MeOH.[41] The decomposition of **25a** in MeOH,[134] like that of **25b** in water,[113] is strongly catalyzed by H^+ ions.

TABLE VI. Kinetic and Thermodynamic Parameters for 1,5, 1,3, and 1,1 Complexes of 2-X-4,6-Dinitroanisoles in MeOH-Me_2SO Mixtures[a,b]

X	% Me_2SO	t, °C	Cpx	k_3, L mol^{-1} s^{-1}	k_{-3}, s^{-1}	K_3, L mol^{-1}	Cpx	k_2, L mol^{-1} s^{-1}	k_{-2}, s^{-1}	K_2, L mol^{-1}	Cpx	k_1, L mol^{-1} s^{-1}	k_{-1}, s^{-1}	K_1, L mol^{-1}	activation and thermodynamic parameters;[c] conditions and comments[d]	ref
SO_2CF_3	O	20	23a	8700	47	185	24a				25a	17.5	1.32×10^{-4}	1.32×10^5	$k_1^{MeOH} = 5.24 \times 10^{-6}$; $k_1^{H^+} = 1.26 \times 10^6$;[e] 0.01 buffer salts	134
CN	O	25	23b				24b				25b			1140	isnc	9, 26
		25										18.8	7.20×10^{-3}	2600	isnc; $\Delta H_1^\circ = 14.2$; $\Delta S_1^\circ = 104.5$; $\Delta H_1^\ddagger = 72$; $\Delta S_1^\ddagger = 21$; $\Delta H_{-1}^\ddagger = 57.8$; $\Delta S_{-1}^\ddagger = -83.5$; in H_2O: $k_{-1} = 8 \times 10^{-3}$; $k_1^{H^+} = 1.73 \times 10^4$ [e]	113
		25													$\Delta H_1^\circ = -11.8$; cd	33
		20										11	5×10^{-3}	2200	isnc	159
	MeOD	25										30.4	5.3×10^{-3}	5736	isnc; $\Delta H_1^\circ = 6.3$; $\Delta S_1^\circ = 74.4$; $\Delta H_1^\ddagger = 69$; $\Delta S_1^\ddagger = 16$; $\Delta H_{-1}^\ddagger = 62.7$; $\Delta S_{-1}^\ddagger = -58.4$	113
	50	20		17000	72	240		4400	8.6	510		310	1.65×10^{-4}	1.9×10^6	isnc	102, 154
CF_3	0	20	23c				24c				25c			14	af	30
	0	20										0.35	0.012	29	isnc	159
	20	20										1.45	4.32×10^{-3}	335	isnc	159
	40	20										5.8	1.15×10^{-3}	5040	isnc	159
	70	20		15000	82	185		2400	8.05	296		130	6×10^{-5}	2.2×10^6	isnc	102, 154
COOMe	0	25	23d				24d				25d	0.22	0.022	10	isnc	119
		25												8.3	LiOMe or n-Bu_4NOMe	120
Cl	0	25	23e				24e				25e	0.18	0.06	3	isnc	119
		25												3.4	LiOMe or n-Bu_4NOMe	120
		20												2.5	af	30
		20										0.28	0.036	7.8	isnc	54
	10	20										0.39	0.019	20.4	isnc	54
	30	20										1.1	6×10^{-3}	183	isnc	54
	50	20										5.5	1.07×10^{-3}	5150	isnc	54
	70	20						795	21	38		37			isnc	54
	80	20						2900	8.1	358		105			isnc	54
	90	20		29000	76	382		10000	2	5000		410	10^{-5}	4.1×10^7	isnc	54
F	0	25	23f				24f				25f			0.3	af	31
		20										0.1[f]	0.4	0.245	isnc	155
	30	20										1.38	0.05	28	isnc	155
	50	20										6.3	0.0125	500	isnc	155
	70	20										63	1.4×10^{-3}	45000	isnc	155
	80	20						950	47.5	20		250	4×10^{-4}	6.3×10^5	isnc	155
	90	20						6000	13.5	450		2000				155
H	0	25	23g				24g				25g			2.88×10^{-4}	af	140
		25												4.6×10^{-5}	af	31
		20												6.76×10^{-5}	af	30
		25										2.12×10^{-3}[f]	42	5.05×10^{-5}	at infinite dilution	156
		25										7.90×10^{-3}	28.7	2.74×10^{-4}	0.2 M NaOMe; $\Delta H_1^\circ = 23.4$; $\Delta S_1^\circ = 11.2$; $\Delta H_1^\ddagger = 70.2$; $\Delta S_1^\ddagger = -39$; $\Delta H_{-1}^\ddagger = 46.8$; $\Delta S_{-1}^\ddagger = -50.2$	156

	25			1.94×10^{-2}	7.63	2.54×10^{-3}	1 M NaOMe		156
	25			1.06×10^{-3}			^{14}C exchange; $\Delta H_1^{\ddagger} = 67.7$; $\Delta S_1^{\ddagger} = -73$[g]		41
85	20			14.80	0.45	33	isnc		108
90	20			76	0.095	800	isnc		108

[a] NaOMe or KOMe unless indicated otherwise. [b] Rate and equilibrium constants as defined by eq 29. [c] Enthalpies in kJ mol^{-1}; entropies in J mol^{-1} K^{-1}. [d] See Table I for abbreviations. [e] k_1^{MeOH} (in s^{-1}) and $k_1^{H^+}$ (in L mol^{-1} s^{-1}) as defined by eq 4 with R = Me or H. [f] $k_1 = k_{-1}K_1$. [g] Calculated from data of ref 41.

TABLE VII. Kinetic and Thermodynamic Parameters for Formation and Decomposition of Various Alkoxy and Hydroxy Meisenheimer Complexes

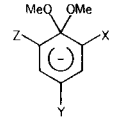
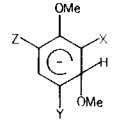
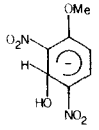
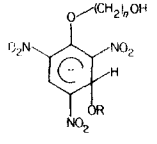
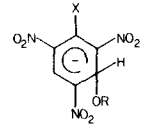
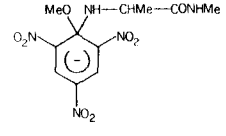
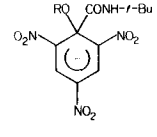
compd	Cpx	X	Y	Z	R	solvent[a]	t, °C	k_f,[b] L mol^{-1} s^{-1}	k_d,[b] s^{-1}	K,[b] L mol^{-1}	activation and thermodynamic parameters;[c] conditions and comments[d]	ref
	30	CN	CN	NO_2		MeOH	25	2.06	0.198	10.40	isnc; $\Delta H_d^{\ddagger} = 49.4$; $\Delta S_d^{\ddagger} = -92$;	32
						MeOH-Me_2SO						
						90:10	25	19.1	0.115	166	isnc; $\Delta H_d^{\ddagger} = 47.2$; $\Delta S_d^{\ddagger} = -100$	32
						85:15	25	87.4	0.094	930	isnc; $\Delta H_d^{\ddagger} = 53$; $\Delta S_d^{\ddagger} = -83.6$	32
							25				$\Delta H^{\circ} = -3.4$; $\Delta S^{\circ} = 36.4$; cd	32
	31	CN	NO_2	CN		MeOH	20	12.9	0.34	38	isnc	118
							25	12.4	0.37	34	isnc; $\Delta H_d^{\ddagger} = 58.5$; $\Delta S_d^{\ddagger} = -85.3$	32
							25				$\Delta H^{\circ} > 0$; cd	32
						MeOH-Me_2SO						
						90:10	25	16.2	0.21	77	isnc; $\Delta H_d^{\ddagger} = 67.3$; $\Delta S_d^{\ddagger} = -28.8$	32
						70:30	25	43.8	0.063	695	isnc; $\Delta H^{\circ} = -10.3$; $\Delta S^{\circ} = 19.6$; cd	32
						50:50	20	457	0.0125	36500	isnc	118
	32	CN	CN	CN		MeOH	25			0.4	isnc	160
						MeOH-Me_2SO						
						70:30	25			280	isnc	160
						50:50	25	0.33	6×10^{-4}	550	isnc	160
						25:75	25	1.75	2×10^{-4}	8000	isnc	160
	35	H	SO_2CF_3	NO_2		MeOH-Me_2SO						
						30:70	20	27.2	1.7	16	isnc	158
						20:80	20	152.5	0.55	277	isnc	158
	36	H	NO_2	SO_2CF_3		MeOH-Me_2SO						
						20:80	20	68.5	0.95	72.1	isnc	158
						10:90	20	664	0.28	2370	isnc	158
	37	H	SO_2CF_3	SO_2CF_3		MeOH-Me_2SO						
						30:70	20	221	2.2	100	isnc	158
						20:80	20	840	0.72	1165	isnc	158
	33	CN	CN	NO_2		MeOH-Me_2SO						
						85:15	25				$\Delta H^{\circ} = 12.7$; cd	32
	34	CN	NO_2	CN		MeOH-Me_2SO						
						60:40	20			2.24	isnc	118
						50:50	20	2800	273	10.25	isnc	118
						30:70	20	31800	46	690	isnc	118
	38	H	NO_2	SO_2CF_3		MeOH-Me_2SO						
						10:90	20			47	isnc	158
	39	H	SO_2CF_3	SO_2CF_3		MeOH-Me_2SO						
						20:80	20			19.3	isnc	158

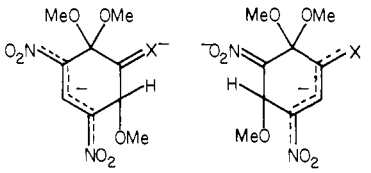
TABLE VII (*Continued*)

compd	Cpx	X	Y	Z	R	solvent[a]	t, °C	k_f,[b] L mol^{-1} s^{-1}	k_a,[b] s^{-1}	K,[b] L mol^{-1}	activation and thermodynamic parameters;[c] conditions and comments[d]	ref
	27					H_2O–Me_2SO 40:60	25	0.013	9.7	1.3×10^{-3}	isnc; $\Delta H_d^{\ddagger} = 55$; $\Delta S_d^{\ddagger} = -40$	67
	42a	$n = 4$			H	H_2O	25	5.38	8.40	0.64	isnc	67
					D	D_2O	25		5.50		$k_d^{H_2O}/k_d^{D_2O} = 1.53$	67
	42b	$n = 6$			H	H_2O	25	12	6	2	0.5 M NaCl; $K_p = 3$[e]	491
	60a	Cl			H	H_2O	25	12	14	0.85	2 M NaCl; $K_p = 15$;[e] $k_A = 0.4$[f]	136
						H_2O	20	9	6	1.5	isnc	77
						H_2O-tBuOH 5:95	25	12000	0.6	2×10^4	isnc	96
	60a'				Me	MeOH	25	912	303	2.58	isnc; $\Delta H_f^{\ddagger} = 54$; $\Delta S_f^{\ddagger} = 10.9$; $\Delta H_d^{\ddagger} = 34.3$; $\Delta S_d^{\ddagger} = -62.3$; $\Delta H^{\circ} = 19.7$; $\Delta S^{\circ} = 73.2$	197
	60a''				Et	EtOH	25	5770	19.7	293	isnc; $\Delta H_f^{\ddagger} = 40$; $\Delta S_f^{\ddagger} = -38.5$; $\Delta H_d^{\ddagger} = 37$; $\Delta S_d^{\ddagger} = -98.5$; $\Delta H^{\circ} = 3$; $\Delta S^{\circ} = 60$	198
	60b	NO_2			H	H_2O	25	2900	0.2	14500	1 M NaCl; $K_p = 24$;[e] $k_A = 140$[f]	136
										24000	isnc	192
	60b''				Et	EtOH	25			$>10^6$	isnc	192
	60c	SO_3^-			H	H_2O	25	0.8	45	0.018	1 M NaCl; $K_p = 32$;[e] $k_A = 0.045$[f]	191
	60d	COO^-			H	H_2O	20	22	9.6	2.29	isnc	77
	60e	O^-			H	H_2O	25	0.26	20	0.013	2 M NaCl; $K_p = 0.8$[e]	136
	60e'				Me	MeOH	25			3×10^{-4}	af	140
	50a	NO_2				MeOH	25	6.5	5.2×10^{-5}	1.3×10^5	isnc; $\Delta H_f^{\ddagger} = 78.2$; $\Delta S_f^{\ddagger} = 32.6$ $\Delta H_d^{\ddagger} = 113.7$; $\Delta S_d^{\ddagger} = 54.3$; $\Delta H^{\circ} = -35.5$; $\Delta S^{\circ} = -21.7$	178
	50b	CN				MeOH	25	3.2	6.3×10^{-4}	4.7×10^3	isnc; $\Delta H_f^{\ddagger} = 96$; $\Delta S_f^{\ddagger} = 87$; $\Delta H_d^{\ddagger} = 91.5$; $\Delta S_d^{\ddagger} = 1$; $\Delta H^{\circ} = 4.5$; $\Delta S^{\circ} = 86$	178
	64a				H	H_2O	25	17.6	0.0156	1130	isnc; $\Delta H_f^{\ddagger} = 46$; $\Delta S_f^{\ddagger} = -65$; $\Delta H_d^{\ddagger} = 81$; $\Delta S_d^{\ddagger} = 11$; $\Delta H^{\circ} = -35$; $\Delta S^{\circ} = -76$	199
	64b				Me	MeOH	25	1130	0.46	548	isnc	199

[a] Sodium or potassium hydroxides or alkoxides. [b] k_f, k_d, and K represent the rate and equilibrium constants for formation and decomposition of the various complexes. [c] Enthalpies in kJ mol^{-1}; entropies in J mol^{-1} K^{-1}. [d] See Table I for abbreviations. [e] K_p for ionization of the OH group. [f] k_A for OH^- attack at the 1-position.

ii. 1,3 and 1,5 Complexes. At methoxide concentrations of 5×10^{-4} to 5×10^{-2} M, the reaction of 2-[(trifluoromethyl)sulfonyl]-4,6-dinitroanisole with MeO^- in MeOH is characterized by a fast kinetic process followed by the slower appearance of **25a**.[134] Whether the initially formed complex is **23a** or **24a** could not be established by NMR due to a rapid methanolysis of the SO_2CF_3 group in basic Me_2SO.[158] Its greater stability relative to that of **12a** suggests, however, that this complex has a p-SO_2CF_3 group rather than a p-NO_2 group, i.e., structure **23a**. No evidence for **24a** has been found. Kinetic and equilibrium data for **23** and **24** (X = CN, CF_3, Cl) have been obtained in some MeOH–Me_2SO mixtures. In these cases, conditions were found where the formation of the purple-colored adducts **23** occurs prior to that of the red-colored adducts **24**.[54,155] In comparing the parameters for **23** to those for **24**, it is clear that the situation is similar to that encountered in comparing the parameters for the corresponding complexes **10** and **11**. Both **23** and **24** form and decompose rapidly, and the lower stability of **23** relative to **24** results from a greater rate of decomposition.[54,102,154] Such an analogy is not unexpected since **23** and **24** are structurally similar to **10** and **11**, respectively. In the case of the CN and CF_3 derivatives, where data are available in the same solvents, this similarity is fully supported by the near identity of the rate and equilibrium constants for formation and decomposition of **10** and **23** as well as for **11** and **24**.[102,154] When X = F, only formation of the 1,3-complex **24f** is detected by SF in 90% Me_2SO.[155] In contrast, detection of **23g** and **24g** (X = H) has been reported in 98% Me_2SO–2% MeOH.[107] Rate and equilibrium constants for formation and decomposition of what is believed to be **27**, i.e., the hydroxyl analogue of **23g**, have been measured in 60% Me_2SO–40% H_2O.[67] When the slow but thermodynamically favored formation of the 1,1-complexes **25** is compared to the fast but thermodynamically nonfavored formation of the 1,5- and 1,3-complexes **23** and **24**, all the arguments previously developed in the 4-X-2,6-DNA series apply. However, the release of steric strain around C_1 is, here, dependent on X. Me_2SO stabilizes complexes **23**, **24**, and **25** to about the same extent.

iii. 1:2 Complexes. As do their isomers **13**, the 1,1-complexes **25** add a second methoxide ion at high KOMe or NaOMe concentrations in MeOH to give diadducts **28** or **29**. In the case of X = CN, NMR



28a-g 29a-g

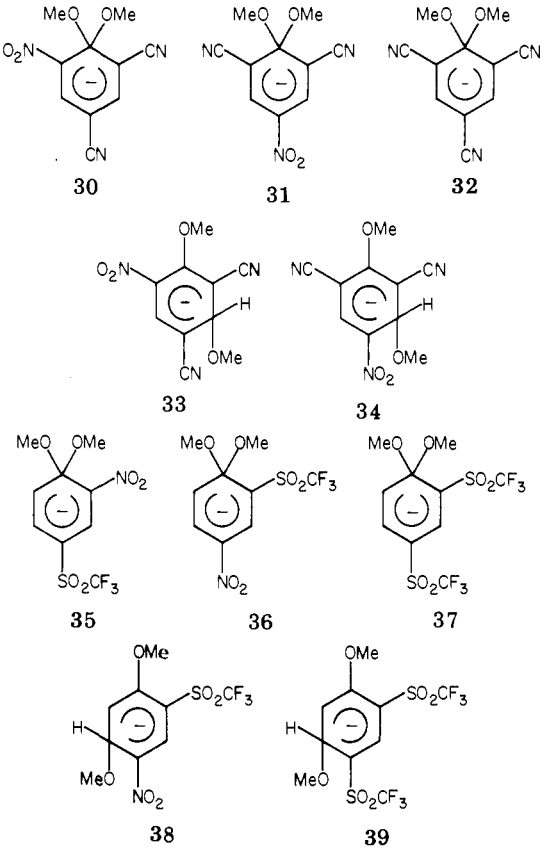
evidence for **29** has been obtained.[26] The estimated values for the equilibrium constants K (as defined in eq 28) are given in Table VIII.

c. Other Substituted Anisoles. The equilibrium formation of the 1,1-dimethoxy complexes **30**, **31**, and **32** according to eq 1 (R = Me) has been investigated in MeOH. The K_1 values at 25 °C are 33.5, 10.4, and 0.4 L mol^{-1} for **31**, **30**, and **32**, respectively,[32,160] as compared with K_1 values of 17 000, 2600, and 280 L mol^{-1} for **13a**, **25b**, and **13c**, respectively.[113] Replacing two nitro groups in the 2- and 4-positions of TNA by cyano groups results in a greater decrease in K_1 than replacing two nitro groups in the 2- and 6-positions: $K_1^{13a}/K_1^{31} = 500$; $K_1^{13a}/K_1^{30} = 1700$. This result is in accord with relative stabilities of the isomeric dinitrocyano complexes **25b** and **13c**[113] and quantum mechanical calculations.[26] More significantly, the stability of the tricyano adduct is 42 500-fold smaller than that of 13a.[160] The effect of increasing the Me_2SO concentration in MeOH on the rates of formation and decomposition of **30**, **31**, and **32** has been studied.[32,160] Calorimetric measurements have provided the $\Delta H_1°$ values for the

TABLE VIII. Equilibrium Constants for Formation of Some 1:2 and 1:3 Complexes and Some Dianions in Methanol

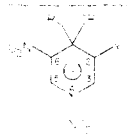
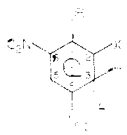
complex or dianion	t, °C	K (KOMe),[a,b] L mol^{-1}	K (NaOMe),[a,c] L mol^{-1}	ref
21a	25		7.8×10^{-4}	140
	20	5.6×10^{-4}	1.6×10^{-4}	30
22	25		8×10^{-4}	140
21j	20	10^{-4}	3.16×10^{-4}	30
29e	20	3.54×10^{-6}	6.45×10^{-6}	30
29f	20	7.41×10^{-6}	1.1×10^{-5}	30
29g	25		1.25×10^{-5}	140
	20	4.26×10^{-6}	4.57×10^{-6}	30
46a	25		≃1	168
	25		140[d]	173
47a	25		1500[d]	174
47b	25		4.36×10^{-5}	140
	20	6.16×10^{-5}	2.1×10^{-5}	30
47c	25		1800[d]	490
63e'	25		0.1	140

[a] K as defined by eq 28 or a similar equation. [b] Values estimated from acidity function determinations (H_M). [c] Values estimated from acidity function determinations (J_M). [d] In 95% Me_2SO–5% MeOH.



30 31 32 33 34 35 36 37 38 39

TABLE IX. Rate and Equilibrium Constants for 1,1- and 1,3-Diethoxy, -Dipropoxy-, and -Diisopropoxy Complexes in Ethanol, Propanol, and 2-Propanol at 25 °C

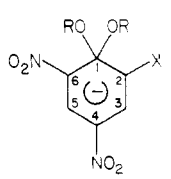
	Cpx	X	R	solvent	k_f,[a] L mol^{-1} s^{-1}	k_d,[a] s^{-1}	K,[a] L mol^{-1}	$k_{f,ip}$ L mol^{-1} s^{-1}	$k_{d,ip}$,[b] s^{-1}	K_{ip},[b] L mol^{-1}	ref
	40a	NO_2	Et	EtOH	17	6×10^{-5}	3×10^5	30			57
	40h	COOEt			0.13	1.3×10^{-3}	100	4	6×10^{-4}	6.7×10^3	57
	40k	Cl			0.14	2.6×10^{-3}	53	0.5	1.7×10^{-3}	300	57
	40n	H			0.01	7	1.5×10^{-3}	0.01	1	0.01	57
							7.41×10^{-4} [c]				162
	40b	NO_2	Pr	PrOH	28		$>2 \times 10^5$	50		$>2 \times 10^5$	60
	40i	COOPr			0.21	3.8×10^{-4}	560	6	7×10^{-4}	8400	60
	40l	Cl			0.21	7.5×10^{-4}	280	0.75	1.7×10^{-4}	450	60
	40o	H			0.016	3.1	5×10^{-3}	0.014	1.3	0.011	60
	40c	NO_2	*i*-Pr	*i*-PrOH	≥50			100			59
	40j	COO*i*-Pr			0.11	7×10^{-5}	1500	10	10^{-3}	10000	59
	40m	Cl			0.10	10^{-4}	1000	1.8	3.6×10^{-3}	500	59
	40p	H			0.01	0.12	0.08	0.009	0.36	0.025	59
	41a	NO_2	Et	EtOH	2100	30	70	1700	30	57	57
	41b	NO_2	Pr	PrOH	4500	16	280	2400	19	125	60
	41c	NO_2	*i*-Pr	*i*-PrOH	8000	≤0.1	≥10^5	2400	0.6	4×10^3	59

[a] k_f, k_d, and K represent k_1, k_{-1}, K_1, and k_2, k_{-2}, K_2 as defined by eq 29 and in the absence of ion pairing: NaOR + crown ether or Me_4NOR. [b] $k_{f,ip}$, $k_{d,ip}$, and K_{ip} represent the same rate and equilibrium constants as determined in the presence of ion pairing (see eq 22: NaOR + $NaClO_4$ or sodium tetraphenylborate. [c] Acidity function determination.

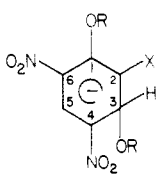
formation of **30** in 15% Me_2SO and of **31** in 20 and 30% Me_2SO.[32,33] They have also provided evidence for the formation of the transient 1,3- complex **33** in 15% Me_2SO.[32] Contrary to **33**, the isomer **34** does not benefit from the stabilizing effect of a *p*-NO_2 group. It has been detected in mixtures with only ≥40% Me_2SO, and its lifetime is about 3 s in 90% Me_2SO.[118]

The trifluoromethylsulfonyl 1,1-complexes **35**, **36**, and **37** have been compared with the dinitro analogue **25g** in MeOH-Me_2SO mixtures.[158] The order of stabilities is **37** > **35** > **36** > **25g**, confirming earlier conclusions on the effect of the SO_2CF_3 group on complex stability.[56] Equilibrium constants for formation of the transient complexes **38** and **39** were also measured in 80 and 90% Me_2SO.[158] In all cases, methoxide ion attack on the SO_2CF_3 group(s) of the parents is a concurrent but slower reaction.[158,161] The results are summarized in Table VII.

d. Miscellaneous Alkoxybenzenes. Equilibrium and kinetic data have been reported for the reactions of sodium ethoxide, sodium propoxide, and sodium isopropoxide with a series of 2-X-4,6-dinitro-1-ethoxy-, -1-propoxy-, and -1-isopropoxybenzenes to give the 1,1-complexes **40** (R = Et, Pr, *i*-Pr; X = NO_2, COOR, Cl, H) in EtOH, PrOH, and *i*-PrOH, respectively.[57,59,60] In the case of the trinitro derivatives, the formation of the 1,3-complexes **41a-c** is observed initially. The results have been interpreted in terms of eq 22 and, when necessary, eq 10. Values of the rate and equilibrium constants in Table IX are derived from experiments conducted in the presence of sodium perchlorate or tetraphenylborate (k_{ip}, k_{-ip}, K_{ip}) or of crown ethers (k_1, k_{-1}, K_1). Tetramethylammonium alkoxides have also been used to avoid ion pairing. Table IX shows that for 1,1-complex formation the sodium alkoxide ion pairs have a greater reactivity than free RO^- ions while the ion paired σ-complexes **40** revert to the reactants less rapidly (R = Et, iPr) or more rapidly (R = Pr; X = COOPr) than their unpaired analogues. In contrast the free RO^- ions are much more reactive than the RO^-, Na^+ ion pairs in forming the 1,3-complexes **41**. These results are consistent with a high tendency of the 1,1-complexes to associate with cations (see section IX).[57,59,60]



40a-p



41a-c

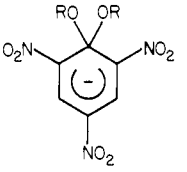
X = NO_2, R = (a) Et; (b) Pr; (c) *i*-Pr; (d) $CH_3OCH_2CH_2$; (e) $ClCH_2CH_2$; (f) $HC{\equiv}CCH_2$; (g) $H_2C{=}CHCH_2$
X = COOR, R = (h) Et; (i) Pr; (j) *i*-Pr
X = Cl, R = (k) Et; (l) Pr; (m) *i*-Pr
X = H, R = (n) Et; (o) Pr; (p) *i*-Pr

As expected from solvent basicities, the K values for RO^- addition to similarly activated substrates are in the order $K^{EtO} < K^{PrO} < K^{i\text{-}PrO}$. The same sequence holds for the rates of formation of the 1,3 complexes. In contrast, the order is *i*-PrO < EtO < PrO for the rates of formation of the 1,1 complexes. This inversion probably reflects greater F strain associated with formation of the 1,1-diisopropoxy complexes.[60] That the complexes **40** have considerably greater stability but form less rapidly than their isomers **41** is qualitatively explicable in the same terms as discussed above for formation of 1,1- and 1,3-dimethoxy complexes.

Spectrophotometric measurements of the apparent equilibrium constant K_c for formation of the adduct **40n** from the reaction of NaOEt and KOEt with 2,4-dinitrophenetole have been used to define an acidity function J_E for ethoxide solutions in EtOH.[162] In EtOD solutions of the same [EtO^-], the K_c value is greater than that in EtOH solutions by a factor of 2.5. This result compares well with the one found for **25g** in MeOH[156] and is consistent with the formulation of EtO^- as an entity containing three hydrogen-bonded solvent molecules.[162]

As that of their dimethoxy analogue **13a**, the decomposition of the picryl 1,1-complexes **40** (R = Et, $CH_3OCH_2CH_2$, $ClCH_2CH_2$, $HC{\equiv}CCH_2$) is catalyzed by pyridinium ions and H_3O^+ in aqueous solution.[144,145]

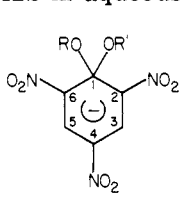
TABLE X. Rate Constants, Solvent Isotope Effects, and Brønsted α Values for the Decomposition of 1,1-Dialkoxy-2,4,6-trinitrocyclohexadienylides in Water at 25 °C[a,b]



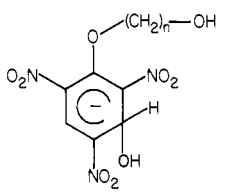
R	Et	Me	$CH_3OCH_2CH_2$	$ClCH_2CH_2$	$HC{\equiv}CCH_2$
pK_a^{ROH},[e] complex[g]	16, 40a	15.54, 13a	14.82, 40d	14.31, 40e	13.55, 40f
$k_{-1}^{H_2O}$, s^{-1}	3.22×10^{-4} 2.96×10^{-4}[f]	4.96×10^{-4}	1.65×10^{-3}	6.09×10^{-3}	5.40×10^{-2}
$k_{-1}^{D_2O}$, s^{-1}			1.21×10^{-3}		4.19×10^{-2}
$k_{-1}^{H_2O}/k_{-1}^{D_2O}$			1.37		1.30
k^{BH^+}, L mol^{-1} s^{-1}					
γ-picoline, H^+ (6.23)[d]	3.82×10^{-2}	3.32×10^{-2}	0.11	0.109	0.645
pyridine, H^+ (5.36)[d]	0.127	8.30×10^{-2}	0.265	0.205	1.15
nicotinamide, H^+ (3.40)[d]		1.25	3.83	2.66	6.05
k^{H^+}, L mol^{-1} s^{-1} (−1.74)[d]	8×10^3 1.20×10^4[f]	3.4×10^3	2.9×10^3	9.2×10^2	8.2×10^2
k^{D^+}, L mol^{-1} s^{-1}	1.4×10^4	6.8×10^3	5×10^3	1.45×10^3	9.9×10^2
k^{H^+}/k^{D^+}	0.49	0.50	0.58	0.637	0.82
α	0.65	0.62	0.53	0.47	0.35

[a] References 144, 145. [b] I = 0.2 M KCl. [c] Rate constants as defined by eq 27. [d] $pK_a^{BH^+}$. [e] References 92, 167. [f] References 138, 166. [g] Also in ref 138: R = Pr (40b), $k_{-1}^{H_2O} = 1.45 \times 10^{-4}$ s^{-1}; R = *i*-Pr (40c), $k_{-1}^{H_2O} = 3.17 \times 10^{-4}$ s^{-1}; R = $CH_2{=}CHCH_2$ (40g), $k_{-1}^{H_2O} = 1.58 \times 10^{-3}$ s^{-1}.

The Brønsted α values coefficients range from 0.35 to 0.65 (Table X), indicating concerted acid catalysis with a transition state like **19**. α increases with increasing basicity of the leaving group. Interestingly, there is a concomitant decrease in the solvent isotope effect (k^{H^+}/k^{D^+}) on the H^+-catalyzed pathway, from 0.82 for the least basic (R = $HC{\equiv}CCH_2$) to 0.49 for the most basic (R = Et) leaving group. The trends in α and k^{H^+}/k^{D^+} are toward the values expected for an A_1 mechanism.[163-165] More O'Ferrall-Jencks diagrams[149-151] have allowed better visualization of the effect of changing the leaving group on the transition state. The uncatalyzed decomposition, i.e., the "water reaction", is a simple alkoxide ion departure, as described in **20**.[144] The solvent isotope effects on this pathway ($k_{-1}^{H_2O}/k_{-1}^{D_2O} \sim 1.30$) have values typical for similar water reactions.[46,69,164] The activation volumes for the uncatalyzed and H^+-catalyzed decompositions of **40a** are −5.6 and +18 cm^3/mol^{-1}, respectively.[166] k_{-1} for **40a** decreases when adding Me_2SO to aqueous solutions. A plot of log k_{-1} vs. N_{Me_2SO} is linear.[166] Rate and activation parameters for the uncatalyzed decomposition of a number of unsymmetrical picryl complexes **2** have been reported: R = Me, R′ = Pr, *i*-Pr, Bu, *i*-Bu, *n*-C_5H_{11}, *i*-C_5H_{11}; R = Et; R′ = Pr, *i*-Pr; R = Pr, R′ = *i*-Pr.[138,139] 1-(4-Hydroxybutoxy)- and 1-(6-hydroxyhexyloxy)-2,4,6-TNB add OH^- to the 3-position of the ring to give **42a** and **42b** in aqueous NaOH.[67,491]



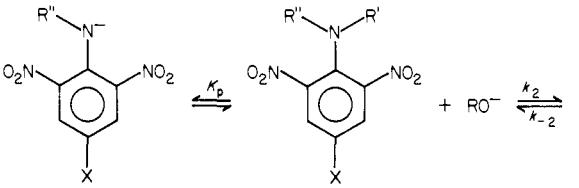
2



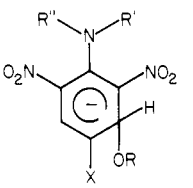
42a, n = 4
42b, n = 6

3. 1-Substituted Trinitro-, Dinitro-, and Mononitrobenzenes

a. 2,4,6-Trisubstituted Anilines and Related Derivatives. Hydroxide and alkoxide ions may react with picramide, N-substituted picramides, or related substrates **43** by addition and proton abstraction processes according to eq 30.[111,130,168-171] Such 1:1 interactions show kinetics characterizing a very fast process which corresponds to deprotonation of the amino group to give the conjugate base **44** and a slower process which corresponds to RO^- addition at the unsubstituted 3-position to give **45**.[15,77,172] In the case of *N*,*N*-dialkyl substrates, only the slow process is observed.[176] Rate and equilibrium data have been obtained for the reactions of OH^-, MeO^-, and EtO^- with compounds **43a–i** in water, MeOH, and EtOH, respectively (Table XI).[15,77,169,172-174] If one excepts *N*-phenylpicramide **43f** which only yields the anion **44f**, complex formation and proton loss are closely balanced, with K_2/K_p ratios varying from 52 for **43e** to 0.65 for **43b** in MeOH.[172] For the *N*-alkylpicramides **43b–f**, the K_p values decrease as the substituent R″ changes along the series Me, *n*-Bu,



44, R′ = H 43

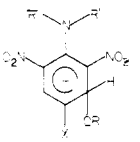
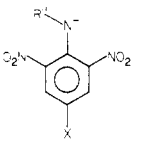


45, R = H
45′, R = Me
45″, R = Et

(30)

X = NO_2; (a) R′ = R″ = H; (b) R′ = H, R″ = Me; (c) R′ = H, R″ = *n*-Bu; (d) R′ = H, R″ = *i*-Pr; (e) R′ = H, R″ = *t*-Bu; (f) R′ = H, R″ = Ph; (g) R′ = R″ = Me
X = CF_3; (h) R′ = R″ = Pr;
X = H (i) R′ = R″ = H

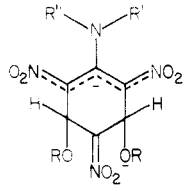
TABLE XI. Rate and Equilibrium Data for 1:1 Interactions of 4-X-2,6-Dinitroanilines with Hydroxide and Alkoxide Ions

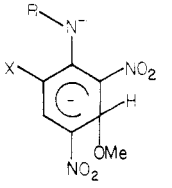
X	R'	R''	R[a]	solvent	t, °C	Cpx	k_2,[b] L mol^{-1} s^{-1}	k_{-2},[b] s^{-1}	K_2,[b] L mol^{-1}	anion	K_p[b]	ref
NO_2	H	H	H	H_2O	25	45a			32.8	44a		169
					20		30	0.7	42.85		3.4	77
			Me	MeOH	25	45a'			38			168
					25		1900	60	32		9	172
			Et	EtOH	−50	45a''	8.7	7.3×10^{-3}	1200			15
					25		6800[c]	1.86[c]	3600[d]			15
	H	Me	Me	MeOH	25	45b'	280	21	13	44b	20	172
				$MeOH-Me_2SO$ 5:95	25						2×10^5	174
	H	*n*-Bu	Me	MeOH	25	45c'	440	20	22	44c	8.3	172
	H	*i*-Pr	Me	MeOH	25	45d'	450	16	28	44d	5.5	172
	H	*t*-Bu	Me	MeOH	25	45e'	270	10.5	26	44e	0.5	172
	H	Ph	Me	MeOH	25	45f'				44f	$>10^4$	172
	Me	Me	Me	MeOH	25	45g'			7			168
				MeOH	25		180	31	6			172
				$MeOH-Me_2SO$ 5:95	25				1400			173
CF_3	Pr	Pr	H	H_2O	25	45h	0.0153[f]	0.368[f]	0.031[f]			176
				H_2O-Me_2SO 60:40	25		0.09	0.093	0.97		4.1[e]	176
				40:60	25		0.46	0.026	17.5			176
				30:70	25		1.99	7.84×10^{-3}	254			176
				20:80	25		6.56	2.65×10^{-3}	2475			176
H	H	H	Me	$MeOH-Me_2SO$ 25:75	25	45i'			~80	44i	~110	175

[a] Sodium or potassium hydroxides; sodium methoxide. [b] Rate and equilibrium constants as defined by eq 30. [c] Calculated from the activation enthalpies; $\Delta H_2^{\ddagger} = 46.4$; $\Delta H_{-2}^{\ddagger} = 38$ (kJ mol^{-1}); $\Delta S_2^{\ddagger} = -13.5$; $\Delta S_{-2}^{\ddagger} = -119$ (J mol^{-1} K^{-1}). [d] $K_2 = k_2/k_{-2}$. [e] K_p for ionization of the OH group of 45h to give 48. [f] Values estimated from linear plots of log k_2, log k_{-2}, and log K_2 vs. N_{Me_2SO}.

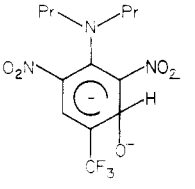
i-Pr, *t*-Bu. This is in the direction expected from inductive effects, but steric interaction between the substituent and the *o*-nitro groups also plays an important role in the variations.[172,175] In the case of **43f**, K_p is more than 10^3-fold greater than other K_p values in the series. This reflects the particularly good electron-delocalizing ability of the phenyl group which stabilizes the anion **44f**. The K_2 values are on the order of those for RO^- addition to TNB. Addition of Me_2SO to the aqueous or methanolic solutions increases both K_p and K_2, but proton abstraction is more favored than base addition.[172-174] The sole product of the 1:1 interaction of *N*-methylpicramide **43b** and MeO^- in 95% Me_2SO–5%-MeOH is **44b**.[174] MeO^- addition at the 3-position of 2,6-dinitroaniline to give **45i** competes with proton loss to give **44i** in MeOH–Me_2SO mixtures.[175] In contrast, only proton loss occurs in the *N*-alkyl 2,4-dinitro series.[175] Equilibrium data for the formation of the 1:2 complexes or dianions **46**, **47**, and **48** are given in Table VII.[168,169,173,174,490] **47b** forms in concentrated NaOMe or KOMe solutions in MeOH.[30]



46a, R' = R'' = R = Me
b, R' = R'' = H; R = Me

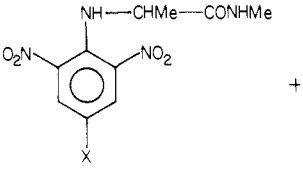


47a, R = Me; X = NO_2
b, R = Me; X = H
c, R = $CH_2CH_2NH_2$; X = NO_2

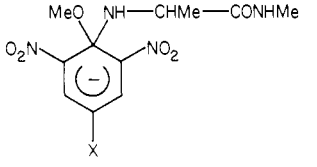


48

The reaction of MeO^- with 2,6-dinitro-4-X-anilino-*N*-methylpropionamides **49a–c** in MeOH is unique in



49



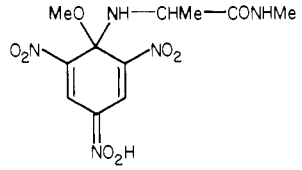
50

a, X = NO_2; b, X = CN; c, X = SO_2Me

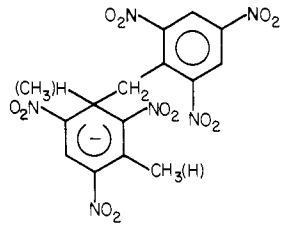
(31)

that base addition takes place at the 1-position to give the 1,1-complexes **50a–c**.[178] There is no anilino NH ionization, 3-complex formation, or nucleophilic displacement of the side chain. Complexes **50** have low rates of formation and decomposition but a high thermodynamic stability, as expected for addition at a substituted carbon. Stabilization of **50** through intramolecular hydrogen bonding between the anilino NH and an *o*-NO_2 group may be responsible for this stability.[178] Addition of piperidine, morpholine, or triethylamine to a methanolic solution of **49** does not displace the amido side chain but results in the for-

mation of **50**.[177] Upon acidification of **50a**, the nitronic acid **51** is formed prior to the recovery of **49a**.[177]



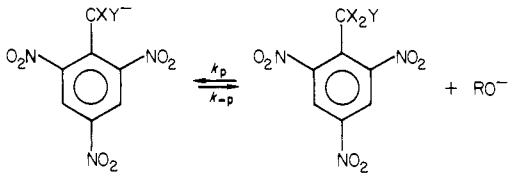
51



52

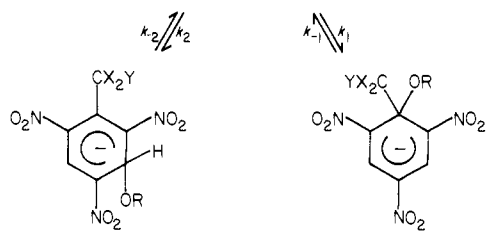
Transient 1,1-intermediates of type **50** have been observed in the reactions of picryl ethers with aliphatic amines.[179,180] RO^- addition at the 1-position of 2,4-dinitro-1-piperidinonaphthalene also yields a 1,1 complex of some stability[181,182] (see section IIB4).

b. 2,4,6-Trinitrotoluene and Derivatives. The major interactions of TNT with OH^- and RO^- (R = Me, Et, *i*-Pr, *t*-Bu) ions are base addition at the 3-position to give the 3-complexes **56a–e** and proton loss from the methyl group to give the anion **53**.[15,84,183–190] When it forms, **56** is produced prior to **53** which is thermodynamically more stable. With TNT in excess of the base or in the presence of surfactants formation of the Janowsky complex **52** may occur[183,190] (see section VID). Buncel, Norris, et al. have also studied the reactions of TNT-d_3 (deuterated methyl group) with EtO^-, *i*-PrO^-, and *t*-BuO^- in EtOH, *i*-PrOH and *t*-BuOH, respectively.[185–188] As shown by the observation of an isotope effect of about 8 in the three systems, the formation of **53** involves a rate-determining proton transfer. In *i*-PrOH and *t*-BuOH, ion-pairing effects strongly affect the reactions.[186–188] Evaluation of the individual roles of free RO^- ions and ion pairs was possible in both σ-complex formation and the proton transfer, using equations similar to eq 22. In *i*-PrOH the free *i*-PrO^- ions are the more reactive species in proton transfer while in σ-complex formation the free ions and ion pairs have comparable reactivity.[186] In *t*-BuOH, free *t*-BuO^- ions are far more reactive than the ion pairs in forming both **53** and **56e**.[188] In contrast with the behavior of TNT, the most stable complex derived from TNBCl



53, X = Y = H
54, X = Y = D
55, X = H; Y = Cl

TNT
TNT-d_3
TNB-Cl



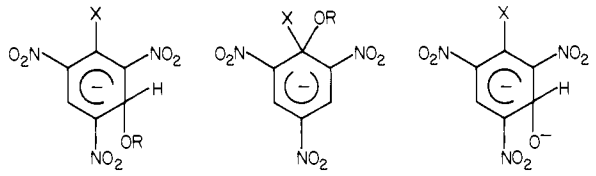
(32)

56, X = Y = H
57, X = Y = D
58, X = H; Y = Cl
a, R = H; b, R = Me;
c, R = Et; d, R = *i*-Pr;
e, R = *t*-Bu

59, X = H; Y = Cl
b, R = Me; c, R = Et

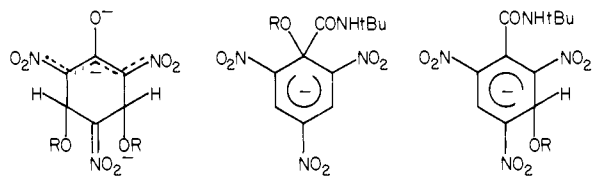
results from addition at the 1-position.[190] **59** has a stability comparable with that of the anion **55**. Proton transfer is largely favored over base addition in the reactions of EtO^- with trinitro-*m*-xylene and trinitromesitylene.[15] Rate and equilibrium data are summarized in Table XII.

c. Miscellaneous Benzene Derivatives. Kinetics and equilibrium data are available for the reactions of a number of 1-X-2,4,6-TNB with OH^- in aqueous solution.[136,191–194] In each case, the 3-hydroxy complex **60**,



60 **61** **62**

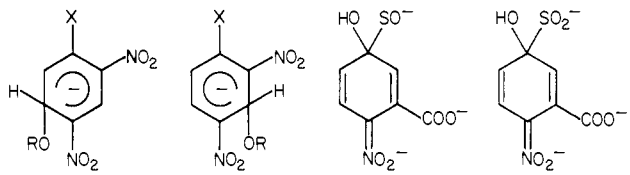
R = H; X = (a) Cl; (b) NO_2; (c) SO_3^-; (d) COO^-; (e) O^-
R = Me; X = (a′) Cl; (e′) O^-
R = Et; X = (a″) Cl; (b″) NO_2



63e, R = H
63e′, R = Me

64a, R = H
64b, R = Me
64c, R = Et

65a, R = H

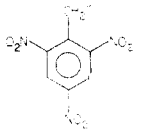
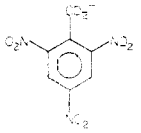
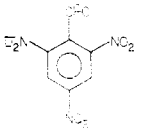
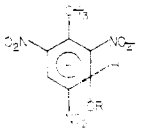
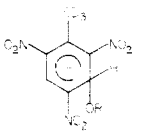
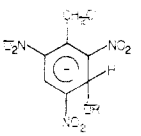
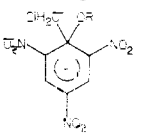


66 **67** **68** **69**

and not the complex **61**,[77,195] is initially formed. Ionization of the added OH group of **60** to give **62** has been observed.[136,191] For X = Cl, NO_2, SO_3^-, nucleophilic displacement occurs in a second step via OH^- attack at the X-bearing carbon of the parents to give picrate ion (**61** is undetected). The major interaction between picrate ion and OH^- in water and MeOH is the formation of the diadducts **63**[136,140,196] (Table VII). A remarkable result is that *N-tert*-butyl-2,4,6-trinitrobenzamide reacts with OH^-, MeO^-, and EtO^- to give the 1,1-complexes **64**.[199] No nucleophilic displacement of the side chain occurs. The stability of these unsymmetrical 1,1-complexes is probably due to the important relief of steric strain which accompanies their formation.[199] In H_2O–Me_2SO mixtures and in the presence of bile salts, the 1,3-complex **65a** is reported to be thermodynamically favored relative to **64a**.[200] All the rate and equilibrium data are listed in Table VIII.

Kinetic evidence exists for the transient formation of complexes **66** and/or **67** in the reactions of OH^- and MeO^- with a number of 1-X-2,4-dinitrobenzenes (X = Cl, Br . . .) in H_2O–Me_2SO and MeOH–Me_2SO mixtures.[201,202] The oxidative decomposition of 3-carboxy-4-nitrobenzenesulfenate in aqueous KOH 15.3 M involves the formation of an observable mononitrobenzene complex which is **68** or **69**. A mixture of these two species is also possible.[203] The lack of a good leaving group is responsible for the appreciable stability

TABLE XII. Kinetic and Thermodynamic Parameters for the Reactions of TNT and Derivatives with Hydroxide and Alkoxide Ions

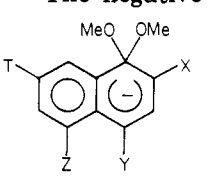
	anion or Cpx	solvent	base[a] (RO^-)	t, °C	k_f,[b] $L\ mol^{-1}\ s^{-1}$	k_d,[b] s^{-1}	K,[b] $L\ mol^{-1}$	comments[c]	ref
	53	H_2O–dioxane 50:50	OH^-	25	2.42	0.0075	323	0.2 M NaCl[i]	183
		MeOH	MeO^-	25	13.3	1.07	12.4	0.5 M $NaClO_4$[i]	183
				25	20			isnc	189
				20			7.1	isnc	84
		MeOH–Me_2SO 60:40		25			225	isnc	189
		50:50		25			530	isnc	189
		40:60		25			1000	isnc	189
		EtOH	EtO^-	25	82	0.045	1820	0.4 M $NaClO_4$[i]	183
				19	63	0.039	2040	isnc	15
				25	138	0.08	1700	isnc	185
		EtOD		25	250			isnc; k^{EtOD}/k^{EtOH} = 1.81	185
		i-PrOH	*i*-PrO^-	30	7123				186
		t-BuOH	*t*-BuO^-	30	2.7×10^5 [d]			$k_{f,ip} = 7 \times 10^3$ [e]	188
	54	EtOD	EtO^-	25	39.1	0.02	2000		185
		EtOH		25	19.8			$k_f^{TNT}/k_f^{TNT\text{-}d_3} = 7$	185
		i-PrOH	*i*-PrO	30	848				186
		t-BuOH	*t*-BuO^-	30	4.2×10^4 [d]			$k_{f,ip} = 8 \times 10^2$ [e]	188
	55	MeOH	MeO^-	25	16	0.065	250	isnc	190
	56b	MeOH	MeO^-	25	280	3000	0.09	isnc	189
		MeOH–Me_2SO 60:40		25	2800	100	28	isnc	189
		50:50		25	5400	35	155	isnc	189
		40:60		25	12000	10	1200	isnc	189
	56c	EtOH	EtO^-	25	1500–3000	80–200	7.5–37.5	isnc	183
				−80	0.019	0.011	1.7	isnc	184
				25	1000[h]	12[h]	80[h]	isnc	184
	56d	*i*-PrOH	*i*-PrO^-	25	1580	3.64	440	isnc	186
	56e	*t*-BuOH	*t*-BuO^-	30	3.8×10^5 [d]			$k_{f,ip} = 1.4 \times 10^3$ [e]	188
	57e	*t*-BuOH	*t*-BuO^-	30	3.8×10^5 [d]			$k_{f,ip} = 1.4 \times 10^3$ [e]	188
	58b	MeOH	MeO^-	25			<20	isnc	190
	58c	EtOH	EtO^-	25	10000	14	700	isnc	190
	58d	*i*-PrOH	*i*-PrO^-	25	10^5 [f]			$k_{f,ip} = 10^4$ [g]	190
	59b	MeOH	MeO^-	25	770	2.2	350	isnc	190
	59c	EtOH	EtO^-	25	7000	<1	$>10^4$	isnc	190

[a] Sodium hydroxide or alkoxides unless indicated otherwise. [b] k_f, k_d, and K refer to the various rate and equilibrium constants of eq 32. [c] See Table I for abbreviations; $k_{f,ip}$ refers to proton loss or base addition steps involving ion pairs RO^-, M^+. [d] KO-*t*-Bu + crown ethers or *n*-Bu_4O-*t*-Bu. [e] KO-*t*-Bu. [f] Me_4NO-*i*-Pr. [g] NaO-*i*-Pr + sodium salts. [h] Calculated at 25 °C from activation and thermodynamic parameters. [i] Rate and equilibrium constants for formation and decomposition of the Janowsky complex 52: k_f = 442, k_d = 3.5, K = 18.9 in MeOH; k_f = 700, k_d = 34.5, K = 20.3 in EtOH; k_f = 3400, k_d = 30, K = 113 in H_2O–dioxane 50:50; see ref 183.

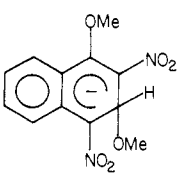
of **68** and/or **69** which would exist predominantly as their conjugate bases.

4. Naphthalenes

1-Methoxy-2,4-dinitronaphthalene reacts with dilute MeO^- solutions in MeOH to give directly the 1,1-complex **70a** according to eq 1.[44,108,120,204] The stability of **70a** (K_1 = 240 L mol^{-1} at 25 °C) is (4.6×10^6)-fold greater and 75-fold lower than that of the 1,1-complexes **25g** and **13a** of 2,4-dinitroanisole and TNA, respectively[204] (Table XIII). This shows that the stabilizing effect of the added aromatic ring, relative to **25g**, is almost the same as that of an additional *o*-NO_2 group.[11,204] The negative activation volume for the



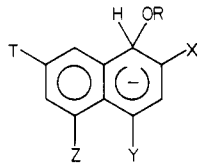
70a, X = Y = NO_2; Z = T = H
b, X = NO_2; Y = CN; Z = T = H
c, X = CN; Y = NO_2; Z = T = H
d, X = Y = Z = NO_2; T = H
e, X = Y = T = NO_2; Z = H
f, X = Y = T = H; Z = NO_2



71

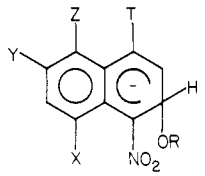
uncatalyzed decomposition of **70a** ($\Delta V_{-1}^{\ddagger}$ = -8.9 cm^3 mol^{-1}) is consistent with a reactant-like rather than with a complex-like transition state.[44] Replacing one of the two NO_2 groups of **70a** by a cyano group gives **70b** and **70c** which both have, as expected, a lower stability.[205] Introduction of a third nitro group at the 5- and 7-positions of **70a** increases the stability by a factor of 130 and 500, respectively.[206,207] The steric interaction between the 4- and 5-NO_2 groups of **70d** which results in some loss of coplanarity and hence to decreased conjugation would be the major factor responsible for the lower stability of this adduct relative to its isomer **70e**.[206,207] The rate of decomposition of **70a** and **70d** is catalyzed, like that of **13a**, by hydronium ion in aqueous solution.[204,206] The k^{H^+} rate constants parallel the order of stability **70a** > **13a** > **70d**. Of interest is that the formation of the less stable purple-colored 1,3-complex **71** may be detected prior to that of **70a** in mixtures with ≥70% Me_2SO.[108] While the stability of **70a** is close to that of the cyano 1,1-complex **13c**, the stability of **71** is 1400-fold smaller than that of the cyano 1,3-complex **12c** and similar to that of the fluoro 1,3-complex **12i**. The surprisingly low stability of **71** results from the absence of a NO_2 group para to the sp^3 carbon. In fact, the structure of **71** resembles that of the 1,5-complexes **23**.[108] Surprisingly, the analogous 1,3-complexes of 1-methoxy-2,4,5- or -2,4,7-trinitronaphthalene have not been observed. The 1,1-complex **70f** from 1-methoxy-5-nitronaphthalene forms in 90% Me_2SO-10% MeOH.[208]

The reactions of OH^- and MeO^- ions with 1,3,6,8-tetranitro-, 1,3,8-trinitro-, and 1,3-dinitronaphthalenes result in equilibrium formation (eq 1) of the hydroxy or methoxy adducts **72**. Similarly, 1,4,5,8- and



72

X = Y = Z = T = NO_2; (a) R = H; (a') R = Me
X = Y = Z = NO_2; T = H; (b) R = H; (b') R = Me
X = Y = NO_2; Z = T = H; (c) R = H; (c') R = Me



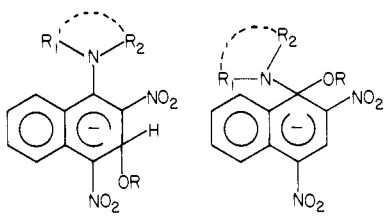
73

X = Y = T = NO_2; Z = H; (a) R = H; (a') R = Me
X = Z = T = NO_2; Y = H; (b) R = H; (b') R = Me
X = T = NO_2; Y = Z = H; (c) R = H; (c') R = Me
X = Y = T = H; Z = NO_2; (d') R = Me

1,3,5,8-tetranitro-, 1,4,5-trinitro-, and 1,5-dinitronaphthalenes give the adducts **73**.[108,208,209] Rate constants for the formation and decomposition of all these complexes have been determined (Table XIII). In a number of cases, the reactions are followed by slower processes shown to be nucleophilic displacements of NO_2 groups, as evidenced by liberation of nitrite ions.[208] Buffer catalysis has been observed in the formation of **72a**.[209]

Complexes of type **72** are clearly different from those of type **73**. In the first series, the incoming lyate ion attacks at a position both ortho and para with respect to the two NO_2 groups in the ring undergoing substitution. In the second series, attack takes place at a position ortho and/or meta with respect to the nitro(s) group(s) in the ring undergoing substitution. This behavior is unique in Meisenheimer arene complexes. However, for the same number of NO_2 groups, complexes **73** are of lower stability than those of type **72**. In each series, the stability order parallels the increase in the number of nitro groups in the second ring, i.e., **72c** < **72b** < **72a** and **73d** < **73c** < **73b** < **73a**. When the tetranitro complexes **73a(a')** and **73b(b')** are compared, the lower stability of the latter is due to noncoplanarity of the two peri NO_2 groups which reduces delocalization of the negative charge.[208] The formation and decomposition of the most stable hydroxy complex **72a** have been studied in D_2O.[209] The observed solvent isotope effects on k_1, k_{-1}, and K_1 are similar to those observed for **25b**, **25g**, and **14a**: $k_1^{H_2O}/k_1^{D_2O}$ = 0.505; $k_{-1}^{H_2O}/k_{-1}^{D_2O}$ = 1.7; $K_1^{H_2O}/K_1^{D_2O}$ = 0.3.

In 90% Me_2SO-10% MeOH, 1-*N*-piperidyl-2,4-dinitronaphthalene reacts with MeO^- according to eq 10 to give the 3-methoxy complex **74a** prior to the more stable unsymmetrical 1,1-complex **75a**.[58,493] Rate and



74a 75a
74b 75b
74c 75c

R = Me; R_1 = R_2 = piperidine
R = Et; R_1 = R_2 = piperidine
R = Et; R_1 = Me; R_2 = *n*-Bu

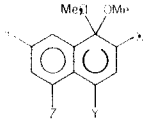
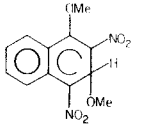
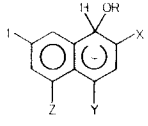
equilibrium parameters for these reactions have been determined by SF (Table XIII). **74a** has a thermodynamic stability similar to that of the 1,3-dimethoxy analogue **71**: K_2^{71}/K_2^{74} = 1.7. Similarly, the 3-ethoxy complexes **74b** and **74c** have been detected prior to their 1,1-isomers in Me_2SO.[210]

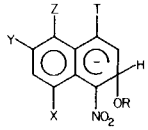
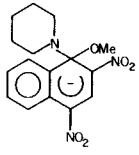
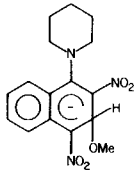
Addition of Me_2SO to aqueous or MeOH solutions enhances the stability of all naphthalene complexes due to an increase in the rates of formation and a decrease in the rates of decomposition.[108,208] The situation is similar to that found for benzene complexes. In contrast, the effect of dioxane is less straightforward.[208] Increasing dioxane concentration only slightly increases the rates of formation of the hydroxy complexes **72b**, **73b**, and **73c**. On the other hand, the decomposition rates are either almost unaffected (**72b**, **73c**) or increased with increasing the amount of dioxane (**73b**). As a result, dioxane does not stabilize σ complexes as effectively as Me_2SO. This result is emphasized by a decrease in the stability of **73b** when dioxane is added to the aqueous solutions.

5. *Heterocyclic Substrates*

a. Substituted Nitropyridines and -Pyrimidines. In agreement with the well-known activating effect of the aza group in nucleophilic heteroatomic substitu-

TABLE XIII. Kinetic and Thermodynamic Parameters for Formation and Decomposition of Hydroxy- and Methoxynaphthalene σ Complexes

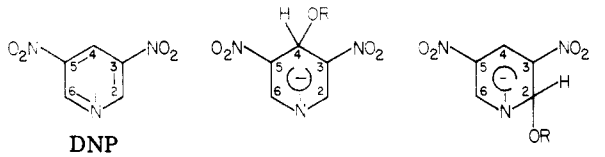
	Cpx	X	Y	Z	T	R	solvent	t, °C	k_f,[b] L mol^{-1} s^{-1}	k_d,[b] s^{-1}	K,[b] L mol^{-1}	activation and thermodynamic parameters,[c] conditions and comments[d]	ref
	70a	NO_2	NO_2	H	H		MeOH	25	0.95	3.95×10^{-3}	240	isnc; $\Delta H_f^{\ddagger} = 55.2$; $\Delta S_f^{\ddagger} = -71$; $\Delta H_d^{\ddagger} = 66.5$; $\Delta S_d^{\ddagger} = -75$; $\Delta H^{\circ} = -11.3$; $\Delta S^{\circ} = 4$	204
								25	0.89	3.9×10^{-3}	228	isnc; $\Delta V_f^{\ddagger} = -13.2$; $\Delta V_d^{\ddagger} = -8.9$; $\Delta V = -4.3$	44
								25			205	LiOMe	120
								20	0.745	2.4×10^{-3}	310	isnc	108
							H_2O	25		1.76×10^{-3}		isnc; $k^{H^+} = 1.5 \times 10^4$ [e]	204
							H_2O–MeOH 70:30[i]	20	3.02	1.32×10^{-3}	2290	isnc; $k^{H^+} = 2.24 \times 10^4$ [e]	147
							MeOH–Me_2SO 70:30	20	4.9	8×10^{-4}	6150	isnc	108
							60:40	20	10	3.77×10^{-4}	26500	isnc	108
	70b	NO_2	CN	H	H		MeOH	25			14.4	isnc	205
	70c	CN	NO_2	H	H		MeOH	25			3.3	isnc	205
	70d	NO_2	NO_2	NO_2	H		MeOH	25	32.8	1.12×10^{-3}	29300	isnc; $\Delta H_f^{\ddagger} = 48.5$; $\Delta S_f^{\ddagger} = -52$; $\Delta H_d^{\ddagger} = 75.2$; $\Delta S_d^{\ddagger} = -49$; $\Delta H^{\circ} = -26.7$; $\Delta S^{\circ} = -3$	206
								35		10^{-3}	1760	^{14}C exchange; $\Delta H_d^{\ddagger} = 75$; $\Delta S_d^{\ddagger} = -57$	42
							H_2O	25		1.59×10^{-4}		isnc; $k^{H^+} = 1.38 \times 10^3$ [e]	206
	70e	NO_2	NO_2	H	NO_2		MeOH	25	62	5.70×10^{-4}	1.09×10^5	isnc; $\Delta H_f^{\ddagger} = 53$; $\Delta S_f^{\ddagger} = -33.5$; $\Delta H_d^{\ddagger} = 82.4$; $\Delta S_d^{\ddagger} = -30$; $\Delta H^{\circ} = -29.4$; $\Delta S^{\circ} = -3.5$	207
	71						MeOH–Me_2SO						
							30:70	20	370	65	5.7	isnc	108
							10:90	20	7800	8.5	916	isnc	108
	72a	NO_2	NO_2	NO_2	NO_2	H	H_2O	25	250	2.25×10^{-2}	11000	at zero ionic strength	209
								25	333	2.38×10^{-2}	14000	10^{-2} M $Na_2B_4O_7$	209
						D	D_2O	25	660	1.40×10^{-2}	47000	10^{-2} M $Na_2B_4O_7$; $k_f^{H_2O}/k_f^{D_2O} = 0.505$ $k_d^{H_2O}/k_d^{D_2O} = 1.7$; $K^{H_2O}/K^{D_2O} = 0.3$	209
	72a'					Me	MeOH	25	2.32×10^4	<3	>7700	isnc; $\Delta H_f^{\ddagger} = 32$; $\Delta S_f^{\ddagger} = -49$	208
	72b	NO_2	NO_2	NO_2	H	H	H_2O	25	3.8	0.12	43		208
							H_2O–dioxane 95:5	25	5.7	0.17	35	isnc, $\Delta H_f^{\ddagger} = 56.9$; $\Delta S_f^{\ddagger} = -39$	208
							87.5:12.5	25	10.2	0.25	42	isnc	208
							75:25	25	18.7	0.20	100	isnc	208
	72b'					Me	MeOH	25	304.6	22	13.8	isnc; $\Delta H_f^{\ddagger} = 48.5$; $\Delta S_f^{\ddagger} = -33$; $\Delta H_d^{\ddagger} = 45.5$; $\Delta S_d^{\ddagger} = -63$; $\Delta H^{\circ} = 3$; $\Delta S^{\circ} = 30$	208
	72c	NO_2	NO_2	H	H	H	H_2O	25	0.29	1.12	0.26	isnc	208
							H_2O–Me_2SO 70:30	25	2.88	0.25	12	isnc	208
							50:50	25	11.4	0.08	140	isnc	208
	72c'					Me	MeOH	25	11.2	124	0.09	extrapolated at zero [MeO^-]	208

							MeOH–Me_2SO						
							60:40	20	174	7.6	23	isnc	108
							40:60	20	1120	1.2	935	isnc	108
	73a	NO_2	NO_2	H	NO_2	H	H_2O	25	12.8	0.02	640	isnc	208
	73a'					Me	MeOH	25	7900	18	438	isnc; $\Delta H_f^{\ddagger} = 37.6$; $\Delta S_f^{\ddagger} = -43.5$; $\Delta H_d^{\ddagger} = 52$; $\Delta S_d^{\ddagger} = -46.5$; $\Delta H^{\circ} = -14.4$; $\Delta S^{\circ} = 3$	208
	73b	NO_2	H	NO_2	NO_2	H	H_2O	25	40[f]	0.10[f]	300[f]		208
							H_2O–dioxane						
							90:10	25	39.5	0.24	170	isnc	208
							80:20	25	35	0.45	80	isnc	208
							70:30	25	94.5	1.25	75	isnc	208
							60:40	25	92	2.4	40	isnc	208
	73b'					Me	MeOH	25	1960	10	196	isnc; $\Delta H_f^{\ddagger} = 27.8$; $\Delta S_f^{\ddagger} = -88$; $\Delta H_d^{\ddagger} = 47.7$; $\Delta S_d^{\ddagger} = -65.6$; $\Delta H^{\circ} = -20$; $\Delta S^{\circ} = -22.4$	208
	73c	NO_2	H	H	NO_2	H	H_2O	25	0.08[g]	0.018[g]	7[g]		208
							H_2O–dioxane						
							90:10	25	0.14	0.015	11	isnc	208
							75:25	25	0.25	0.024	11.5	isnc	208
	73c'					Me	MeOH	25			1.5[h]		208
	73d'	H	H	NO_2	H	Me	MeOH–Me_2SO						
							10:90	25	7.4	0.6	12.3	isnc	208
	75a						MeOH–Me_2SO						
							10:90	25	2.53	1.8×10^{-4}	1.4×10^4	isnc; $\Delta H_f^{\ddagger} = 51$; $\Delta S_f^{\ddagger} = -64.4$; $\Delta H_d^{\ddagger} = 114$; $\Delta S_d^{\ddagger} = 66$; $\Delta H^{\circ} = -63$; $\Delta S^{\circ} = -130.4$	58
	74a						MeOH–Me_2SO						
							10:90	25	492	0.95	520	isnc; $\Delta H_f^{\ddagger} = 48$; $\Delta S_f^{\ddagger} = -32$; $\Delta H_d^{\ddagger} = 59$; $\Delta S_d^{\ddagger} = -47$; $\Delta H^{\circ} = -11$; $\Delta S^{\circ} = 15$	58

[a] Sodium or potassium hydroxides and methoxides unless indicated otherwise. [b] k_f, k_d, and K represent k_1, k_{-1}, K_1 or k_2, k_{-2}, K_2 as defined by eq 1 or 10. [c] ΔH in kJ mol^{-1}, ΔS in J mol^{-1} K^{-1}, ΔV in cm^3 mol^{-1}. [d] See Table I for abbreviations. [e] k^{H^+} in L mol^{-1} s^{-1}, as defined by eq 4 with R = H. [f] Estimated values from plots of k_f, k_d, and K against % dioxane. [g] Extrapolated values from plots of k_f and k_d against [dioxane]; $K = k_f/k_d$. [h] Estimated values due to decomposition. [i] 75% H_2O–25% MeOH by weight.

tion reactions, electron-deficient pyridines and pyrimidines easily form stable hydroxy and alkoxy σ complexes.[53,82,114,115,212-220] For facilitation of comparison of the corresponding heteroaromatic dimethoxy complexes with those of 4-X-2,6- and 2-X-4,6-DNA, the investigated methoxy pyridines and pyrimidines are numbered as substituted anisoles, starting from the methoxy-bearing carbon. The available kinetic and thermodynamic parameters are given in Table XIV.

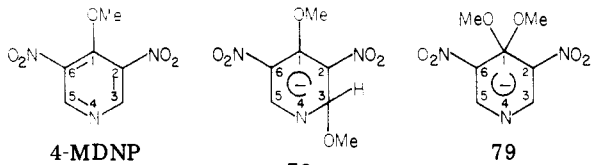
3,5-Dinitropyridine (DNP) behaves in a fashion analogous to 1-X-3,5-DNB toward OH^- and MeO^- in H_2O-Me_2SO and MeOH-Me_2SO mixtures[82,215] (see eq 25). Base addition at C-4 to give the complexes **76** is



DNP

76a R = H 77a
76b R = Me 77b

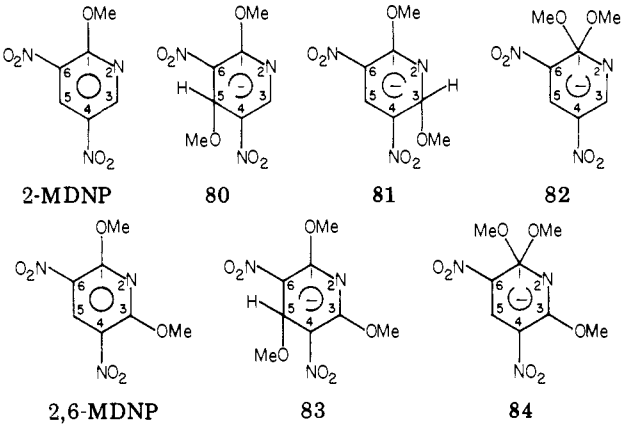
kinetically favored, but isomerization occurs to give the more stable complexes **77** which have a NO_2 group para to the sp^3 carbon. The 4-complexes **76a** and **76b** have a stability intermediate between those of TNB (**5a,b**) and cyano analogues (**10a',a**), but the 2-complexes **77a** and **77b** are more stable than **5a** and **5b**: both ratios K^{77a}/K^{5a} and K^{77b}/K^{5b} are ~3.[82] This points out the remarkable effect of *o*-aza functionality relative to an *o*-NO_2 group on complex stability. This result is also substantiated by the greater stability of the 1,3-dimethoxy complex **78** relative to the TNA analogue **12a**: K^{78}/K^{12a} = 4.3.[53] **78** forms prior to the 1,1-complex **79**



4-MDNP 78 79

in the reaction of MeO^- with 4-methoxy-3,5-dinitropyridine (4-MDNP) in MeOH and MeOH-Me_2SO mixtures.[53] That 4-MDNP behaves as a 4-aza-2,6-dinitroanisole is shown by the fact that the ratios k_2/k_1, k_{-2}/k_{-1}, and K_2/K_1 of the rate and equilibrium constants (as defined by eq 26) for formation and decomposition of **78** and **79** are at the expected places in the sequences of Table IV.[53] The effect of going from MeOH to 90% Me_2SO-10% MeOH increases the lifetime of **78** by a factor of 3×10^3.[53]

2-Methoxy-3,5-dinitropyridine (2-MDNP) does not behave as the analogous 2-X-4,6-DNA. MeO^- attack on 2-MDNP yields the 1,3-complex **81** as the stable entity and not the 1,1-complex **82**.[214,217] This result is important in that it unambiguously confirms that release of steric strain on addition to the 1-position of anisoles is one of the most important factors governing the stability of the 1,1-dimethoxy complexes. Steric strain around the OMe group is clearly reduced in 2-MDNP compared with other parents in the series. This is further evidenced by comparing the results for 2-MDNP to those for 4-MDNP and 2,6-dimethoxy-3,5-dinitropyridine (2,6-MDNP).[217] On the one hand, the 1,3-complex **81** has rate and equilibrium constants similar to those for its structurally similar isomer **78**, showing that it is not unusually stable. On the other

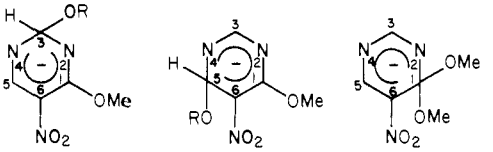


2-MDNP 80 81 82

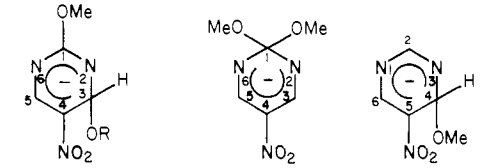
2,6-MDNP 83 84

hand, 2,6-MDNP reacts with MeO^- ions to form the 1,1-complex **84** which has a structure close to that of the undetectable analogue **82**. The stability of **84** is ~60-fold lower than that of **81** due to an "unexpectedly" high rate of decomposition.[217] By analogy, there is no doubt that the lack of observation of the 1,1-complex **82** is the result of its lower stability relative to that of the 1,3-isomer **81**. At high [MeO^-], the formation of the 1,5-complex **83** was seen to precede that of **84** in the mixtures rich in Me_2SO.[217] Also to be noted is that demethylation of 2-MDNP and 2,6-MDNP, via an S_N2 mechanism, competes with the formation of the adducts and yields the anions derived from 2-hydroxy-3,5-dinitro- and 2-hydroxy-6-methoxy-3,5-dinitropyridines.[214,217] Addition of Me_2SO to the MeOH solutions considerably decreases the rate of this irreversible reaction whereas it greatly enhances complex stability.[217]

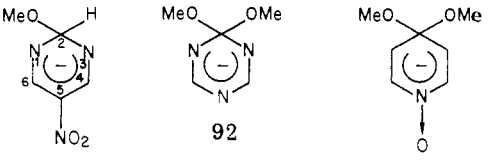
In agreement with the results obtained for 2-MDNP, 4-methoxy-5-nitro- and 2-methoxy-5-nitropyrimidines react with MeO^- to give the complexes **85b** and **88b**, respectively.[213,219,220] Kinetic studies show no evidence



85a R = H 86a 87
85b R = Me 86b



88a, R = H 89 90
b, R = Me



91 92 93

for isomerization into the 1,1-isomers **87** and **89**, or for formation of the 1,5-complex **86b** in MeOH-Me_2SO mixtures.[219] However, ^1H NMR experiments have confirmed the presence of **89** (~5%) at final equilibrium in Me_2SO.[220] Kinetic and equilibrium data have

TABLE XIV. Kinetic and Thermodynamic Parameters for Formation and Decomposition of Hydroxy- and Methoxypyridine and pyrimidine σ Complexes

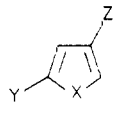
Cpx	R	solvent[a]	t, °C	k_f,[b] L mol^{-1} s^{-1}	k_d,[b] s^{-1}	K[b] L mol^{-1}	activation and thermodynamic parameters;[c] conditions and comments[d]	ref
77a	H	H_2O	25	34	2.82	12	isnc; $\Delta H_f^{\ddagger} = 57$; $\Delta S_f^{\ddagger} = -23.4$; $\Delta H_d^{\ddagger} = 49.8$; $\Delta S_d^{\ddagger} = -66.9$; $\Delta H^{\circ} = 7.2$; $\Delta S^{\circ} = 43.5$	82
			20	23.5	2	11.75	isnc	82
		H_2O-Me_2SO 80:20	20	51.5	0.65	79.5	isnc	82
		60:40	20	138	0.12	1150	isnc	82
77b	Me	MeOH	25	2460	35.5	69.5	isnc; $\Delta H_f^{\ddagger} = 52.2$; $\Delta S_f^{\ddagger} = -4.2$; $\Delta H_d^{\ddagger} = 43.5$; $\Delta S_d^{\ddagger} = -71$; $\Delta H^{\circ} = 8.7$; $\Delta S^{\circ} = 67$	82
			20	1740	24	72.5	isnc	82
		MeOH-Me_2SO 80:20	20	4560	7.6	600	isnc	82
76a	H	H_2O-Me_2SO 60:40	20	345	9	38.4	isnc	82
		50:50	20	1025	3.5	293	isnc	82
79		MeOH	20	13.8	5×10^{-3}	2770	isnc	114
			20	16.5	5.75×10^{-3}	2870	isnc	53
			25	23	8.6×10^{-3}	2680	isnc; $\Delta H_f^{\ddagger} = 47.6$; $\Delta S_f^{\ddagger} = -58.5$; $\Delta H_d^{\ddagger} = 58$; $\Delta S_d^{\ddagger} = -90$; $\Delta H^{\circ} = -10.4$; $\Delta S^{\circ} = 31.5$	53
		MeOH-Me_2SO 80:20	20	48	2.37×10^{-3}	20200	isnc	53
		50:50	20	330				53
78		MeOH	25	390	33.2	11.7	isnc; $\Delta H_f^{\ddagger} = 43$; $\Delta S_f^{\ddagger} = -50.6$; $\Delta H_d^{\ddagger} = 39$; $\Delta S_d^{\ddagger} = -85.3$; $\Delta H^{\circ} = 4$; $\Delta S^{\circ} = 34.7$	53
			20	275	25	11	isnc	53
		MeOH-Me_2SO 80:20	20	630	6.95	91	isnc	53
		50:50	20	3710	0.7	5300	isnc	53
81		MeOH	20			1.91	isnc	214
			20	415	125	3.32	isnc	217
		MeOH-Me_2SO 70:30	20	2520	27	93.5	isnc	217
			25	3600	40	90	isnc; $\Delta H_f^{\ddagger} = 38$; $\Delta S_f^{\ddagger} = -49$; $\Delta H_d^{\ddagger} = 44$; $\Delta S_d^{\ddagger} = -66$; $\Delta H^{\circ} = -6$; $\Delta S^{\circ} = 17$	217
		50:50	20	17200	3	5730	isnc	217
		30:70	20	60000	0.5	1.2×10^5	isnc	217
84		MeOH	20	10.5[e]	180[e]	0.058[f]		217
		MeOH-Me_2SO 70:30	20	101	19.8	5.1	isnc	217
		50:50	20	300	5.75	52	isnc	217
		30:70	20	2500	0.91	2750	isnc	217
83		MeOH-Me_2SO 40:60	20			6.6	isnc	217
		30:70	20			45	isnc	217
		20:80	20			660	isnc	217
85a	H	H_2O-Me_2SO 50:50	20	39.5	0.04	990	isnc	219
		40:60	20	111	0.015	7400	isnc	219
85b	Me	MeOH-Me_2SO 60:40	20	456	39	11.7	isnc	219
		50:50	20	1045	20	52	isnc	219
		40:60	20	2250	10	225	isnc	219
88a	H	H_2O-Me_2SO 50:50	20	320	7.4	43.5	isnc	219
		40:60	20	1120	2.5	450	isnc	219
88b	Me	MeOH-Me_2SO 50:50	20	9600	177	54.2	isnc	219
		40:60	20	27600	90	307	isnc	219
		30:70	20	54000	50	1080	isnc	219
91		MeOH	20	540	19.3	28	isnc	219

[a] Sodium or potassium hydroxides or alkoxides. [b] k_f, k_d, and K represent the rate and equilibrium constants for formation and decomposition of the various complexes. [c] Enthalpies in kJ mol^{-1}; entropies in J mol^{-1} K^{-1}. [d] See Table I for abbreviations.

also been obtained for the hydroxy complexes **85a** and **88a** in H_2O–Me_2SO mixtures.[219] Due to the presence of a *p*-nitro group, **85a** and **85b** decompose much more slowly than their isomers **88a** and **88b** in a given medium. In contrast with an earlier NMR report,[220] kinetic experiments have revealed that MeO^- ions attack 5-nitropyrimidine to give first the complex **90** which subsequently decomposes to **91**.[219] A ^1H NMR reinvestigation of the reaction in Me_2SO has confirmed the kinetic observations.[219] Rate and equilibrium parameters have been obtained for the formation and decomposition of the most stable complex **91**. No complex

formation has been observed in the reactions of MeO^- with 2-methoxypyrimidine and 2-methoxy-1,3,5-triazine. However, the reported rapid exchange of the methoxyl group of this latter compound with MeO^- in MeOH probably proceeds via the 1,1-complex **92**.[213] With ^{14}C-exchange techniques, a rate constant of 1.1×10^{-6} L mol^{-1} s^{-1} has been reported for formation of **93** in MeOH at 34.9 °C.[41]

b. Activated Furans, Thiophenes, and Selenophenes. Nitro-activated furans, thiophenes, and selenophenes **94** and **96** react with MeO^- ion in MeOH to give complexes **95** and **97** according to eq 1.[49,221-232]



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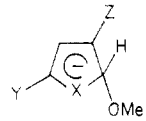
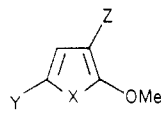
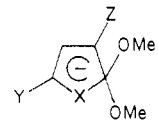


95

X = O; (a) Y = Z = NO_2; (b) Y = NO_2, Z = CN; (c) Y = NO_2, Z = H
X = S; (d) Y = Z = NO_2; (e) Y = NO_2, Z = CN; (f) Y = CN, Z = NO_2; (g) Y = NO_2, Z = H
X = Se; (h) Y = Z = NO_2; (i) Y = NO_2, Z = CN; (j) Y = CN, Z = NO_2

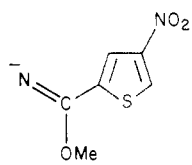


96

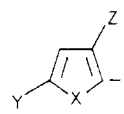


97

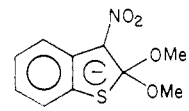
X = S; (a) Y = Z = NO_2; (b) Y = NO_2, Z = CN; (c) Y = CN, Z = NO_2; (d) Y = H, Z = NO_2
X = Se; (e) Y = Z = NO_2



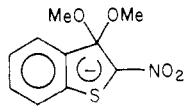
98



99



100



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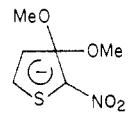
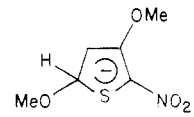


102



103

The kinetic and thermodynamic parameters determined for the various reactions studied are listed in Table XV.

Formation and decomposition of the very stable *gem*-dimethoxydinitrothiophene and -selenophene adducts **97a** and **97e** have been studied in buffer solutions and the data analyzed by coupling eq 1 and 4.[49] The pK_a^{MeOH} values are 11.36 and 10.07, respectively, but MeOH attack on the parents is not a significant process. In the case of the furans **94a-c**, ring opening competes with complex formation so that **95a-c** are seen only as short-lived species.[230] In the reaction of MeO^- with 2-cyano-4-nitrothiophene **94f**, the formation of **95f** is followed by the slower appearance of methyl 4-nitro-2-thiophenecarboxyimidate **98** which arises from concurrent MeO^- attack at the CN group of **94f**.[226,231] Dinitro- and cyanonitrothiophenes **94d**, **94e**, and selenophenes **94h-j** undergo a very rapid H/D exchange process at the 2-position in MeOD. The reaction presumably proceeds via the carbanion **99**.[233]

For similarly activated rings, the K_1 values are in the order O > Se >> S. For example, the ratios K_1^O/K_1^{Se} and K_1^O/K_1^S are equal to about 12 and 10^3, respectively, in the case of the 4-cyano-2-nitro complexes **95b**, **95e**, and **95i**. Complex stability thus decreases with decreasing the electronegativity of the heteroatom and increasing the aromaticity of the parent. The k_1 values for MeO^- addition are also in the order O > Se > S. This is in agreement with the known relative reactivities of furan, thiophene, and selenophene substrates toward nucleophilic reagents.[235-237]

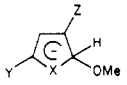
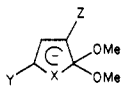
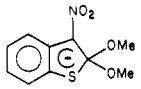
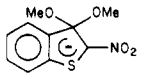
All the complexes **95** and **97** are remarkably stable compared to methoxy and *gem*-dimethoxy analogues of the 1-X-3,5-DNB and 4-X-2,6- and 2-X-4,6-DNA series (X = NO_2, CN, H). No appreciable release of steric strain occurs, however, upon formation of **97**.[49,223,229] The lower aromaticity of the parent heterocycles relative to the parent benzenes is one of the two major factors responsible for this result.[49,223] The other is the differences in the geometry of five- and six-membered rings.[49,223,229] In **94** and **96**, the X-C_2-C_3 angle has a value close to that for a tetrahedral carbon (110.7° in furan,[238] 111.5° in thiophene,[239] 110.40° in selenophene[240]) while the analogous angle in the benzene series is ~120°. Complex formation thus involves much less bond strain in the five- than in the six-membered systems.[49,223]

On the basis of results for the thiophene and selenophene series, the stability sequence is in the order 2,4-dinitro > 2-nitro-4-cyano > 2-cyano-4-nitro.[231] The replacement of a NO_2 group by a CN group in the "para-like" position of the sp^3 carbon thus has a much more important effect on complex stability than a similar replacement in the "ortho-like" position. This shows that, as in benzene series, a "para-like" NO_2 group plays a predominant role in the delocalization of the negative charge of the adducts. The higher stability of the *gem*-dimethoxy complexes **97** relative to the monomethoxy analogues **95** is due to the stabilizing influence of the two methoxy groups at the sp^3 carbon.[229,231] That **95** and **97** form at similar rates has been accounted for by the absence of appreciable F strain on approach of MeO^- to the methoxy-bearing carbon of **96**.[229] The high stability of the dinitro and cyanonitro adducts is emphasized by the high enthalpies of activation associated with their decomposition. The $\Delta H_{-1}^{\ddagger}$ values are 79, 96, and 81 kJ mol^{-1} for the selenophene complexes **95h**, **95i**, and **95j**, respectively.[231]

The reactions of 2-methoxy-3-nitro- and 3-methoxy-2-nitrobenzothiophenes with MeO^- ion to give the complexes **100** and **101** have been investigated in MeOH.[234] As expected, the added aromatic ring increases complex stability. Thus, **100** is 60-fold more stable than **97d**. Similarly, **101** is easily formed while its analogue **102** has not yet been detected.[222] Instead, the complex **103**, which benefits from the stabilizing effect of a "para-like" NO_2 group, has been characterized in the reaction of MeO^- with 2-nitro-3-methoxythiophene.[222]

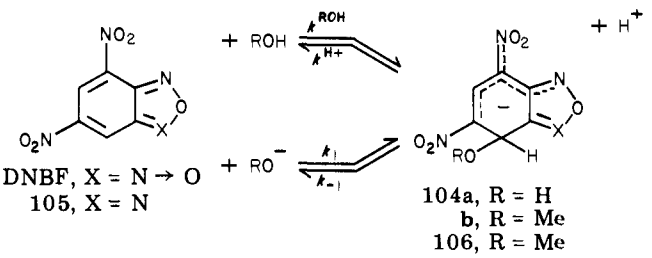
c. Nitro-2,1,3-benzoxadiazoles and Benzoxadiazole *N*-Oxides. Related Compounds. Considerable work has been done on Meisenheimer complexes of nitro-2,1,3-benzoxadiazoles and corresponding *N*-oxides.[46,47,241-252] One of the reason for this interest is that formation of such complexes is implicated in the explanation of the antileukemic activity of these compounds which are commonly known as nitrobenzo-

TABLE XV. Kinetic and Thermodynamic Parameters for Formation and Decomposition of Methoxy and Dimethoxy Complexes of Furan, Thiophene, and Selenophene Derivatives in Methanol[a]

	Cpx	X	Y	Z	t, °C	k_1,[b] L mol^{-1} s^{-1}	k_{-1},[b] s^{-1}	K_1,[b] L mol^{-1}	activation and thermodynamic parameters;[c] conditions and comments[d]	ref
	95a	O	NO_2	NO_2	25	4.5×10^3	$\leq 9 \times 10^{-3}$	$\geq 5 \times 10^5$	isnc	230
	95b	O	NO_2	CN	25	57	3.2×10^{-4}	1.8×10^5	isnc	230
	95c	O	NO_2	H	25	1.37×10^{-2}	10^{-4}	137	0.2 M $NaClO_4$	230
	95d	S	NO_2	NO_2	25	15	1.87×10^{-2}	800	0.2 M $NaClO_4$	225
					25	14.9	1.75×10^{-2}	850	isnc; $\Delta H_1^{\ddagger} = 51.8$; $\Delta S_1^{\ddagger} = -48.3$; $\Delta H_{-1}^{\ddagger} = 46.4$; $\Delta S_{-1}^{\ddagger} = -122$; $\Delta H_1^{\circ} = 5.4$; $\Delta S_1^{\circ} = 74$	231
	95e	S	NO_2	CN	25	0.78	5.2×10^{-3}	150	isnc	229
					25	0.63	5×10^{-3}	126	isnc; $\Delta H_1^{\ddagger} = 58.7$; $\Delta S_1^{\ddagger} = -51$; $\Delta H_{-1}^{\ddagger} = 70.8$; $\Delta S_{-1}^{\ddagger} = -50.8$; $\Delta H_1^{\circ} = -12$; $\Delta S_1^{\circ} \sim 0$	231
	95f	S	CN	NO_2	25	2.38	0.35	6.8	isnc; $\Delta H_1^{\ddagger} = 66.2$; $\Delta S_1^{\ddagger} = -14.6$; $\Delta H_{-1}^{\ddagger} = 53.3$; $\Delta S_1^{\ddagger} = -73.8$; $\Delta H_1^{\circ} = 13$; $\Delta S_1^{\circ} = 59$	231
	95g	S	NO_2	H	25	1.8×10^{-3}	3.2×10^{-4}	5.6	0.2 M $NaClO_4$	230
	95h	Se	NO_2	NO_2	25	27.7	4.8×10^{-4}	5.78×10^4	0.01 M buffer salts; $\Delta H_1^{\ddagger} = 58.7$; $\Delta S_1^{\ddagger} = -19.6$; $\Delta H_{-1}^{\ddagger} = 79.2$; $\Delta S_{-1}^{\ddagger} = -41.8$; $\Delta H_1^{\circ} = -20.5$; $\Delta S_1^{\circ} = 22$	231
	95i	Se	NO_2	CN	25	1.37	9.55×10^{-5}	1.43×10^4	0.01 M buffer salts; $\Delta H_1^{\ddagger} = 70.4$; $\Delta S_1^{\ddagger} = -3.3$; $\Delta H_{-1}^{\ddagger} = 95.7$; $\Delta S_{-1}^{\ddagger} \sim 0$; $\Delta H_1^{\circ} = -25$; $\Delta S_1^{\circ} \sim -4$	231
	95j	Se	CN	NO_2	25	2.62	5.37×10^{-3}	490	isnc; $\Delta H_1^{\ddagger} = 66$; $\Delta S_1^{\ddagger} = -16$; $\Delta H_{-1}^{\ddagger} = 81$; $\Delta S_{-1}^{\ddagger} = -16$; $\Delta H_1^{\circ} = -15$; $\Delta S_1^{\circ} \sim 0$	231
	97a	S	NO_2	NO_2	25	36		$>4 \times 10^5$	0.2 M $NaClO_4$	223, 225
					25	40.7			isnc; $\Delta H_1^{\ddagger} = 41.4$; $\Delta S_1^{\ddagger} = -74$;	49
					20	28.2	7.8×10^{-5}	3.6×10^5	0.01 M buffer salts; $k^{MeOH} = 10^{-7}$; $k^{H^+} = 1.05 \times 10^4$;[e] $pK_a^{MeOH} = 11.36$	49
	97b	S	NO_2	CN	25	4.85	1.94×10^{-4}	2.5×10^4	isnc	229
	97c	S	CN	NO_2	25	2.14	1.4×10^{-3}	1.53×10^3	isnc	229
	97d	S	H	NO_2	20	1.3×10^{-3}	2.2×10^{-4}	6	at zero ionic strength	232
	97e	Se	NO_2	NO_2	25	102			isnc; $\Delta H_1^{\ddagger} = 51$; $\Delta S_1^{\ddagger} = -35$	49
					20	69	1.04×10^{-5}	6.8×10^6	0.01 M buffer salts; $k^{MeOH} = 5.75 \times 10^{-7}$; $k^{H^+} = 2.65 \times 10^3$;[e] $pK_a^{MeOH} = 10.07$	49
	100				25	0.215	5.8×10^{-4}	370	isnc	234
	101				25	0.047	7.5×10^{-5}	600	isnc	234

[a] Sodium or potassium methoxide. [b] k_1, k_{-1}, and K_1 as defined by eq 1. [c] Enthalpies in kJ mol^{-1}, entropies in J mol^{-1} K^{-1}. [d] See Table I for abbreviations. [e] k^{MeOH}, in s^{-1}, and k^{H^+}, in L mol^{-1} s^{-1}, as defined by eq 4 with R = Me.

furazans and nitrobenzofuroxans, respectively.[243,253-256] The results are summarized in Tables XVI and XVII (dinitro and mononitro complexes, respectively). The adduct **104a** is the most stable hydroxy σ complex in



DNBF, X = N → O
105, X = N

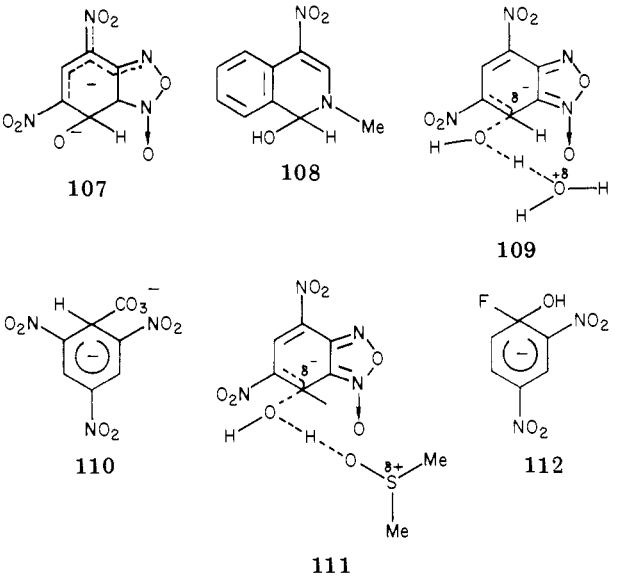
104a, R = H
b, R = Me
106, R = Me

aqueous solution known to date. It forms completely from 4,6-dinitrobenzofuroxan (DNBF) in the absence of any added hydroxide ion.[46] The $pK_a^{H_2O}$ value is 3.75 at 25 °C;[46] i.e., **104a** is almost 10^{10}-fold more stable than the TNB complex **5a**. Ionization of the OH group of **104a** occurs at pH ≥ 10.6. The $pK_a^{H_2O}$ for formation of the dianion **107** is 11.30 at 25 °C.[46] Similar $pK_a^{H_2O}$ values have been reported for ionization of the OH group of pseudobases like **108** which have a thermodynamic stability close to that of **104a**.[257,258] The kinetics of formation and decomposition of **104a** have been thoroughly investigated at different temperatures between pH 1 and 13.[46,246] Analysis of the results has been made in terms of eq 1 and 4. As shown by the pH-rate profiles of Figure 4, *104a forms exclusively from the attack of water molecules on DNBF at pH ≤ 7*. There is no other report of this kind in the field of Meisenheimer complexes. The fact that water reacts so efficiently ($k^{H_2O} = 3.45 \times 10^{-2}$ s^{-1}) with neutral DNBF to give **104a** reflects the high electrophilic character of this compound, a consequence of both the strong electron-withdrawing effect of the annelated furoxan ring and the relatively low aromaticity of the benzofuroxan system. The unique stability of **104a** is emphasized by the high enthalpy of activation for its uncatalyzed decomposition ($\Delta H_{-1}^{\ddagger} = 92$ kJ mol^{-1}).[46] The low k^{H^+} value

TABLE XVI. Rate and Equilibrium Constants for Formation and Decomposition of 4,6-Dinitrobenzofuroxan and Benzofurazan Complexes

Cpx	X	R	solvent		t, °C	k^{ROH},[a] s^{-1}	k^{H^+},[a] L mol^{-1} s^{-1}	k_1,[a] L mol^{-1} s^{-1}	k_{-1},[a] s^{-1}	pK_a[a]	K_1,[a] L mol^{-1}	conditions	ref
104a	N → O	H	H_2O[b]		25	0.0345	146	33500	2.5×10^{-6}	3.75	1.78×10^{10} [d]	0.2 M KCl	46
										3.77			243
					20[c]	0.0245	100	27400	1.35×10^{-6}	3.73	2.75×10^{10} [d]	0.2 M KCl	46
					20	0.019	80	27000	1.15×10^{-6}	3.62	2.4×10^{10} [d]	0.5 M Me_4NCl	252
		D	D_2O[f]		20	0.0147	264	30200	8×10^{-7}	4.38	1.7×10^{10} [d]	0.2 M KCl	46
		H	H_2O–Me_2SO	70:30	20	0.056	71	77000	1.12×10^{-6}	3.1	6.9×10^{11} [d]	0.5 M Me_4NCl	252
				50:50	20	0.191	46.6	3.3 × 10^5	6.5×10^{-9}	2.4	4.47×10^{13} [d]	0.5 M Me_4NCl	252
				10:90	20	1.33	37			1.5	7.25×10^{20} [d]	0.5 M Me_4NCl	252
104b	N → O	Me	MeOH		20	0.03	4.68×10^4	1.87×10^6	8.9×10^{-5}	6.46	2.1×10^{10} [e]	0.01 M buffer salts	267
106	N	Me	MeOH		20	0.028	2.09×10^4	9.3 × 10^5	2×10^{-5}	6.05	4.65×10^{10} [e]	0.01 M buffer salts	267
113b			MeOH		20	4.46×10^{-3}	1780	2.52×10^5	4.9×10^{-6}	5.93	5.14×10^{10} [e]	0.02 buffer salts	47

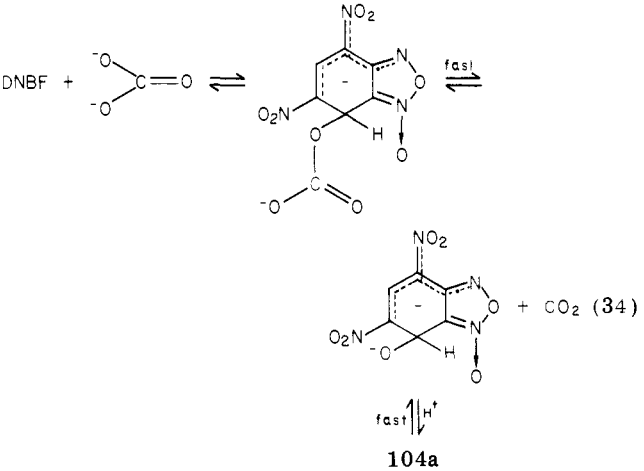
[a] Rate and equilibrium constants as defined by eq 1 and 4 with R = H, Me. [b] Activation and thermodynamic parameters (in kJ mol^{-1} or J mol^{-1} K^{-1}): $\Delta H^{\ddagger}$ (k^{H_2O}) = 48.5; $\Delta S^{\ddagger}$ (k^{H_2O}) = −110; $\Delta H^{\ddagger}$ (k^{H^+}) = 51.5; $\Delta S^{\ddagger}$ (k^{H^+}) = −30.5; $\Delta S''$ = −3; ΔH° = −79.5; $\Delta H_1^{\ddagger}$ (k_1) = 37.6; $\Delta S_1^{\ddagger}$ (k_1) = −32.4; $\Delta H_{-1}^{\ddagger}$ (k_{-1}) = 92; $\Delta S_{-1}^{\ddagger}$ (k_{-1}) = −42; ΔH_1° = −54.4; ΔS_1° = 9.6. [c] Rate constants k^{BH} and k^{B^-} (eq 33) for buffer catalysis, in L mol^{-1} s^{-1}; acetate (pK_a = 4.64); k^{BH} = 0.011; k^{B^-} = 0.0175; bicarbonate (pK_a = 6.34); k^{B^-} = 58; PO_4H^{2-} (pK_a = 6.72): k^{B^-} = 0.185; *p*-cyanophenoxide (pK_a = 7.89): k^{B^-} = 19.8; borate (pK_a = 9.12): k^{B^-} = 27.5; carbonate (pK_a = 9.98): k^{B^-} = 2370. [d] Calculated from $K_1 = K_a/K_s$ where K_s is the autoprotolysis constant of water and water–Me_2SO mixtures at the chosen ionic strength. [e] Calculated from $K_1 = k_1/k_{-1}$. [f] k^{H_2O}/k^{D_2O} = 1.67; k^{H^+}/k^{D^+} = 0.38; k_1^H/k_1^D = 0.905; k_{-1}^H/k_{-1}^D = 1.69; K_1^H/K_1^D = 0.585.



(146 L mol^{-1} s^{-1}) for the H^+-catalyzed decomposition is also remarkable.[46] Another noteworthy result is that formation and decomposition of **104a** are subject to general base and general acid catalysis, respectively, with an observed rate constant k_{obsd} fitting the equation

$$k_{obsd} = k^{H_2O} + k^{H^+}[H^+] + k_1[OH^-] + k_{BH}[BH] + k_{B^-}[B^-] \quad (33)$$

where k_{BH} and k_{B^-} are the second-order rate constants for catalysis by the acid and basic buffer species, respectively[46] (k_{-1} is negligible). From the observed buffer catalysis and isotope effects, the reaction of water with DNBF should proceed via a transition state such as **109** which represents general base catalyzed water attack with a second water molecule acting as a base catalyst.[46] Abnormally high values, as compared with those for other base catalysts, have been obtained for the rate constants k^{B^-} for base catalysis by CO_3H^- and CO_3^{2-} ions.[46] This extra reactivity has been interpreted in terms of nucleophilic catalysis and visualized as shown in eq 34.[46,259,260] The fact that DNBF readily displaces



CO_2 from bicarbonate solutions,[261-264] together with the observation of the complex **110** in benzene containing dicyclohexyl crown-6,[265] gives strong support to the proposed mechanism.

The conversion of DNBF into **104a** has been also studied in water–Me_2SO mixtures. As expected, Me_2SO

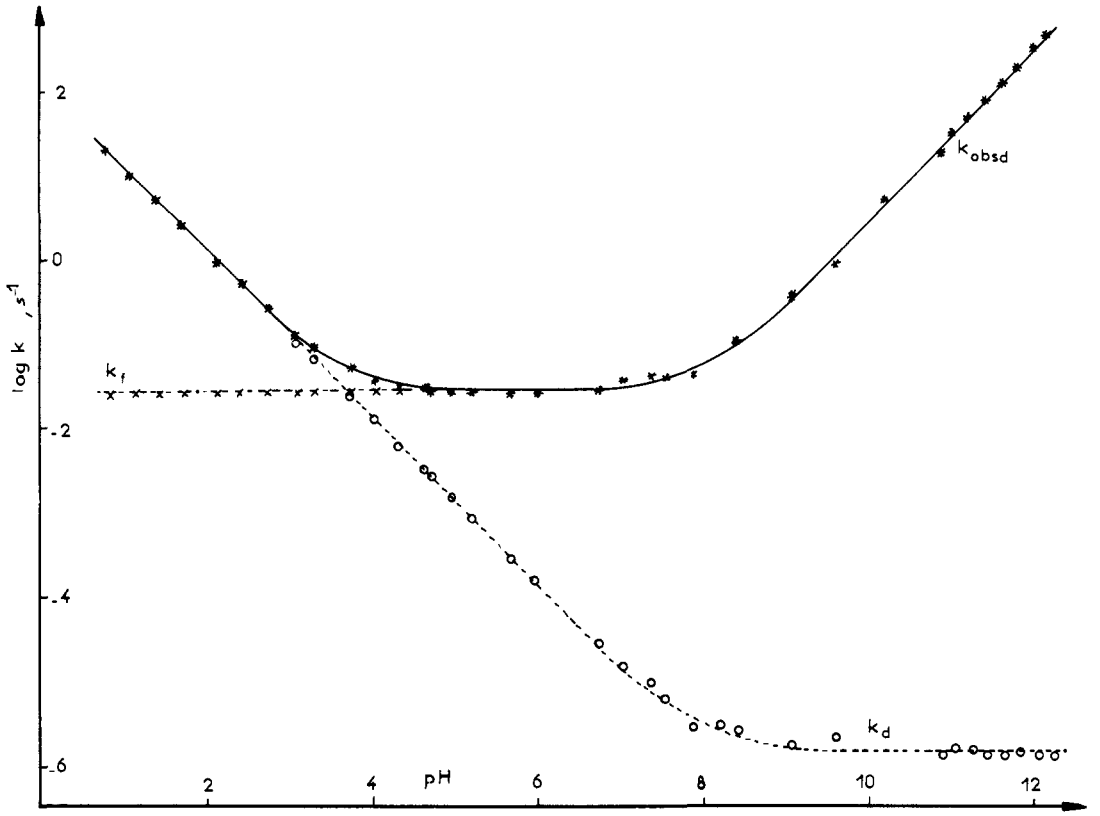
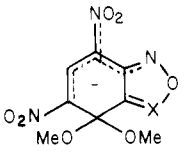


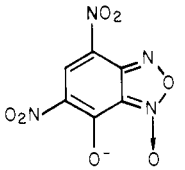
Figure 4. pH dependence of k_{obsd}, k_f, and k_d for the formation and decomposition of the hydroxyl σ complex **104a** of DNBF in aqueous solution.[46] I = 0.2 M, t = 20 °C.

strongly enhances the stability of **104a** which is completely formed in an 0.001 M HCl solution in 70% Me_2SO.[252] However, the most significant feature is that water attack on DNBF is strongly favored. The first-order rate constant k^{H_2O} changes from 0.019 s^{-1} in H_2O to 1.33 s^{-1} in 90% Me_2SO. Considering the decrease in the water content of the solutions and assuming that only one water molecule participates in the reaction, this increase in k^{H_2O} reflects a 10^3-fold increase in the ability of a water molecule to act as a nucleophile.[252] The reaction probably proceeds via a transition state such as **111** where the Me_2SO molecule is the base catalyst. Interestingly, this result compares well with previous data reported for the solvolysis of 2,4-dinitrofluorobenzene in the same solvent mixtures,[266] in accord with the fact that the rate-determining step of this reaction is the formation of the intermediate σ-complex **112**.

Methanol attack on DNBF, 4,6-dinitrobenzofurazan, and 7-methoxy-4,6-dinitrobenzofurazan is the only pathway leading to the formation of the methoxy and dimethoxy complexes **104b**, **106**, and **113b** at pH ≤ 9



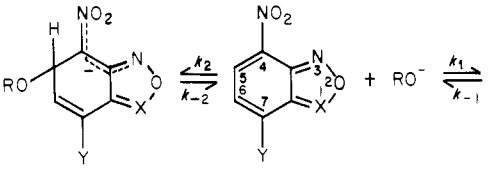
113a, X = N → O
b, X = N



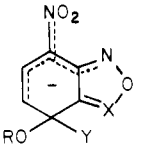
114

in MeOH.[47,267] The phenomenon is more significant than in the case of the tris(trifluoromethylsulfonyl)-benzene complex **9**,[48] in agreement with the 10^3-fold higher stability of these complexes relative to **9**. The pK_a^{MeOH} values for formation of **104b**, **106**, and **113b** are 6.46, 6.05, and 5.93, respectively, at 20 °C.[47,49,267] The *gem*-dimethoxy complex **113a** has been reported.[268] However, its formation occurs competitively, with a facile demethylation of the parent 7-methoxy-4,6-dinitrobenzofuroxan which yields the anion **114**. The ease of this demethylation process is accounted for by the high acidity of the corresponding hydroxy compound. The $pK_a^{H_2O}$ for formation of **114** is ~-3.7, i.e., 4 pK units lower than the $pK_a^{H_2O}$ of picric acid.[268]

4-Nitro- and 4-nitro-7-methoxybenzofuroxans and -benzofurazans **115a–d** react with MeO^- to initially yield



116 **115**



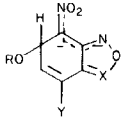
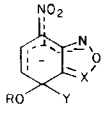
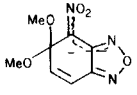
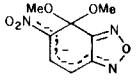
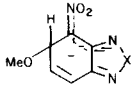
(35)

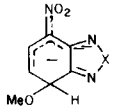
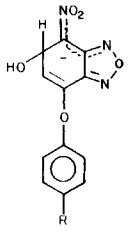
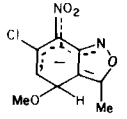
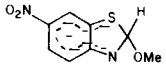
117

X = N→O, R = Me, Y = (a) H; (b) OMe
R = H, Y = (a') H
X = N, R = Me, Y = (c) H; (d) OMe; (e) F; (f) Cl; (g) Br; (h) Me; (i) SMe; (j) SC_6H_5; (k) $SO_2C_6H_5$
R = H, Y = (c') H; (f') Cl; (l') -NH$(CH_2)_2$S-S-2-py,
py = pyridyl

the 5-methoxy complexes **116a–d** which then rearrange to the thermodynamically more stable isomers **117a–d**.[245,247,248,250,251] The rates of formation and decomposition, and therefore the stabilities, are similar for complexes **116a–d** on the one hand and for **117a–d** on

TABLE XVII. Rate and Equilibrium Constants for Formation and Decomposition of Hydroxy and Methoxy σ Complexes of Nitrobenzofurazans, Nitrobenzofuroxans, and Related Compounds

	Cpx	X	Y	R	solvent[a]	t, °C	k_f,[b] L mol^{-1} s^{-1}	k_d,[b] s^{-1}	K,[b] L mol^{-1}	activation and thermodynamic parameters,[c] conditions and comments[d]	ref
	116a	N→O	H	Me	MeOH	25	1950	4.57	427	isnc; $\Delta H_f^{\ddagger} = 43.5$; $\Delta S_f^{\ddagger} = -38.5$; $\Delta H_d^{\ddagger} = 49.5$; $\Delta S_d^{\ddagger} = -66$; $\Delta H^{\circ} = -6$; $\Delta S^{\circ} = 27.5$	251
	116b	N→O	OMe	Me	MeOH	20	348	5	69.6	isnc	251
	116c	N	H	Me	MeOH	25	1200	8.5	141	isnc; $\Delta H_f^{\ddagger} = 38.9$; $\Delta S_f^{\ddagger} = -54.3$; $\Delta H_d^{\ddagger} = 53.3$; $\Delta S_d^{\ddagger} = -47.2$; $\Delta H^{\circ} = -14.4$; $\Delta S^{\circ} = -7$	251
	116d	N	OMe	Me	MeOH	25	350	16	22	isnc	245
						20	347	9.2	37.7	isnc	251
	116e	N	F	Me	MeOH	25	5800	2.5	2300	isnc; $k_A = 3500$[e]	242, 245
	116f	N	Cl	Me	MeOH	25	5100	1.8	2800	isnc; $k_A = 7.7$[e]	242, 245
	116f'			H	H_2O	25	72	8.6×10^{-3}	7900	in aqueous buffers at $I = 0.1$ M; $pK_a = 10.1$	269
					H_2O	25			17300	spectrophotometric titration; $pK_a = 9.76$	270
	116g	N	Br	Me	MeOH	25	5200	3.8	1300	isnc; $k_A = 2$[e]	242, 245
	116h	N	Me	Me	MeOH	25	580	36	16.1	isnc	245
	116i	N	SMe	Me	MeOH	25	490	10	49	isnc	245
	116j	N	SC_6H_5	Me	MeOH	25	520	9.6	54	isnc	245
	116k	N	$SO_2C_6H_5$	Me	MeOH	25	43000	~3	~14300	isnc	245
	116l'	N	*l*	H	H_2O	25			6.9×10^4	$pK_a = 9.16$	269
	117a	N→O	H	Me	MeOH	25	28.5	~3.35×10^{-3}	~8500	isnc; $\Delta H_f^{\ddagger} = 45.5$; $\Delta S_f^{\ddagger} = -63.5$; $\Delta H_d^{\ddagger} = 45.5$; $\Delta S_d^{\ddagger} = -145$; ΔH° slightly >0; ΔS° ~80	251
	117b	N→O	OMe	Me	MeOH	20	12.02	2.29×10^{-3}	5250	isnc; $k^{MeOH} = 1.45 \times 10^{-8}$; $k^{H^+} = 7.94 \times 10^4$[f]	250, 251
	117c	N	H	Me	MeOH	25	6	2.04×10^{-3}	2940	isnc; $\Delta H_f^{\ddagger} = 56$; $\Delta S_f^{\ddagger} = -46.8$; $\Delta H_d^{\ddagger} = 52.4$; $\Delta S_d^{\ddagger} = -120$; $\Delta H^{\circ} = 3.6$; $\Delta S^{\circ} = 73$	251
	117c'	N	H	H	H_2O	25			2200	isnc; $pK_a = 10.65$	243
	117d	N	OMe	Me	MeOH	25	14.5	7.1×10^{-3}	2050	isnc	245
						20	7.56	3.55×10^{-3}	2135	isnc; $k^{MeOH} = 1.26 \times 10^{-8}$; $k^{H^+} = 1.76 \times 10^5$[f]	250, 251
	119				MeOH	25	147	0.116	1300	isnc	244
	120a				MeOH	25	20.1	5.56×10^{-3}	3600	isnc	244
					MeOH	25			5100	isnc	241
	123a	S			MeOH	25	3.55[g]	400[g]	8.87×10^{-3}	isnc	274
					MeOH-Me_2SO						
					30:70	25	640	28	22.9	isnc	274
					20:80	25	2830	13.8	205	isnc	274
	123b	Se			MeOH	25	6.31[g]	72[g]	0.087	isnc	274
					MeOH-Me_2SO						
					50:50	25	148	13.2	11.2	isnc	274
					30:70	25	900	6	150	isnc	274

	124a	S	MeOH	25	0.087[g]	0.62[g]	0.14	isnc	274
			MeOH-Me_2SO						
			50:50	25	2	0.097	20.6	isnc	274
			30:70	25	24	0.04	600	isnc	274
	124b	Se	MeOH	25	0.087[g]	0.0436[g]	2	isnc	274
			MeOH-Me_2SO						
			50:50	25	2.34	8×10^{-3}	292.5	isnc	274
			40:60	25	5.84	0.005	1168	isnc	274
	122a	R = lysozyme	H_2O	25	90	0.7	130	pH >12.7	249
			H_2O	25	4.95[h]			10.5 < pH < 12.7	249
	122b	R = $CH_3CONH-\underset{\displaystyle CH_2}{\underset{\vert}{CH}}-CONH_2$	H_2O	24	20.05[i]	0.018[i]	1100[i]	$\Delta H_f^{\ddagger} = 59$; $\Delta S_f^{\ddagger} = -65.4$	249
	125		MeOH	25	15,[j] 1.8[k]	8.3,[j] 0.44[k]	1.8,[j] 4.1[k]	isnc	275
	126		MeOH-Me_2SO						
			30:70	25	30	11	2.77	isnc	277
			20:80	25	48	4.1	11.7	isnc	277
			10:90	25	136	1.13	120	isnc	277

[a] Sodium or potassium hydroxides or alkoxides. [b] k_f, k_d, and K represent the rate and equilibrium constants as defined by eq 1, 10, or 35. [c] Enthalpies in kJ mol^{-1}, entropies in J mol^{-1} K^{-1}. [d] See Table I for abbreviations. [e] k_A for MeO^- addition at the 7-carbon. [f] k^{MeOH} in s^{-1}, k^{H^+} in L mol^{-1} s^{-1} as defined by eq 4 with R = Me. [g] Values estimated from linear plots of log k_f and log k_d vs. N_{Me_2SO}. [h] k_f in s^{-1}; refers to the unimolecular formation of 122a (see text). [i] Errors were made in tabulating the data of Table II in ref 249. [j] Assuming complex formation to be the first step of the reaction; see ref 275. [k] Assuming complex formation to be the second step of the reaction. [l] Y = $NH(CH_2)_2SS$-2-py, py = pyridyl.

TABLE XVIII. Kinetic and Thermodynamic Parameters for Spiro Complexes

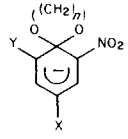
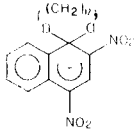
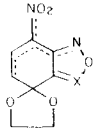
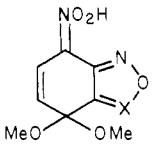
	Cpx	n	X	Y	solvent[a]	t, °C	Kk_1,[b] L mol^{-1} s^{-1}	k_{-1},[b] s^{-1}	KK_1,[b] L mol^{-1}	activation and thermodynamic parameters;[c] conditions and comments[d]	ref
	134a[f,g]	2	NO_2	NO_2	H_2O	25			1.8×10^7	isnc	293
						25	1.6×10^6	0.095	1.68×10^7	aqueous buffers	64
						25	7.25×10^5	0.045	1.6×10^7	1 M NaCl; $\Delta H_1^{\ddagger} = 18$; $\Delta S_1^{\ddagger} = -73$; $\Delta H_{-1}^{\ddagger} = 57.7$; $\Delta S_{-1}^{\ddagger} = -77$; $\Delta H_1^{\circ} = -39.7$; $\Delta S_1^{\circ} = 4$	67
						25				$k^{H^+} = 2200$,[e] $k^{BH} = 0.9$ (CH_3COOH); 2.3 (HCOOH) 12 ($CH_2ClCOOH$)[e]	69
					D_2O	25				$k^{D^+} = 3300$;[e] $k^{H^+}/k^{D^+} = 0.66$	69
					MeOH	20	1.74×10^6	0.025	6.97×10^7	0.01 M buffer salts	291
	134b[h]	3	NO_2	NO_2	H_2O	25	19.7	0.87	22.6	1 M NaCl; $\Delta H_1^{\ddagger} = 40$; $\Delta S_1^{\ddagger} = -85.3$; $\Delta H_{-1}^{\ddagger} = 50.6$; $\Delta S_{-1}^{\ddagger} = -76$; $\Delta H_1^{\circ} = -10.6$; $\Delta S_1^{\circ} = -9.3$	67
					D_2O	25	26.6	0.69	38.6	1 M NaCl; $Kk_1^{H_2O}/Kk_1^{D_2O} = 0.74$; $k_{-1}^{H_2O}/k_{-1}^{D_2O} = 1.26$; $KK_1^{H_2O}/KK_1^{D_2O} = 0.585$	67

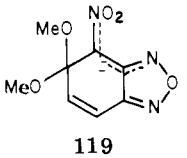
TABLE XVIII (*Continued*)

	Cpx	n	X	Y	solvent[a]	t, °C	Kk_1,[b] L mol^{-1} s^{-1}	k_{-1},[b] s^{-1}	KK_1,[b] L mol^{-1}	activation and thermodynamic parameters;[c] conditions and comments[d]	ref
	134d[f,h]	2	NO_2	H	H_2O	25	>30	>620	0.05	isnc	64
					H_2O–Me_2SO 98:2	25	59.5	1450	0.041	0.5 M KCl	66
					80:20	25	173	719	0.24	0.5 M KCl	66
					50:50	25	4010	124	32.1	0.5 M KCl	66
					35:65	25	35300	50	705	0.5 M KCl	66
					MeOH		>5.5	>500	0.011	isnc	63
	134e	3	NO_2	H	H_2O–Me_2SO 48:52	25	0.26	10.3	0.025	unspecified	67
	134f	4	NO_2	H	H_2O–Me_2SO 48:52	25	0.015	33	4.5×10^{-4}	unspecified	67
					40:60	25	0.094	26	3.6×10^{-3}	$\Delta H_{-1}^{\ddagger} = 42.3$; $\Delta S_{-1}^{\ddagger} = -75$	67
	134g[f,i]	2	H	NO_2	H_2O	25	160	137	1.3	isnc	64
					MeOH	25	80	360	0.22	isnc; NaOMe and Bu_4NOMe	63
	136a[f,j]	2			H_2O	25	9×10^4	2.3	3×10^4	aqueous buffers; $k^{H^+} = 1.8 \times 10^4$;[e] $k^{BH} = 25$ (CH_3COOH); 60 (HCOOH); 300 ($CH_2ClCOOH$);[e]	64 69
					D_2O	25		1.7		$k_{-1}^{H_2O}/k_{-1}^{D_2O} = 1.35$	69
					MeOH[k]	25	2.5×10^4	6.5	3800	isnc	63
	136b[m]	3			H_2O	25	1.7	0.85	2	isnc	289
					H_2O–Me_2SO 80:20	25	2.9	0.28	10	isnc	289
					60:40	25	10	0.07	140	isnc	289
					40:60	25	90			isnc	289
	136c	4			H_2O	25	0.6	0.64	0.9	isnc	289
					H_2O–Me_2SO 80:20	25	1.2	0.30	4	isnc	289
					60:40	25	3.5	0.09	40	isnc	289
	143a		N → O		H_2O	20	5500	1.34×10^{-3}	4.10×10^6	0.2 M KCl; aqueous buffers; $k^{H^+} = 5.9$;[e] $k^{BH} = 0.011$ (CH_3COOH); 0.024 (HCOOH); 0.11 ($CH_2ClCOOH$)[e]	68
					D_2O	20	7500	1.1×10^{-3}	6.8×10^6	0.2 M KCl; $Kk_1^{H_2O}/Kk_1^{D_2O} = 0.73$; $k_{-1}^{H_2O}/k_{-1}^{D_2O} = 1.22$; $KK_1^{H_2O}/KK_1^{D_2O} = 0.60$; $k^{D^+} = 9.3$;[e] $k^{H^+}/k^{D^+} = 0.63$	68
					MeOH	20	3.98×10^3	6.31×10^{-3}	6.31×10^5	0.01 M buffer salts; $k^{H^+} = 3 \times 10^3$ [e]	291
	143b		N		H_2O	20	3.1×10^6	0.25	1.24×10^7	0.2 M KCl; aqueous buffers; $k^{H^+} = 2700$;[e] $k^{BH} = 4.75$ (CH_3COOH); 11.7 (HCOOH); 41 ($CH_2ClCOOH$)[e]	68
					D_2O	20	4.35×10^6	0.20	2.17×10^7	0.2 M KCl; $Kk_1^{H_2O}/Kk_1^{D_2O} = 0.71$; $k_{-1}^{H_2O}/k_{-1}^{D_2O} = 1.25$; $KK_1^{H_2O}/KK_1^{D_2O} = 0.57$	68
					MeOH	20	7.60×10^5	2.10	3.62×10^5	0.01 M buffer salts; $k^{H^+} = 3.8 \times 10^6$ [e]	291

[a] Sodium or potassium hydroxides or methoxides unless indicated otherwise. [b] Rate and equilibrium constants as defined by eq 14. [c] Enthalpies in kJ mol^{-1}; entropies in J mol^{-1} K^{-1}; $\Delta H_1^{\ddagger}$ and $\Delta S_1^{\ddagger}$ refer to Kk_1; ΔH_1° and ΔS_1° to KK_1. [d] See Table I for abbreviations. [e] k^{H^+} and k^{BH} in L mol^{-1} s^{-1} as defined by eq 15 and 36. [f] For formation of the 1:2 complexes; k_2 in L mol^{-1} s^{-1}; k_{-2} in s^{-1}; K_2 in L mol^{-1}, as defined by eq 37. [g] For 139a, $k_2 = 0.09$; $k_{-2} = 0.9$; $K_2 = 0.1$. [h] For 139b, $k_2 = 0.5$; $k_{-2} = 0.7$; $K_2 = 0.8$. [i] For 139c, $k_2 = 0.06$; $k_{-2} = 0.1$; $K_2 = 0.6$. [j] For 140, $k_2 = 0.04$; $k_{-2} = 0.04$; $K_2 = 1$. [k] The data reported for 136a in ref 62 probably correspond to a mixture of this spiro complex and its 1,1-dimethoxy analogue 70a. [l] For the analogous spiro complex of 1-(2,2-dimethyl-3-hydroxypropoxy)-2,4,6-TNB, in water at 25 °C, $I = 0.25$ M NaCl; $Kk_1 = 4.6$; $k_{-1} = 0.4$; $KK_1 = 11.5$; see ref 491. [m] For the analogous spiro complex of 1-(2,2-dimethyl-3-hydroxypropoxy)-2,4-dinitronaphthalene in water at 25 °C. isnc: $Kk_1 = 7$, $k_{-1} = 3.5$; $K_1 = 2$; see ref 491.

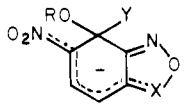
the other. This shows quite clearly that the furazan and furoxan moieties have about the same effect on complex stability.[251] The greater stabilities of the adducts **117a–d** relative to their isomers **116a–d** has been explained in terms of an extensive delocalization of the negative charge through the NO_2 group para to the sp^3 carbon.[244,245,251] The recent finding that complexes of the type **117** have a high tendency to form nitronic acids, such as **118**, in acidic medium in MeOH strongly supports this hypothesis.[250] The pK_a^{MeOH} for ionization of **118a** and **118b** are 4.4 and 4.8, respectively, at 20



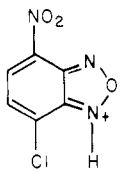


119

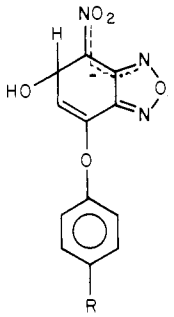
118a, X = N→O
b, X = N



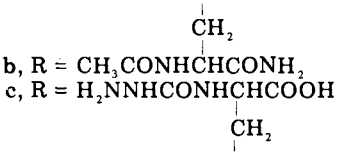
120a, X = N; R = Me; Y = OMe
b, X = N; R = Y = H
c, X = N→O; R = Y = H



121



122a, R = lysozyme



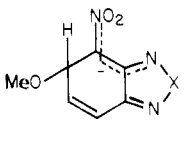
b, R = $CH_3CONHCHCONH_2$
c, R = $H_2NNHCONHCHCOOH$

°C.[250] Rate and equilibrium constants have also been reported for **119** and **120a** in MeOH.[241,244] The stability of these complexes which do not have a NO_2 group para to the sp^3 carbon is lower than that of the analogue **117d**. The hydroxyl complexes **117a′,c′** and **120b,c** are formed in aqueous hydroxide solutions.[243] The stability order is **117c′ > 117a′ > 120c > 120b**, but only the K_1 value for **117c′** has been measured: $K_1 \sim 2200$ L mol^{-1}.[243]

Formation of the adducts **116e–g(f′)** occurs prior to nucleophilic displacement of the halogen atom (F, Cl, Br) in the reactions of MeO^- and OH^- with 7-halogeno-4-nitrobenzofurazans.[242,245,269,270] The proposal that the first reversible and rapid reaction occurring between OH^- and the chloro compound **115f**, commonly known as NBDCl, is associated with deprotonation of the cation **121** is untenable.[271] Protonation of unsubstituted benzofurazan and benzofuroxan occurs only in very acidic media ($pK_a \sim -8$).[272,273]

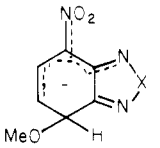
NBDCl has been used as a reactivity probe and as a fluorescent labeling reagent in the study of a number of proteins and enzyme derivatives. Most of the 7-X-substituted-4-nitrobenzofurazans obtained in the reactions add OH^- to the 5-position in a rapid and reversible step in aqueous solution. The kinetics of this process has been investigated in the case of the NBD-lysozyme, *N*-acetyl-(*O*-NBD)-L-tyrosinamide, and glycyl-(*O*-NBD)-L-tyrosine systems which yield the complexes **122a–c**.[249] While the formation of **122b** and **122c** compares well with that of **116f′**, the formation of **122a** occurs much more rapidly and does not depend on the OH^- concentration in the pH range 10–12.7. In this enzyme system, OH^- addition to the NBD moiety would occur subsequently to a rate-determining conformational change in the protein molecule.[249] This latter will be induced by ionization of a tyrosine hydroxyl group.

4-Nitro-2,1,3-benzothiadiazole and -selenadiazole are the sulfur and selenium analogues of 4-nitrobenzofurazan. The complexes **123a,b** are formed under kinetic control but rapidly isomerize to the more stable **124a,b** in MeOH–Me_2SO mixtures.[274] In each series,

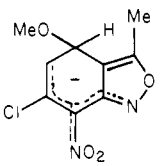


123a
b

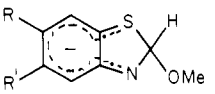
X = S
X = Se



124a
b



125

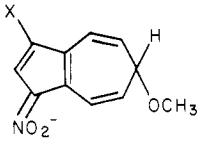


126, R = NO_2; R′ = H
127, R = H; R′ = NO_2

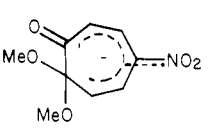
the stability is in the order O > Se > S; i.e., it decreases with decreasing electronegativity of the heteroatom and increasing aromaticity of the system.[274] The complex **125** initially forms in the reaction of MeO^- with 6-chloro-3-methyl-7-nitroanthranil which gives 4-acetyl-7-methoxybenzofuroxan as a final product.[275] Both 5- and 6-nitro-1,3-benzothiazoles add MeO^- at C_2 to give **126** and **127**[276,277] which are unstable due to a subsequent ring opening. The kinetics of formation of **126** have been studied in MeOH–Me_2SO mixtures rich in Me_2SO[277] (Table XVII).

6. Nonbenzenoid Aromatics

Certain nonbenzenoid aromatics, i.e., azulenes and tropones, add bases to form stable or detectable 1:1 complexes. No systematic thermodynamic studies of the interactions have been made. However, on the basis of the reported changes occurring in the UV-visible spectra, upon MeO^- addition in MeOH, the following estimates of the equilibrium constant K_1 (eq 1) associated with formation of the complexes **128a**, **128b**, and **129** are obtained: $K_1^{128a} \sim 10^3$, $K_1^{128b} \sim 20$, $K_1^{129} \geq 20$ L mol^{-1}.[278–280]



128a, X = NO_2
b, X = CN



129

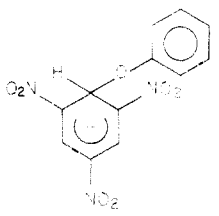
TABLE XIX. Rate and Equilibrium Constants for Formation and Decomposition of Phenoxy Complexes of TNA in H_2O-Me_2SO Mixtures[a,f]

Cpx	X	% Me_2SO	t, °C	k_1, L mol^{-1} s^{-1}	k_{-1}, s^{-1}	K_1, L mol^{-1}	pK_a[f]
132a	H	0	25	80[b]	1900[b]	0.042[b,c]	
		50	25	425[d]	850	0.5[e]	
		60	25	645[d]	645	1[e]	
		80	25	3600	320	10.9[e]	
		90	30	50000	175	285[c]	15.42
132b	*p*-MeO	90	30	60000	50	1200[c]	16.14
132c	*p*-Cl	90	30	9700[d]	2100	4.68[e]	14.15
132d	*p*-Br	90	30	8700[d]	2500	3.47[e]	14.10
132e	*m*-Cl	90	30	3130[d]	4000	0.77[e]	13.58
132f	*m*-Br	90	30	4000[d]	5000	0.80[e]	13.45

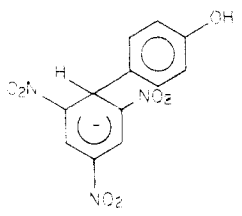
[a] Reference 288; I = 0.25 M Me_4NCl; k_1, k_{-1}, and K_1 as defined by eq 1. [b] Values estimated from the linear plots of log k_1, log k_{-1} vs. N_{Me_2SO}. [c] Calculated as $K_1 = k_1/k_{-1}$. [d] Calculated as $k_1 = K_1k_{-1}$. [e] Determined spectrophotometrically. [f] pK_a of respective phenols extrapolated to zero concentration in 90% Me_2SO.

C. Phenoxy Complexes

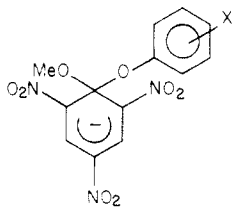
In contrast to alkoxide complexes, it has been difficult to detect and characterize aryloxide complexes. Due to their ambident character, phenoxide ions may in fact attack via oxygen or the para carbon atoms.[283-287] In the case of TNB, **130** is the kinetically controlled com-



130



131



132

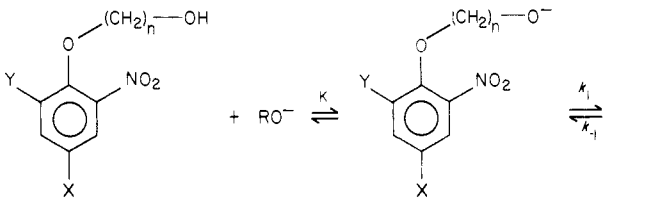
X = (a) H; (b) *p*-MeO; (c) *p*-Cl; (d) *p*-Br; (e) *m*-Cl; (f) *m*-Br

plex while **131** is the thermodynamically more stable product (see section VID).[283-287] The kinetics of the reaction of TNA with phenoxide ion has been studied in H_2O-Me_2SO mixtures with ≥50% Me_2SO.[288] The 1-methoxy-1-phenoxy complex **132a** is formed initially according to eq 1 but is rapidly converted to the 3-hydroxy complex **14a**. This in turn slowly decomposes to picrate ion. The k_1, k_{-1}, and K_1 values for formation and decomposition of **132a** have been determined,[288] with the SFTJ technique. Plots of log k_1 and log k_{-1} vs. N_{Me_2SO} are linear, allowing extrapolation of the rate constants to water solution and comparison with similar data for **13a**. Phenoxide ion departure from **132a** is found to be more than 10^6 times faster than MeO^- departure from **13a** whereas the rates of ArO^- and MeO^- attack on TNA are very similar. The kinetics of complex formation between TNA and various substituted phenoxide ions was also measured in 90% Me_2SO-10% water.[288] Both the rates of phenoxide ion attack and of phenoxide ion departure strongly depend on the pK_a of the respective phenols. Brønsted-type plots of log k_1 and log k_{-1} vs. pK_a have slopes of ~0.60 (β_{nuc}) and −0.70 (β_{lg}), respectively.[288] The results are summarized in Table XIX.

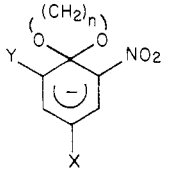
D. Spiro Complexes

1. 1-(n-Hydroxyalkoxy)nitroarenes

a. Effect of Ring Size on Complex Stability. With the exception of the 1-(4-hydroxybutoxy)benzene derivatives **133c** and **133f**, the ethers **133** and **135** (GOH) cyclize in basic media as shown in eq 14 to give the respective complexes **134** and **136**.[62-64,66,67,289-291] Equilibrium (KK_1) and rate (Kk_1, k_{-1}) constants for these reactions have been reported in water, MeOH, and water-Me_2SO mixtures (Table XVIII). As might be expected from the isolation of the OH group from the aromatic system, the results indicate that the K values for its ionization depend little upon n and the aromatic moiety.[63,64,66-68,289] Therefore, changes in the rates of formation (Kk_1) and the stabilities (KK_1) largely reflect those in the rate and equilibrium constants associated with the cyclization step (k_1, K_1). K has been estimated to be ≤1 L mol^{-1} and is most probably ≃ 0.3 L mol^{-1} in water.[64,67,68] This corresponds to a pK_a value ≃ 14.5.

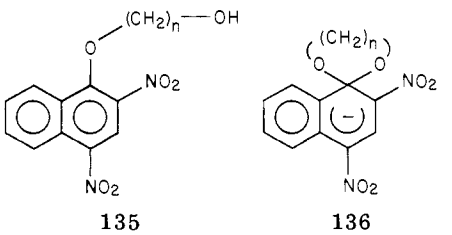


133a-g (GOH) (GO⁻)



134a-g

X = Y = NO_2; (a) n = 2; (b) n = 3; (c) n = 4
X = NO_2, Y = H; (d) n = 2; (e) n = 3; (f) n = 4
X = H, Y = NO_2; (g) n = 2



135 136

a, n = 2; b, n = 3; c, n = 4

The KK_1 values for complex formation in the $n = 2$ series are 1.60×10^7, 3×10^4, 1.3 and 0.05 L mol^{-1} in water at 25 °C for **134a**, **136a**, **134g**, and **134d**, respectively.[64,289] A similar sequence is observed in MeOH.[62,63,291] The stability order thus parallels the increase in activation of the aromatic system, as found for noncyclic analogues. Increasing the ring size from five to six to seven members causes a dramatic decrease in complex stability, the effect being most pronounced with the trinitrobenzene derivatives, least with the dinitrobenzene derivatives, and intermediate with the dinitronaphthalene derivatives.[67,289] Thus, **134b**, **134e**, and **136b** ($n = 3$) are, respectively, 7×10^5, 2.56×10^3, and 1.7×10^4 times less stable than their analogues with $n = 2$. When $n = 4$, only the naphthyl complex **136c** has been characterized.[289] In the case of the trinitro derivative **133c**, the formation of the 1,3-complex **42a** rather than of **134c** is favored.[67] Similarly, the formation of the 1,5-hydroxy complex **137** competes with formation of **134f** in aqueous Me_2SO.[67] The decrease in complex stability on increasing ring size is mainly due to a decrease in the rate of ring formation (k_1). Differences in loss of rotational freedom of the side chain on ring formation, in ring strain, and in steric bulk at the 1-position in the complexes are each, in part, responsible for the decrease in k_1 on going from $n = 2$ to $n = 4$.[67]

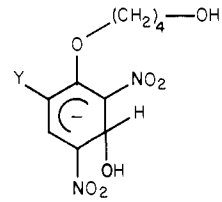
gem-Dimethyl substitution at C-2 of the side chain in the 1-(3-hydroxypropoxy) ethers **133b** and **135b** does not significantly affect the rate and equilibrium parameters for spiro complex formation.[491] This is unusual since it is well-known that when *gem*-dimethyl substituents are introduced into a methylene side chain, equilibrium and rate constants for cyclization are generally increased.[492]

b. Intra- vs. Intermolecular Leaving Group Departure. The spiro complexes with $n = 2$ have a much greater stability but decompose much faster than their 1,1-dimethoxy analogues.[64,67] Ring opening of **134a** is about 82 times faster than MeO^- departure from the 1,1-complex of TNA, **13a** ($k_{-1} = 5.51 \times 10^{-4}$ s^{-1} in water[138]), k_{-1} in the case of **136a** is ~1500 times faster than MeO^- departure from the naphthyl complex **70a** ($k_{-1}^{H_2O} = 1.76 \times 10^{-3}$ s^{-1}; $k_{-1}^{MeOH} = 3.95 \times 10^{-3}$ s^{-1} [204]), and k_{-1} for **134d** is about 17 times greater than MeO^- departure from **25g** ($k_{-1} = 42$ s^{-1} in MeOH).[156] There has been much discussion about the possible reasons for this behavior.[67] At present, three factors are believed to contribute to these changes: they are (a) relief of steric strain upon complex decomposition, (b) difference in the basicity of the respective leaving groups, and (c) p–π overlap of the lone pairs of the nonleaving oxygen with the C–O bond being broken.[67] The second factor is supported by the observation that the rate of alkoxide ion departure from *gem*-dialkoxy complexes increases with decreasing pK_a of the respective alcohols[144] (section IIB2d). In view of the estimated K values, the pK_a of the OH group of the parent ethers ($n = 2$) is lower than that of MeOH by ≥0.7 pK unit. This pK_a difference likely accounts for part of the differences in k_{-1}.[144]

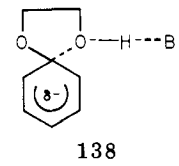
c. Buffer Catalysis. No evidence has been found for buffer catalysis in the formation of **134** and **136**. This indicates that in eq 14 the parent ethers GOH and the oxyanions GO^- are in rapid equilibrium, and the internal cyclization step is rate determining. In contrast, general acid catalysis of the decomposition of the adducts **134a** and **136a** has been observed in H_2O,[69] with a rate constant k_{obsd} fitting the equation

$$k_{obsd} = k_{-1} + k^{H^+}[H^+] + k^{BH}[BH] \qquad (36)$$

Brønsted plots of log k^{BH} vs. pK_a values for the catalyzing acids are linear, with slopes of the order of 0.5. The results are consistent with a concerted mechanism and the transition state **138**.[67,69] The microscopic reverse of this acid decomposition path, i.e., the general base catalyzed cyclization of GOH, has not been observed because complex formation is disfavored at pH values where such cyclization would be most effective. The uncatalyzed ring opening of **134a** and **136a** is shown to be a unimolecular reaction, as described by the k_{-1} step in eq 14, and not a bimolecular reaction occurring through **138** (B = OH).[69] In accord with this mechanism, the reaction proceeds at similar rates in H_2O and D_2O: $k_{-1}^{H_2O}/k_{-1}^{D_2O} = 1.3$ for **136a**.[69]



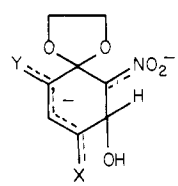
42a, Y = NO_2
137, Y = H



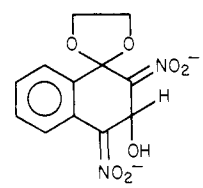
138

The k^{H^+} values for ring opening of **134a** ($k^{H^+} = 2.2 \times 10^3$ L mol^{-1} s^{-1})[69] and **136a** ($k^{H^+} = 1.80 \times 10^4$ L mol^{-1} s^{-1})[69] are of the same order as those for MeO^- departure of the picryl and naphthyl 1,1-dimethoxy complexes **13a** ($k^{H^+} = 3.5 \times 10^3$ L mol^{-1} s^{-1})[144] and **70a** ($k^{H^+} = 1.48 \times 10^4$ L mol^{-1} s^{-1}).[204] This suggests that those factors responsible for the much faster noncatalyzed spiro complex ring opening must be ineffective in the acid-catalyzed reactions, or that a new, compensating factor plays a role in the acid-catalyzed leaving group departure, or both. According to Bernasconi,[67] relief of steric strain and p–π overlap of the lone pairs of the nonleaving oxygen with the C–O bond being broken would be less effective in the acid-catalyzed reaction. In addition, the lower acidity of MeOH compared to that of the OH group in GOH now favors MeO^- departure. Further work in this area is needed to more fully understand this behavior.

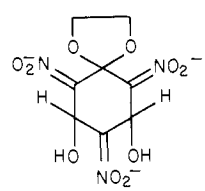
d. 1:2 Complexes. At NaOH concentrations >0.1 M in aqueous solution, the spiro complexes **134** and **136** ($n = 2$) add OH^- at unsubstituted carbon to give the diadducts **139** and **140** according to eq 37.[64] Rate and



139a, X = Y = NO_2
b, X = NO_2; Y = H
c, X = H; Y = NO_2



140



141

$$\text{spiro} + OH^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{1:2 complex} \qquad (37)$$

equilibrium parameters for these complexes are given in Table XIX. **139a** can add another OH^- to give the

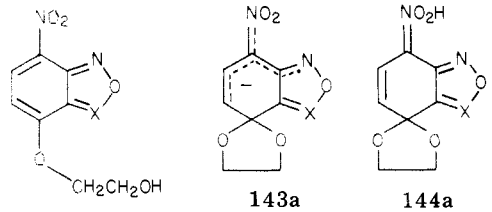
colorless triadduct 141[64] which has an absorption similar to that of the trimethoxide complex **22** of TNA.

2. 2,4-Dinitrophenyl Glucosyl Ether and Related Derivatives

Addition of glucose has been shown to accelerate the decomposition of 2,4-dinitrofluoro- and -chlorobenzenes in aqueous NaOH and cetyltrimethylammonium bromide (CTAB).[292] There is kinetic and spectroscopic evidence that the reactions involve the intermediate formation of 2,4-dinitrophenyl glucosyl ether. At high pH, this ether cyclizes to give a detectable spiro complex which has a visible absorption similar to that of **134d**. Analogous results are obtained with sorbose and sorbitol. The sorbitol complex is long-lived under some experimental conditions (0.1 M sorbitol, 0.01 M NaOH, 0.025 M CTAB).[292]

3. 7-(2-Hydroxyethoxy)-4-nitrobenzofurazan and -benzofuroxan

Cyclization of **142a** and **142b** occurs in basic media in H_2O and MeOH to give **143a** and **143b**, which have

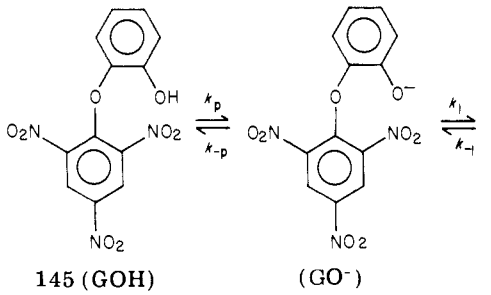


a stability of the order of that of the picryl complex **134a**.[68,291] The pK_a values are 7.46 and 6.93 for **143a** and **143b**, respectively, in water, as compared with a pK_a of 6.70 for **134a** (at 20 °C). Despite their *similar* stability, **143a** and **143b** have *drastically different* rates of formation and decomposition.[68,291] Both the Kk_1 and k_{-1} values are more than 10^2 times greater for **143b** than for **143a** (Table XIX). Comparison with the less stable dimethoxy analogues **117d** and **117b** shows that **143b** decomposes much more rapidly than **117d** while **143a** and **117b** decompose at rather similar rates ($k_{-1}^{143b}/k_{-1}^{117d} \simeq 600$; $k_{-1}^{143a}/k_{-1}^{117b} = 2.7$ in MeOH).[68,291] On the basis of the results obtained in the benzene and naphthalene series, **143b** is a "normal" and **143a** is an "abnormal" compound. This behavior has been attributed to a destabilizing electrostatic effect of the *N*-oxide group on the transition state for formation and decomposition of **143a**.[68]

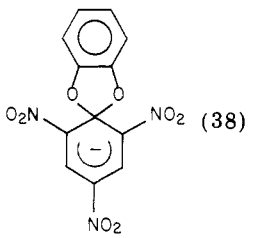
Just as for **134a** and **136a**, the decomposition of **143a** and **143b** is subject to general acid catalysis with Brønsted α values of 0.43 and 0.44 in water and 0.48 and 0.49 in MeOH, respectively.[68,291] A noteworthy result is that protonation of **143a** and **143b** occurs in the most acidic media in MeOH to give the nitronic acids **144a** and **144b**.[291] The pK_a^{MeOH} for ionization of these acids are both equal to 4.28; i.e., they are close to those found for the *gem*-dimethoxy analogues **118a** and **118b**. The nitronic acid of **134a** is not observed under similar conditions.[291]

4. Catechol 2,4,6-Trinitrophenyl Ether

The spiro complex **146** is very stable and forms partially from the parent catechol ether **145** in the absence of any added base in water, water-Me_2SO, and water-EtOH mixtures[294,295] (eq 38). The interconversion of



145 (GOH) (GO⁻)



146 (38)

145 and **146** is too fast in aqueous solution, even for TJ measurements. However, when this technique and buffer solutions are used, a kinetic study was possible over a pH range 4–6 in 50% H_2O–50% Me_2SO.[294] The system is unique in that it is the first example of oxygen-bonded spiro complex formation not obeying eq 14. The reasons for this are the following: (1) There is a very strong buffer dependence of the observed reciprocal relaxation time $1/\tau$ associated with formation of **146**. This is typical for proton transfer reactions at pH values not too far from neutrality.[20,296] (2) The dependence of $1/\tau$ on the total buffer concentration is not linear but curvilinear (Figure 5). Such curvature is usually indicative of a mechanism where there is a change in the rate-limiting step. In the present case, the reaction is described by eq 38, and *there is a change from rate-limiting proton transfer in the GOH ⇄ GO⁻ step (k_p, k_{-p}) to a rate-limiting C–O bond formation/breaking (k_1, k_{-1})*. k_p and k_{-p} are defined by eq 39 and 40, respectively. k_p^S, k_p^{OH}, and k_p^B refer to the depro-

$$k_p = k_p^S + k_p^{OH}[OH^-] + k_p^B[B] \quad (39)$$

$$k_{-p} = k_{-p}^{SH^+}[H^+] + k_{-p}^S + k_{-p}^{BH}[BH] \quad (40)$$

$$\frac{1}{\tau} = \frac{k_p k_1}{k_{-p} + k_1} + \frac{k_{-p} k_{-1}}{k_{-p} + k_1} \quad (41)$$

tonation of **145** by the solvent, the hydroxide ion, and the buffer base, respectively, whereas $k_{-p}^{SH^+}$, k_{-p}^S, and k_{-p}^{BH} refer to the protonation of GO^- by the solvated proton, the solvent, and the buffer acid, respectively. Assuming GO^- to be a "steady-state" intermediate, the expression for $1/\tau$ is given by eq 41. Although the kinetic analysis is not simple, all the rate and equilibrium parameters of eq 38 were determined.[294] Calculations were based, in particular, on the characteristic values of $1/\tau$ at high or low buffer concentrations and the fact that k_{-p}^{BH} for reprotonation of GO^- ($pK_a^{GOH} \simeq 10.3$) by a buffer acid such as chloracetic acid ($pK_a = 3.7$ in the mixture) is certainly close to the diffusion-controlled limit of $\simeq 10^{10}$ L mol^{-1} s^{-1}.[296] The data are summarized in Table XX.

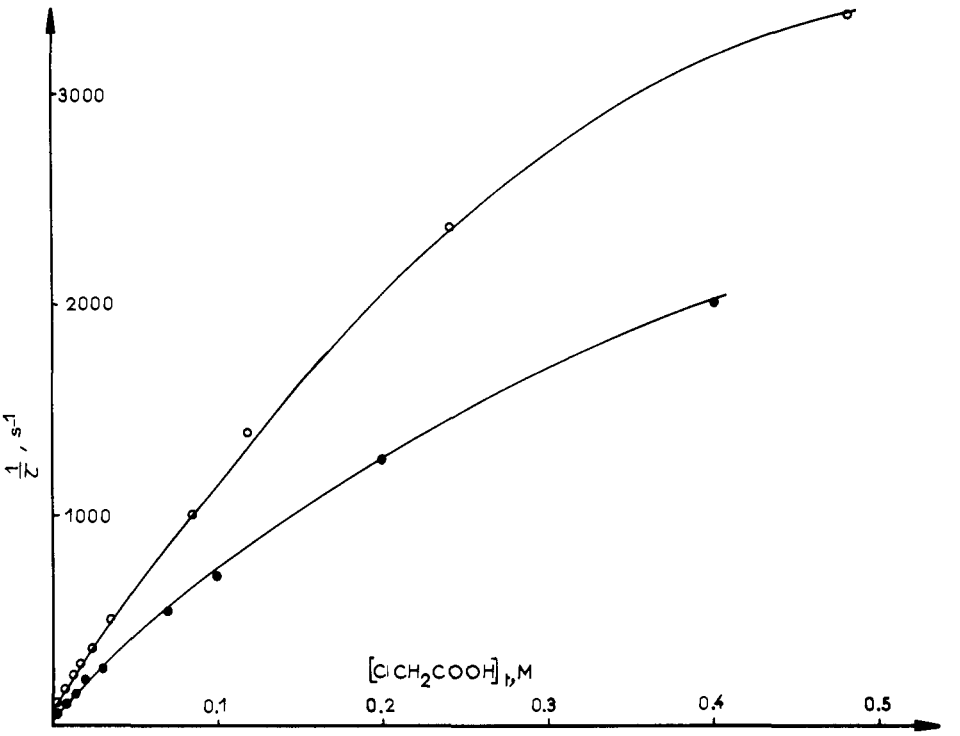


Figure 5. Representative plots of $1/\tau$ vs. total chloroacetate buffer concentration for the cyclization of catechol 2,4,6-trinitrophenyl ether **145** into the spiro complex **146**[294] in 50% H_2SO–50% Me_2SO: (○) pH 4.06; (●) pH 4.36; I = 0.5 M, t = 25 °C.

TABLE XX. Equilibrium and Rate Constants for Formation and Decomposition of the Picryl Spiro Complexes of Catechol (**146**), Adenosine (**148**), and Glycol (**134a**)

	146[a,n]	**148**[b]	**134a**
KK_1, L mol^{-1} [e]	6.90×10^9	1.23×10^9	1.68×10^7 [c] 1.6×10^7 [d]
pK_a	5.25[f]	4.83	6.78
Kk_1, L mol^{-1} [e]	6.90×10^{13}	$>3 \times 10^9$	1.6×10^6 [c] 7.25×10^5 [d]
K, L mol^{-1} [e]	5.75×10^4	≃0.3	≃0.3
pK_a^{GOH} [g]	10.34	≃14.5	≃14.5
k_1, s^{-1} [e]	1.2×10^9	$>10^{10}$	5.3×10^6 [c] 2.4×10^6 [d]
k_{-1}, s^{-1} [e]	10^4	>2.5	0.095[c] 0.045[d]
k_p^S, s^{-1} [h]	3.9	$\simeq 1.5 \times 10^{-4}$ [k]	$\simeq 1.5 \times 10^{-4}$ [k]
$k_{-p}^{SH^+}$, L mol^{-1} s^{-1} [h]	8×10^{10}	$\simeq 5 \times 10^{10}$ [j]	$\simeq 5 \times 10^{10}$ [j]
k_p^{OH}, L mol^{-1} s^{-1} [h]	10^{10} [j]	$>3 \times 10^8$ [l]	$>3 \times 10^8$ [l]
k_{-p}^S, s^{-1} [h]	$\simeq 1.7 \times 10^5$	$\geq 10^9$ [j]	$\geq 10^9$ [j]
k^{H^+}, L mol^{-1} s^{-1} [i]	-	310	2200[m]

[a] Reference 294 at 25 °C in 50% H_2O-50% Me_2SO; I = 0.5 M KCl. [b] Reference 301 at 20 °C in water; I = 0.2 M KCl. [c] Reference 64 at 25 °C in water; isnc. [d] Reference 67 at 25 °C in water; I = 1 M NaCl. [e] K, K_1, k_1, and k_{-1} as defined by eq 14 and 38. [f] $K_a = KK_1K_S$ with $K_S = 8 \times 10^{-16}$; ref 294. [g] $K_a^{GOH} = KK_S$. [h] k_p^S, $k_{-p}^{SH^+}$, k_p^{OH}, and k_{-p}^S as defined by eq 39 and 40. [i] k^{H^+} as defined by eq 15. [j] Estimated (ref 296). [k] Estimated from $k_p^S = KK_Sk_{-p}^{SH^+}$. [l] Estimated from $k_p^{OH} = Kk_{-p}^S$. [m] Reference 69. [n] Rate constants k_p^B and k_{-p}^{BH} as defined by eq 39 and 40, in L mol^{-1} s^{-1}; acetate: $k_p^B = 6.8 \times 10^4$, $k_{-p}^{BH} = 3 \times 10^9$; formate: $k_p^B = 5.9 \times 10^3$; $k_{-p}^{BH} = 5.45 \times 10^9$; chloroacetate: $k_p^B = 1.2 \times 10^3$; $k_{-p}^{BH} = 10^{10}$.

Comparison with the results for the picryl complex **134a**[64,67] provides an explanation for rate limiting proton transfer in the formation of **146**.[294] The requirement for such behavior is $k_1 > k_{-p}$. In the case of **134a**, $Kk_1 = 1.6 \times 10^6$ L mol^{-1} s^{-1}.[64] Since a reasonable estimate of K is ≃ 0.3 L mol^{-1} [297] (p$K_a^{GOH} \simeq 14.5$), this leads to an estimated $k_1 \simeq 5 \times 10^6$ s^{-1}. Due to the low acidity of GOH, protonation of GO^- even by the weakest acid in the system, i.e., the solvent, is very fast, with $k_{-p}^S \simeq 10^9$ s^{-1}.[296] Thus k_{-p} can never be lower than ≃ 10^9 s^{-1}, and k_1 is $<<k_{-p}$ under all experimental conditions. A similar situation prevails in the formation of complexes **134**, **136**, and **143**. In contrast, k_{-p}^S is relatively small in reaction 38, as a consequence of the relatively high acidity of GOH.[294] As a result, protonation of GO^- occurs mainly through the $k_{-p}^{SH^+}$ and k_{-p}^{BH} steps where the experimental conditions are suitable. Even though these latter steps are diffusion controlled or nearly so, proton transfer is then rate limiting because k_1 is very high (1.2×10^9 s^{-1}) and the $k_{-p}^{SH^+}$ and k_{-p}^{BH} steps are bimolecular reactions and thus become very fast only at high H^+ or high buffer concentrations.[294] The rate-enhancing effect of Me_2SO and the greater conformational rigidity of the catecholate ion GO^- relative to its alkoxide analogue are responsible for the much higher k_1 value for formation of **146** in 50% Me_2SO compared to that for **134a** in water. The different k_{-1} values for these two complexes essentially reflect the difference

TABLE XXI. Rate and Equilibrium Parameters for 1:1 and 1:2 Sulfite Complexes of 1-X-2,4,6-Trinitrobenzenes in Water

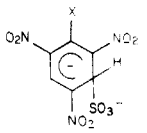
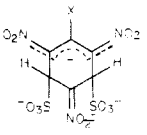
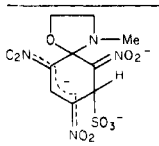
Cpx	X	t, °C	k_f,[a] L mol^{-1} s^{-1}	k_d,[a] s^{-1}	K,[a] L mol^{-1}	activation and thermodynamic parameters;[b] conditions and comments[c]	ref
							
150a	H	25			512	zero ionic strength	307, 309
		25			267	I = 0.144 M; ΔH° = −16.7; ΔS° = −9.5	309
		20			250[d]	I = 0.3 M	305
		25	3.54×10^4	125	286	no added salt	312
		25	3.58×10^4	130	272	I = 0.6 M	312
		25	3.7×10^4	115	322	isnc; $\Delta H_f^\ddagger$ = 31.3; $\Delta S_f^\ddagger$ = −52.7; $\Delta H_d^\ddagger$ = 47.6; $\Delta S_d^\ddagger$ = −47.7; ΔH° = −16.3; ΔS° = −5	315
150b	OMe	20			210	I = 0.3 M	305
		25	4800	35	140	I = 0.3 M	316
150c	NH_2	20			1.01×10^4	I = 0.3 M	305
		25	5.7×10^4	7	8600	I = 0.14 M; $\Delta H_f^\ddagger$ = 28.4; $\Delta S_f^\ddagger$ = −58.5; $\Delta H_d^\ddagger$ = 46.4; $\Delta S_d^\ddagger$ = −73; ΔH° = −18; ΔS° = 14.5	311
150d	NHMe	20			5.4×10^4	I = 0.3 M	305
		25	1.4×10^4	0.2	6.8×10^4	I = 0.14 M; $\Delta H_f^\ddagger$ = 30.5; $\Delta S_f^\ddagger$ = −61.5; $\Delta H_d^\ddagger$ = 56; $\Delta S_d^\ddagger$ = −67.7; ΔH° = −25.5; ΔS° = 6.2	311
150e	NMe_2	20			5.4×10^4	I = 0.3 M	305
		25	4100	0.14	3×10^4	I = 0.14 M; $\Delta H_f^\ddagger$ = 26.7; $\Delta S_f^\ddagger$ = −85.3; $\Delta H_d^\ddagger$ = 57.7; $\Delta S_d^\ddagger$ = −68.5; ΔH° = −31: ΔS° = −16.8	311
150f	Me	25			5.6	I = 0.14 M	309
		25	800[e]	300[e]	2.6[e]	I = 0.3 M	319
150g	CH_2Cl	25	4000	77	55	I = 0.3 M	319
150h	O^-	20			1.2[f]	zero ionic strength	196
		25	280	110	2.5	I = 0.3 M	316
		25	600	110	5.5	I = 2.1 M	316
150i	SO_3^-	25	60	42	1.4	I = 0.3 M	191
		25	140	42	3.3	I = 2.1 M	191
150j	NO_2	22			$\geq 10^6$	no added salt	192
152	CHO	25			2150[g]	I = 0.14 M	309
		24			1.84×10^4[g]	I = 0.14 M; ΔH° = −10; ΔS° = 47.5	310
157	NMeR[h]	25	4040	0.15	2.69×10^4	I = 1.8 M	317
							
151a[i]	H	20			9.2	I = 0.3 M	305
		20			0.5	zero ionic strength	305
151a-t		25	195	21	9.3	I = 0.3 M	312
		25	311	20	15.6	I = 0.9 M	312
		25	1390	16	86.8	I = 4.5 M	312
151a-c		25	1.2	0.13	9.2	I = 0.3 M	312
		25	1.6	0.12	13.3	I = 0.9 M	312
		25	6.3	0.14	45	I = 4.5 M	312
151b	OMe	20			900	I = 0.3 M	305
		20			58	zero ionic strength	305
		25	170	0.12	1400	I = 0.3 M	316
151c	NH_2	20			18.4	I = 0.3 M	305
		20			1.05	zero ionic strength	305
		25			≃6[j]	I = 0.14 M; ΔH° = −37.6; ΔS° = −50	311
		25	140	7	20	I = 0.3 M	316
151d	NHMe	20			1800	I = 0.3 M	305
		20			110	zero ionic strength	305
		25			1300[j]	I = 0.14 M; ΔH° = −46; ΔS° = −92	311
		25	330	0.16	2000	I = 0.3 M	316
151e	NMe_2	20			6.2×10^4	I = 0.3 M	305
		20			2300	zero ionic strength	305
		25			2.6×10^4[j]	I = 0.14 M; ΔH° = 58.8; ΔS° = −117	311
		25	310	6×10^{-3}	5×10^4	I = 0.3 M	316
151f	Me	25	42	1.16	36	I = 0.3 M	319
151g	CH_2Cl	25	55	1.7	32	I = 0.3 M	319
151h	O^-	20			0.016	zero ionic strength	196
		25	250	4	60	I = 2.1 M	316
151i	SO_3^-	25	18	0.14	130	I = 2.1 M	191
154[k]	CHO	24			31.7	I = 0.14 M; ΔH° = −35.6; ΔS° = −91	310
158	NMeR[h]	25	1560	4.8×10^{-3}	3.25×10^5	I = 1.8 M	317

TABLE XXI (*Continued*)

Cpx	X	t, °C	k_f,[a] L mol^{-1} s^{-1}	k_d,[a] s^{-1}	K,[a] L mol^{-1}	activation and thermodynamic parameters;[b] conditions and comments[c]	ref
159			94[l]	8.45[l]	11.1[l]	I = 1.8 M	317



[a] k_f, k_d, and K represent the rate and equilibrium constants associated with formation and decomposition of the various complexes. [b] Enthalpies in kJ mol^{-1}; entropies in J mol^{-1} K^{-1}. [c] Ionic strength maintained with Na_2SO_4 or KNO_3. [d] In 70% Me_2SO-30% H_2O, $K \geq 5 \times 10^4$ L mol^{-1}. [e] Extrapolated from linear plots of log k_f, log k_d, and log K vs. N_{Me_2SO}. [f] In 50% Me_2SO-50% H_2O; K = 10 L mol^{-1}. [g] The 1:1 complex may be 152 or 153. [h] R = CH_2CH_2OH. [i] This adduct is probably 151a-*t* (see text). [j] Values calcualated at 25 °C from the temperature dependence of K (ref 311). [k] The 1:2 complex may be 154 or 155. [l] k_f, k_d, and K correspond to the formation and decomposition of 159 from the spiro complex 156.

TABLE XXII. Equilibrium Constants for Formation of 1:1 and 1:2 Complexes of TNB and Thiolate or Thiophenoxide Ions

RS$^-$	solvent	t, °C	Cpx	K_1, L mol^{-1}	Cpx	K_2,[a] L mol^{-1}	ref
EtS^-	H_2O	20	160	170	161	12000	320
	H_2O-MeOH 70:30	20		1100		2200	320
	20:80	20		4800		35	320
	MeOH	20		3500		10	95, 320
	H_2O-EtOH 70:30	20		3000		1500	320
	20:80	20		45000		23	320
	EtOH	20		25000		7	320
GS^-	H_2O	25	162[b]	28			322
$C_6H_5S^-$	MeOH	20	166a	1.95			95
	EtOH	20		35			320
	H_2O-EtOH 50:50	20		40			320
	5:95	22		43.2			321
	MeOH-Me_2SO 50:50	20		190			39
	20:80[c]	20		4700			39
	Me_2SO	20		9×10^4			39
p-$OMeC_6H_4S^-$	H_2O-EtOH 5:95	22	166b	450			321
p-Me-		22	166c	143			321
m-Me-		22	166d	69			321
p-F-		22	166e	34			321
m-OMe-		22	166f	29.5			321
p-Cl-		22	166g	6			321
m-$COCH_3$-		22	166h	4.9			321
p-Br-		22	166i	4.8			321
m-Cl-		22	166j	2.2			321
m-Br-		22	166k	2			321
p-$COCH_3$-		22	166l	0.5			321
o-Me-		22	166m	70			321
o-NH_2-		22	166n	59			321

[a] Extrapolated at zero ionic strength. [b] k_1 = 2900 L mol^{-1} s^{-1}; k_{-1} = 102 s^{-1}; unspecified ionic strength. [c] Estimated values in 85% Me_2SO–15% MeOH; $k_1 > 5 \times 10^6$ L mol^{-1} s^{-1}; $k_{-1} > 10^3$ s^{-1} at t = 20 °C (ref 95).

TABLE XXIII. Equilibrium and Kinetic Data for Dithiolane Complexes

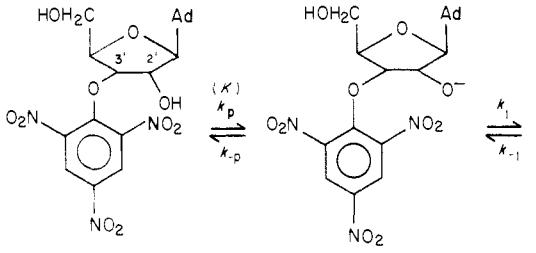
	168	169a		169b	
	H_2O[a,b]	H_2O[c,g]	MeOH[d,g]	H_2O[c,g]	MeOH[d,g]
pK_a	5	1.16	5.89	2.03	6.42
KK_1, L mol^{-1} [e]	10^9	5.79×10^{12}	4.04×10^{10}	8.50×10^{11}	1.09×10^{10}
K_1[e,f]	10^5	5.79×10^8		8.50×10^7	
Kk_1, L mol^{-1} s^{-1}	4×10^{10}	1.9×10^{10}	1.51×10^9	1.02×10^{10}	5.25×10^8
k_1, s^{-1} [f]	4×10^6	1.9×10^6		1.02×10^6	
k_{-1}, s^{-1} [e]	38	3.28×10^{-3}	0.0374	0.012	0.048

[a] t = 25 °C; ref 329. [b] Drodz et al. report KK_1 = 2500 L mol^{-1} in 50% H_2O-50% EtOH; ref 295. [c] t = 20 °C; I = 0.2 M KCl; ref 330. [d] t = 20 °C; I = 0.01 M buffer salts; ref 330. [e] Not statistically corrected. [f] Calculated assuming $K = 10^4$ L mol^{-1} in water. [g] pK_a for ionization of the nitronic acids; for 170a: $pK_a^{H_2O}$ = 0.85; pK_a^{MeOH} = 5.05; for 170b: $pK_a^{H_2O}$ = 0.83; pK_a^{MeOH} = 5.02.

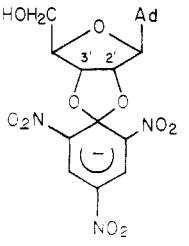
in basicity of the two oxygens ($k_{-1} = 10^4$ s^{-1} for **146**, k_{-1} = 0.095 s^{-1} for **134a**).[294]

5. 3′-O-(2,4,6-Trinitrophenyl)adenosine

The picryl complex of adenosine **148** has a very high thermodynamic stability in aqueous solution, as reflected by a pK_a value of 4.83 at 20 °C.[301] Due to the stereoselectivity of the ring opening of **148** which occurs exclusively at the 2′-oxygen to give **147** as the only one ether,[300] a kinetic study of the conversion of **147** into **148** is possible in the pH range 3–7.5.[301] Instead of obeying eq 14, as expected for a system involving deprotonation of an alcoholic OH group, the rates depend curvilinearly on the buffer concentration. As for **146**, the results are consistent with a mechanism where the proton transfer of the GOH ⇄ GO^- step is, at least



147 (GO⁻)



148

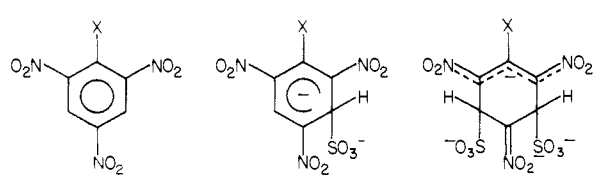
partially, rate limiting at low buffer concentrations. Since the OH group of **147** has a weak acidity,[302] protonation of GO⁻, even by the solvent, is very fast ($k_{-p}^{S} \simeq 10^9$ s^{-1}), and the proton transfer is rate limiting because of a remarkably high rate of cyclization of GO⁻. Analysis of the results yields 3×10^9 L mol^{-1} s^{-1} as a *lower* limit for Kk_1. Assuming $K \simeq 0.3$ L mol^{-1},[302] this leads to $k_1 \geq 10^{10}$ s^{-1}. This k_1 value is consistent with the cyclization step being faster than the proton-transfer step at low buffer concentrations. It also corresponds to the highest rate of nucleophilic attack on an aromatic carbon measured to date. The results are given in Table XX.

III. Sulfur-Bonded σ Complexes

It is well-known that in nucleophilic substitution reactions sulfur bases are considerably more reactive than oxygen bases. This is not expected on the basis of their Brønsted basicities (pK_a values).[7,9,11,304] Thus, a number of such bases easily react with activated aromatics to form sulfur-bonded σ complexes as stable or transient species.[95,191,196,305-332] Kinetic and thermodynamic data have been reported for reactions of TNB derivatives with sulfite,[191,196,305-319] thiolate,[95,320,322,325] and thiophenoxide ions.[39,321,331] Spiro complex formation has also been the subject of some investigation.[329,330,332] The results are summarized in Tables XXI-XXIII.

A. Sulfite Complexes

In aqueous solution, sulfite ions react with the TNB derivatives **149** to give the 1:1 complexes **150** and the



149 **150** **151**

(a) X = H (149 = TNB); (b) X = OMe (149 = TNA); (c) X = NH_2; (d) X = NHMe; (e) X = NMe_2; (f) X = Me (149 = TNT); (g) X = CH_2Cl (149 = TNBCl); (h) X = O^-; (i) X = SO_3^-; (j) X = NO_2

1:2 complexes **151**.[191,196,305-319] Except in the case of TNB, examination by SF spectrophotometry of the interactions shows the presence of two well-separated time-dependent processes: a fast reaction producing the 1:1 complex **150** and a slower reaction giving the 1:2 complex **151**.[191,315,316] In agreement with eq 42 and 43,

$$\mathbf{149} + SO_3^{2-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{150} \qquad (42)$$

$$K_1 = [\mathbf{150}]/([\mathbf{149}][SO_3^{2-}])$$

the measured relaxation times $1/\tau_1$ and $1/\tau_2$ for these processes obey eq 44 and 45, respectively. In contrast,

$$\mathbf{150} + SO_3^{2-} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathbf{151} \qquad (43)$$

$$K_2 = [\mathbf{151}]/([\mathbf{150}][SO_3^{2-}])$$

when aqueous solutions of TNB and $Na_2SO_3 \geq 3 \times 10^{-3}$ M are mixed, three, instead of two, separated kinetic processes are observed.[312] The results have been interpreted in terms of formation of the two isomeric cis and trans complexes **151a**-*c* and **151a**-*t*, according to eq 46.[312] These complexes, which have very similar

$$1/\tau_1 = k_{-1} + k_1[SO_3^{2-}] \qquad (44)$$

though not identical UV-visible spectra, were *later* unambiguously characterized by proton NMR.[313,314] Rate and equilibrium parameters for the three steps were determined from the $[SO_3^{2-}]$ dependence, according to eq 44, 45, and 47, of the three relaxation times.

$$\frac{1}{\tau_2} = k_{-2} + \frac{k_2 K_1 [SO_3^{2-}]^2}{1 + K_1[SO_3^{2-}]} \qquad (45)$$

$$\mathrm{TNB} + 2SO_3^{2-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{150a} + SO_3^{2-} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathbf{151a}\text{-}t \quad \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathbf{151a}\text{-}c \qquad (46)$$

$$\frac{1}{\tau_3} = k_{-3} + \frac{k_3 K_1 [SO_3^{2-}]^2}{1 + K_1[SO_3^{2-}](1 + K_2[SO_3^{2-}])} \qquad (47)$$

Data for all complexes **150** and **151** are given in Table XXI.

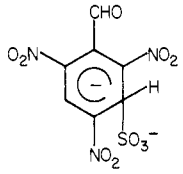
It is noteworthy that the isomeric 1:2 complexes **151a**-*c* and **151a**-*t* are of approximately the same stability but have quite different rates of formation and decomposition. For instance, at $I = 0.3$ M, $K_2/K_3 = 1.01$, $k_2/k_3 = 163$, and $k_{-2}/k_{-3} = 161$. This clearly indicates that there is an effect on the respective transition states which is not present (or present to a smaller extent) in either the 1:1 complex **150a** or in the two diadducts.[333] It has been proposed that the trans isomer **151a**-*t* is first formed.[312] That **151a**-*c* has similar stability to **151a**-*t* but is formed less rapidly was rationalized in terms of electrostatic repulsion between the sulfite groups present in the transition state for its formation but reduced by ring distortion in the complex itself. The failure to observe cis-trans isomerism in other diadducts **151b-j** might result from similar rates of dissociation of the cis and trans complexes.[20] However, the absence of such isomerism in NMR experiments suggests that one of the isomers is, in fact, thermodynamically preferred. Significantly, the k_2 values for formation of **151** with X = OMe, NH_2, NHMe, NMe_2, and O^- are all very similar to the k_2 value

found for formation of **151a**-*t*.[316] On this basis, it has been suggested that the corresponding 1:2 complexes are the trans isomers. This is probably also the case with X = Me, CH_2Cl, and SO_3^-.

Changing the ionic strength I of the medium does not appreciably affect the equilibrium constant K_1 when X is an uncharged substituent.[311,312,315,316] In contrast, the K_1 values for X = O^- and SO_3^-[191,196,316] and all the K_2 values strongly increase with increasing I, as expected for formation of multicharged adducts.[311,312,315,316] The kinetic data show that, except in the case of picrate and sulfonate systems where k_1 is lowered due to the initial negative charge, changes in K_1 with substituent X derive largely from changes in k_{-1}. Similarly, changes in the k_{-2} values govern those in the K_2 values. This suggests that the respective transition states for 1:1 and 1:2 complex formation are "reactant-like" rather than "product-like". Solvation differences, steric factors, and, in the case of picramide and *N*-methylpicramide, hydrogen bonding of amino protons to the adjacent NO_2 groups will play a major role in determining the relative stabilities of the complexes and the observed trends in the enthalpies and entropies of reaction.[311,316]

The 1:1 complexes **150** have much higher stabilities than the analogous hydroxide adducts. For instance, the ratio $K_1^{SO_3^{2-}}/K_1^{OH^-}$ is of about 75 for X = H, SO_3^-, 100 for X = OMe, and 200 for X = NH_2, O^-. Clearly, the carbon basicity of SO_3^{2-} ion is greater than that of OH^- for attack on the parent aromatics. However, comparison of the k_{-1} values indicates that SO_3^{2-} is a better leaving group than OH^-. The stability of 1:1 complexes is enhanced in water–Me_2SO mixtures.[305,319] Thus, K_1 for formation of **150a** is $\simeq$ 100 times greater in 70% Me_2SO than in water. In contrast, there is little tendency to form 1:2 complexes in media rich in Me_2SO.[305] These latter, which bear four negative charges, may be compared to inorganic salts and are poorly solvated by the aprotic solvent.

2,4,6-Trinitrobenzaldehyde has an unusual behavior in that SO_3^{2-} addition occurs at both the unsubstituted ring positions and at C-1 to give the 1:1 complexes **152** and **153** and the 1:2 complexes **154** and **155**.[310] Both **154**



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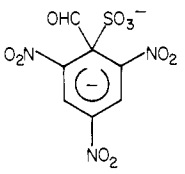

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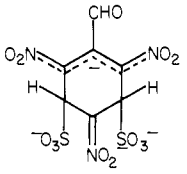

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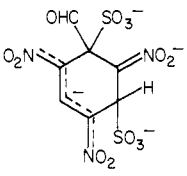
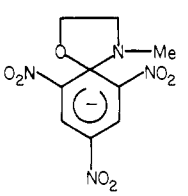


155

and **155** should exist as cis and trans isomers.[310] Search for new examples of cis–trans isomerism in diadducts has led Bernasconi to investigate the attack of SO_3^{2-} on *N*-methyl-*N*-(β-hydroxyethyl)picramide.[317] The three complexes **157**, **158**, and **159** are formed in addition to the spiro complex **156**. Although this study does not provide evidence for cis–trans isomerism in the diadducts **158** and **159**, it does include features of interest in a complex equilibrating system. Rate and equilibrium parameters for the three sulfite complexes are in Table XXI while those for the spiro complex **156**, which have been determined in the absence of SO_3^{2-}, are given in Table XXIX (see section V).



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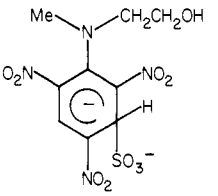

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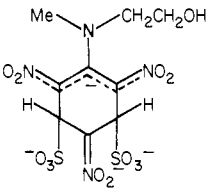

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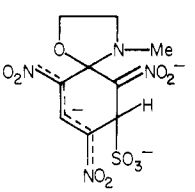
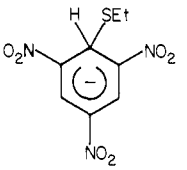


159

B. Thiolate Complexes

The equilibrium constants K_1 [=[**160**]/([TNB]·[EtS^-])] and K_2 [=[**161**]/([**160**][EtS^-])] for the reversible formation of the 1:1 and 1:2 thioethoxide complexes of TNB have been spectrophotometrically measured in water, MeOH, EtOH, and the corresponding solvent mixtures.[95,320] The formation of **160** is largely favored



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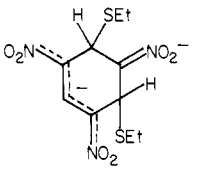

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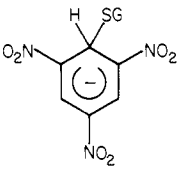

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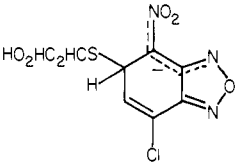


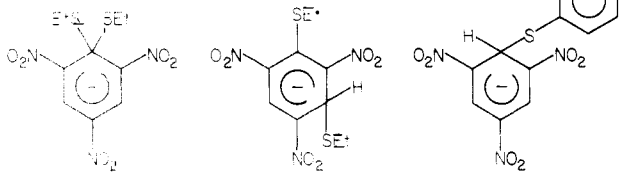
163

relative to **161** in both alcohols. The K_1 and K_2 values are equal to 25 000 and 7 L mol^{-1} in EtOH and 3500 and 10 L mol^{-1} in MeOH, respectively. In contrast, 1:2 complex formation is the major interaction in water: K_2 = 12 000, K_1 = 170 L mol^{-1}. The enhanced stability of **161** in water reflects the better solvation of its localized negative charge by this solvent than by alcohols. As found for the sulfite complexes, the K_2 values are strongly dependent on the ionic strength. Comparison of the K_1 values for **160** with those for the hydroxide, methoxide, and ethoxide analogues (**5a–c**) results in the following carbon basicity order: $EtS^- > EtO^- > MeO^- > OH^-$.[320] No evidence for cis–trans isomerism in **161** has been obtained so far.

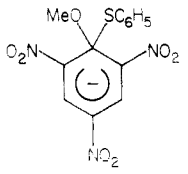
There has been no kinetic study of the TNB–SEt^- system. In this regard, it is of interest that rate and equilibrium parameters have been reported for the reaction of TNB with glutathione (GSH) to give the 1:1 complex **162** in aqueous solution.[322] The forward and reverse rate constants are k_1 = 2900 L mol^{-1} s^{-1} and k_{-1} = 102 s^{-1}, leading to a K_1 value of 28 L mol^{-1}. Thus, **162** is 8 times more stable than the hydroxide complex

5a. Nevertheless, GS^- is a better leaving group than OH: $k_{-1}^{162}/k_{-1}^{5a} \simeq 10$. Also to be noted is the high equilibrium constant $K_1 = 1.8 \times 10^6$ L mol^{-1} reported for formation of the complex **163** of NBDCl and CH_2-OH-CH_2S^-.[323]

Evidence has been obtained for formation of the 1,1- and 1,3-diethylthio complexes **164** and **165**.[324,325] In



164 165 166a-n



167

contrast with what was found for the dialkoxy analogues, **165** is appreciably more stable than **164**. However, no quantitative data are available because these adducts are formed too rapidly and are transient species due to a subsequent substitution of the *p*-NO_2 group by EtS^-. EtS^- attacks 2,4,6-trinitrophenetole to give a mixture of 1,1 and 1,3 complexes of about the same stability.[328]

C. Thiophenoxide Complexes

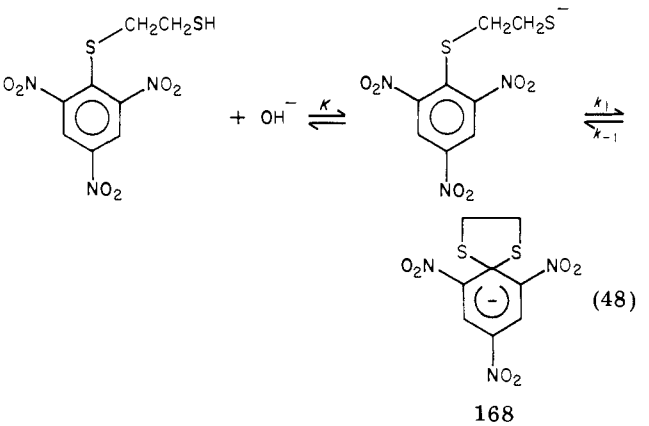
TNB reacts with a number of substituted thiophenoxide ions to give the 1:1 complexes **166a-n** (see Table XXII). The carbon basicities of the ArS^- ions, as measured by the values of the equilibrium constant K_1 = [**166**]/([TNB][ArS^-]) determined in 95% EtOH-5% water, show a greater susceptibility to change in the X substituent than do the proton basicities, although the general behavior pattern is similar.[321] A plot of log K_1 for meta and para substituents vs. pK_a of the corresponding thiophenols is linear with a slope 1.24. The steric effects have more importance on the stability of the adducts than on the acidity of ArSH. The carbon basicity of *o*-methylthiophenoxide ion is thus reduced relative to its proton basicity, due to an unfavorable steric compression between the methyl group and the adjacent NO_2 group in **166m**.[321,334]

There have been measurements of K_1 for the TNB-thiophenoxide and -4-aminothiophenoxide complexes in various EtOH-water and MeOH-water mixtures, respectively.[320] Evidence for the formation of some 1:2 complex was obtained at high [ArS^-] in mixtures of high water content. Of great importance is a calorimetric study of the formation of **166a** which provides the heats of reaction and the heats of transfer of the starting materials and the complex in the whole range of MeOH-Me_2SO mixtures.[39] These data are analyzed in section VIII.

The complex **167** of TNA and $C_6H_5S^-$ has been reported in MeOH-Me_2SO mixtures rich in Me_2SO. From NMR experiments, its rate of decomposition was estimated to be $\simeq 9$ s^{-1} at -70 °C and 800 s^{-1} at -40 °C in 25% Me_2SO-75% MeOH.[331]

D. Spiro Complexes

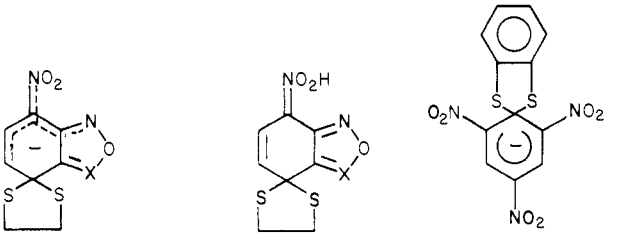
1-[(2-Mercaptoethyl)thio]-2,4,6-TNB cyclizes in water according to eq 48 to give the spiro complex **168** which



(48)

168

$$k_{obsd} = k_{-1} + \frac{Kk_1[OH^-]}{1 + K[OH^-]} \qquad (49)$$



169a X = N→O 170a 171
b X = N b

is half-formed at pH 5.[329] **169a** and **169b** similarly form from the parent nitrobenzofuroxan and -benzofurazan in water and MeOH.[330] These complexes have a remarkably high stability: pK_a^{169a} = 1.16; pK_a^{169b} = 2.03 in water. The pH-rate profiles for the interconversion of the thiols and the complexes are shown in Figure 6. They are remarkable in that they reveal no catalysis of the decomposition of **168**, **169a**, and **169b** by H^+. In the picryl system, the observed rates strictly obey eq 49 over the entire investigated pH range with $k_{obsd} = k_{-1}$ at low pH ($K[OH^-] << 1$, $K \simeq 10^4$ L mol^{-1}). In the annelated systems, where protonation occurs in the most acidic media to give **170a** and **170b**, decreasing pH causes a decrease in the rates of reversion of the complexes to the parents. The concomitant resulting increase in the lifetime of the transient nitronic acids has allowed NMR characterization of **170a** in Me_2SO-CF_3COOD mixtures.[330] The resistance to acids of the dithiolane complexes is explicable in terms of the low basicity of sulfur, a "soft" base, relative to oxygen.[335] Significantly, a dramatic increase in the rate of decomposition occurs when adding Hg^{2+}, a "soft" acid, to the solutions.[329]

The dithiolane complexes are much more stable than their oxygen analogues ($\Delta pK \simeq 5$). This is due to the greater acidity of thiols relative to alcohols rather than to higher K_1 values for internal cyclization of the GS^- ions; in fact, K_1 is lower than, or of the same order as, those for internal cyclization of the GO^- ions. This result contrasts with the higher carbon basicities found for SO_3^{2-} and EtS^- ions relative to oxygen bases in the

reaction with TNB. Possible factors accounting for this behavior are (1) differences in the stabilizing effects of multiple alkoxy and thioalkoxy substitution at the sp^3 carbon and (2) destabilization of the sulfur complexes due to steric compression between the two sulfur atoms at C-1 and between the dithiolane ring and the ortho substituents.[329] This latter factor could be essentially responsible for the greater ease of C–S bond breaking in **168** relatively to **169a** and **169b**.[330] The formation of the complex **171** from the parent dithiocatechol picryl ether has been detected at −60 °C in MeOH prior to formation of 1,3-dinitrothianthrene.[332]

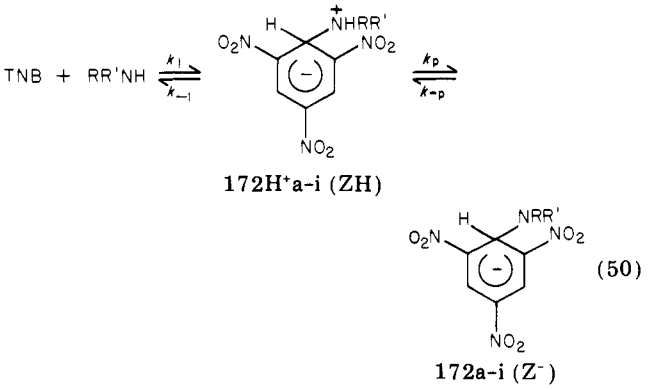
IV. Nitrogen- and Phosphorus-Bonded σ Complexes

Activated aromatics have long been known to form anionic σ complexes with primary and secondary aliphatic and alicyclic amines.[5,6,9,11,17,336] In contrast, it is just recently that Buncel et al. have observed the formation of similar complexes from aromatic amines[337,338] and Onys'ko et al. have characterized the first complexes from phosphorus bases.[378–385] Extensive kinetic and thermodynamic studies of the amine systems have been made.[17–19,339–347] They are of considerable interest because they have led to a reconsideration of long-accepted ideas regarding the mechanism of base catalysis in S_NAr reactions with amine nucleophiles.[17–19] Other characterized nitrogen-bonded σ complexes include those formed from azide ions,[348,349] indolide, pyrrolide, and imidazolide ions,[350,351] liquid ammonia,[352] and hydroxylamine.[353] Formation of such complexes is also postulated in the meta bridging reactions of amidines with TNB and polynitronaphthalenes (see section VIC).[354] However, there are very little kinetic and thermodynamic data on these systems.

A. Complexes from Aliphatic, Alicyclic, and Aromatic Amines

1. Rate Equations and Mechanisms: Rate-Limiting Proton Transfer

a. TNB Complexes of Aliphatic and Alicyclic Amines. Addition of primary or secondary amines to TNB initially yields a zwitterion **172H⁺** (ZH) which then loses an alkylammonium proton to give the anionic σ-complex **172** (Z^-) according to eq 50. Earlier studies



172H⁺a-i (ZH)

(50)

172a-i (Z^-)

(a) methylamine; (b) butylamine; (c) dimethylamine; (d) pyrrolidine; (e) piperidine; (f) isopropylamine; (g) benzylamine; (h) 2,2,2-trifluoroethylamine; (i) diethylamine

carried out in Me_2SO and acetonitrile have provided the equilibrium constants K_c (=$[Z^-][RR'NH_2^+]/([TNB]\cdot[RR'NH]^2)$) for the overall interaction of TNB with 2 equiv of amine to give **172** as its alkylammonium salt.[336,355] Using the TJ technique, Bernasconi has investigated in detail the mechanism of eq 50 in aqueous solvents.[339,341,347] Data are available in 90% water–10% dioxane for the TNB–methylamine, –dimethylamine, –*n*-butylamine, –pyrrolidine, and –piperidine complexes **172a–e** and in 70% water–30% Me_2SO for the three latter systems. Figures 7 and 8 are typical for the dependence of the reciprocal relaxation time $1/\tau$ which characterizes reaction 50 upon pH and amine concentration.[347] *The results are consistent only with a mechanism where proton transfer between ZH and Z^- is rate limiting under certain conditions.* Assuming ZH to be a "steady-state" intermediate, $1/\tau$ is given by eq 51 under pseudo-first-order conditions. Here, k_p and k_{-p} are defined by eq 52 and 53 where k_p^{OH} and k_p^{Am}

$$\frac{1}{\tau} = \frac{k_1 k_p[RR'NH]}{k_{-1} + k_p} + \frac{k_{-1}k_{-p}}{k_{-1} + k_p} \quad (51)$$

$$k_p = k_p^{OH}[OH^-] + k_p^{Am}[RR'NH] \quad (52)$$

$$k_{-p} = k_{-p}^{S} + k_{-p}^{AmH^+}[RR'NH_2^+] \quad (53)$$

are the rate constants for deprotonation of ZH by OH^- and by the amine, respectively, and k_{-p}^{S} and $k_{-p}^{AmH^+}$ are the rate constants for protonation of Z^- by the solvent and the conjugate acid of the amine, respectively. Deprotonation of ZH by the solvent (k_p^S) and protonation of Z^- by the solvated proton ($k_{-p}^{SH^+}$) are negligible pathways under the conditions of the various studies. The plots of Figures 7 and 8 are accounted for by two limiting situations: (1) $k_p >> k_{-1}$. In this case, proton transfer is rapid, and eq 51 reduces to

$$\frac{1}{\tau} = k_1[RR'NH] + \frac{k_{-1}[H^+]}{K_a^{ZH}} \quad (54)$$

where K_a^{ZH} (=$[Z^-][H^+]/[ZH]$) is the acid dissociation constant of ZH. Plotting $1/\tau$ vs. [RR'NH] yields straight lines with equal slopes (k_1) and pH-dependent intercepts. The condition for eq 54 is met at high pH where $k_p^{OH}[OH^-] >> k_{-1}$ and/or at high amine concentration where $k_p^{Am}[RR'NH] >> k_{-1}$. For example, in Figure 8, parallel straight lines of slope k_1 are seen at pH ≥ 12.23 for all amine concentrations and at pH ≤ 11.84 only for amine concentrations ≥0.1 M. The observation, at low pH and high piperidine concentrations, of straight lines whose slope is somewhat smaller than k_1 was attributed to a rate-retarding salt or medium effect by the amine hydrochloride.[347] The concentration of this salt is quite high in these experiments. In the butylamine reaction, this effect is so important that it results in negative slopes for the linear plots of $1/\tau$ vs. [RR'NH].

(2) $k_p << k_{-1}$. In this case, deprotonation of ZH is rate-limiting in the forward direction and protonation of Z^- rate determining in the reverse direction. Equation 51 becomes

$$\frac{1}{\tau} = \frac{k_1}{k_{-1}}(k_p^{OH}[OH^-] + k_p^{Am}[RR'NH])[RR'NH] + k_{-p}^{S} + k_{-p}^{AmH^+}[RR'NH_2^+] \quad (55)$$

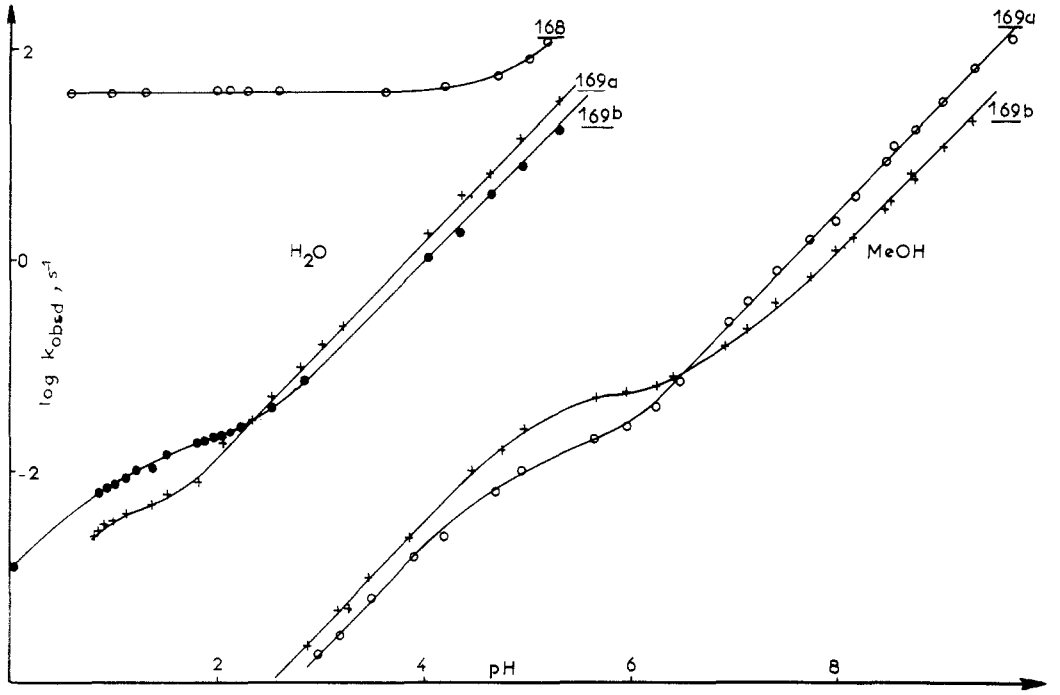


Figure 6. pH–rate profiles for the formation and decomposition of the dithiolan spiro complexes **168** (t = 25 °C) and **169a** and **169b** (t = 20 °C) in water and methanol.[329,330]

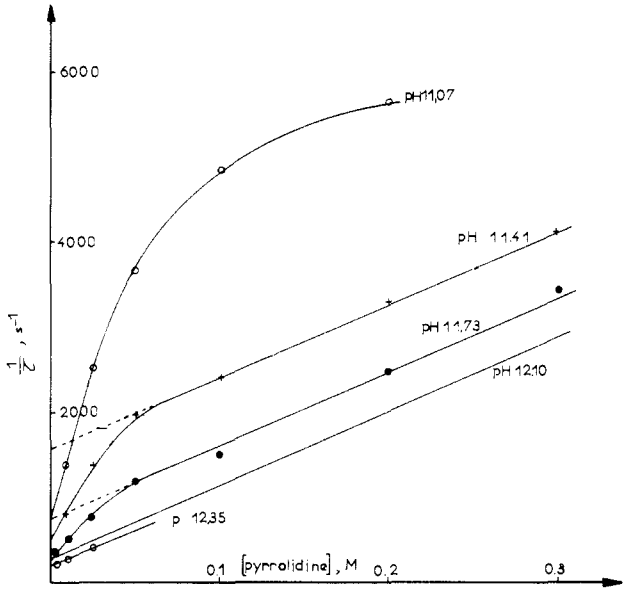


Figure 7. Representative plot of $1/\tau$ vs. the pyrrolidine concentration for the formation of **172d** in 70% H_2O–30% Me_2SO at 20 °C.[347]

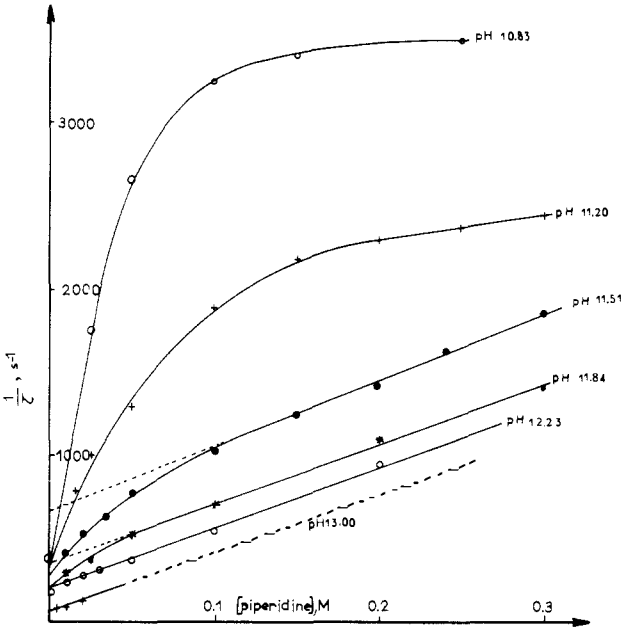


Figure 8. Representative plot of $1/\tau$ vs. the piperidine concentration for the formation of **172e** in 70% H_2O–30% Me_2SO at 20 °C.[347]

The $k_{-p}^{AmH^+}[RR'NH_2^+]$ term is responsible for the observed increase in the initial slopes with decreasing pH in Figures 7 and 8. This is because for a given free amine concentration, the proportion of $RR'NH_2^+$ increases with decreasing pH. When [RR'NH] is increased, the relationship $k_p << k_{-1}$ progressively changes to $k_p \simeq k_{-1}$ and finally to $k_p >> k_{-1}$ with $1/\tau$ given by eq 54. This explains the curvature of the plots of Figures 7 and 8 until the straight lines with slopes k_1 are reached. Table XXIV summarizes the kinetic and thermodynamic parameters associated with reaction 50 in the two solvent mixtures.

Just recently, two reports have appeared describing a kinetic analysis of the formation of the adducts **172b** and **172e–g**[356] in Me_2SO and **172h** in Me_2SO and acetonitrile.[357] Depending upon the system under study, the proton-transfer step is found to be rapid (trifluoroethylamine),[357] rate determining over the entire range of amine concentrations (piperidine)[356] or only at low amine concentrations (benzylamine, *n*-butylamine, isopropylamine)[356] in Me_2SO. In marked contrast with what occurs in Me_2SO, proton transfer is rate determining in the case of **172h** in acetonitrile.[357] This result has been explained in terms of the much lower ability of CH_3CN, relative to Me_2SO, to solvate cations.[357] The zwitterion **172h,H**$^+$ would thus decompose very rapidly in CH_3CN ($k_{-1}^{CH_3CN} >> k_{-1}^{Me_2SO}$), accounting for a situation where $k_{-1} >> k_p$.

b. The Aniline–TNB Complex. While TNB itself does not undergo reaction with aniline in Me_2SO–

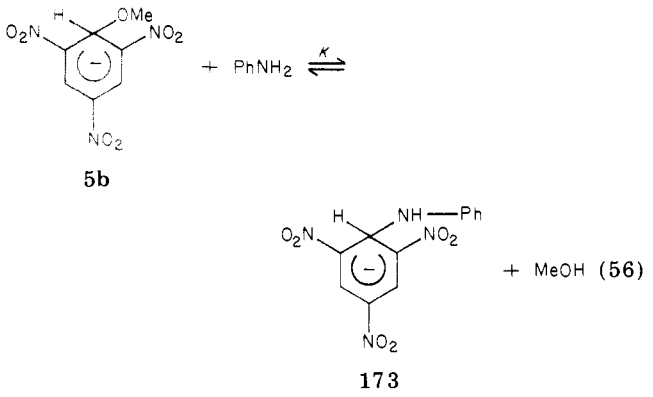
TABLE XXIV. Rate and Equilibrium Constants for the Reaction of Various Amines with TNB in Aqueous Dioxane, Aqueous Me_2SO, or Me_2SO[a]

	amine/complex							
	n-butylamine/172b			piperidine/172e			pyrrolidine/172d	
solvent *t*, °C; ref	10% dioxane[i] 25; 339, 347	30% Me_2SO[j] 20; 347	Me_2SO[k] 25; 356	10% dioxane[i] 25; 339, 347	30% Me_2SO[j] 20; 347	Me_2SO[k] 25; 356	10% dioxane[i] 25; 339, 347	30% Me_2SO[j] 20; 347
k_1, L mol^{-1} s^{-1}	123	250	4.5×10^4	3×10^3	4.1×10^3	$>6 \times 10^4$	8.1×10^3	9×10^3
k_{-1}, s^{-1}	1.5×10^5	1.4×10^5 [c]	2.3×10^4 [h]	2.1×10^6	1×10^6	$>7 \times 10^3$ [h]	1.5×10^6	6.2×10^5
K_1, L mol^{-1}	8.2×10^{-4}	1.78×10^{-3} [c]	2[h]	1.43×10^{-3}	4×10^{-3}	9[h]	5.80×10^{-3}	1.45×10^{-2}
K_c, L mol^{-1}	0.19[d]	0.66[d]	10^3	0.37[d]	1.6[d]	4.5×10^3 [m]	1.45[d]	4.93[d]
$K_1K_a^{ZH}$	3.94×10^{-12}	1×10^{-11} [c]		2.87×10^{-12}	9.85×10^{-12}		7.25×10^{-12}	1.88×10^{-11}
K_a^{ZH}	4.8×10^{-9}	5.6×10^{-9} [c]		2×10^{-9}	2.4×10^{-9}		1.25×10^{-9}	1.3×10^{-9}
$K_a^{AmH^+}$ [b]	2.1×10^{-11} [e]	1.51×10^{-11} [f]	7.95×10^{-12} [v]	7.6×10^{-12} [e]	6.03×10^{-12} [f]		5×10^{-12} [e]	3.80×10^{-12} [f]
$K_a^{ZH}/K_a^{AmH^+}$ [b]	230	370[c]	500[h]	260	400	500[h]	250	340
k_p^{OH}, L mol^{-1} s^{-1}	5×10^9 [g]	5×10^8 [g]		5×10^9 [g]	5×10^8 [g]		5×10^9 [g]	5×10^8 [g]
k_{-p}^{S}, s^{-1}	5.2×10^3	143[c]		1.25×10^4	330		2×10^4	620
k_p^{Am}, [b] L mol^{-1} s^{-1}			3×10^7		1.6×10^7	5×10^4		1.7×10^7
$k_{-p}^{AmH^+}$, [b] L mol^{-1} s^{-1}			6×10^4		3.9×10^4	100		5.1×10^4
k_p^{Dabco}, L mol^{-1} s^{-1}			1×10^7			1.2×10^4		

	amine/complex						
solvent *t*, °C; ref	methylamine/ 172a 10% dioxane[i] 25; 347	dimethylamine/ 172c 10% dioxane[i] 25; 347	benzylamine/ 172g Me_2SO[k] 25; 356	isopropylamine/ 172f Me_2SO 25; 356	diethylamine/ 172i Me_2SO 20; 336	trifluoro-ethylamine/ 172h Me_2SO[n] 25; 357	aniline/ 173 Me_2SO[n] 25; 346
k_1, L mol^{-1} s^{-1}	160	6.25×10^3	1.3×10^4	8×10^3			>1
k_{-1}, s^{-1}	1.5×10^5	7.5×10^5'	6×10^4 [h]	2×10^4 [h]			$>10^7$;[s] $>10^5$ [t]
K_1, L mol^{-1}	1.07×10^{-3}	8×10^{-3}	0.2[h]	0.4[f]			$\simeq 10^{-7}$;[s] $\simeq 10^{-5}$ [t]
K_c, L mol^{-1}	0.25[d,l]	0.96[d]	105	200	13	0.8[o]	1.7[p,q]
$K_1K_a^{ZH}$	5.35×10^{-12}	1.84×10^{-11}					
K_a^{ZH}	5×10^{-9}	2.3×10^{-9}					$\simeq 0.2$;[s] $\simeq 0.002$[t]
$K_a^{AmH^+}$ [b]	2.2×10^{-11} [e]	1.85×10^{-11} [e]			3.16×10^{-11} [v]		2.5×10^{-5} [u]
$K_a^{ZH}/K_a^{AmH^+}$ [b]	230	120	500	500[h]			$\simeq 10^4$;[s] $\simeq 10^2$ [t]
k_p^{OH}, L mol^{-1} s^{-1}	5×10^9 [g]	5×10^9 [g]					
k_{-p}^{S}, s^{-1}	5×10^3	1.1×10^4					
k_p^{Am}, [b] L mol^{-1} s^{-1}		1.2×10^7	7.5×10^6	7.5×10^6			
$k_{-p}^{AmH^+}$, [b] L mol^{-1} s^{-1}		1×10^5	1.5×10^4	1.5×10^4			
k_p^{Dabco}, L mol^{-1} s^{-1}			4×10^6	2×10^6			$\simeq 10^9$;[r] $\simeq 10^7$ [r]

[a] Rate and equilibrium constants are defined by eq 50, 52, 53, and 65. [b] $AmH^+ = RR'NH_2^+$ or $PhNH_3^+$; Am = RR'NH or $PhNH_2$. [c] Values estimated by assuming $K_a^{ZH}/K_a^{AmH^+} = 370$; see discussion in ref 347. [d] Calculated from $K_c = K_1K_a^{ZH}/K_a^{AmH^+}$. [e] Literature data in water. [f] From pH measurements. [g] Assumed values; see discussion in ref 347. [h] Values estimated by assuming $K_a^{ZH}/K_a^{AmH^+} = 500$; see discussion in ref 356. [i] $I = 0.5$ M NaCl. [j] $I = 0.5$ M KCl. [k] $I = 0.1$ M Et_4NClO_4. [l] $K_c = 2000$ at 20 °C in Me_2SO; ref 336. [m] $K_c = 0.05$ at 20 °C in acetonitrile; ref 355. [n] $I = 0.1$ M Et_4NCl. [o] $K_c \simeq 6 \times 10^{-3}$ at 30.6 °C in acetonitrile. [p] K as defined by eq 64. [q] $K \simeq 0.8$ L mol^{-1} at 30 °C in Me_2SO; $K = 0.08$ L mol^{-1} at 30.6 °C in acetonitrile; ref 357. [r] Assumed values; see discussion. [s] Values calculated by $k_p^{Dabco} \simeq 10^9$ L mol^{-1} s^{-1}. [t] Values calculated by assuming $k_p^{Dabco} \simeq 10^7$ L mol^{-1} s^{-1}. [u] A value of $K_a^{PhNH_3^+} = 2.5 \times 10^{-4}$ has been reported from electrode measurements; Kolthoff, I. M.; Chantooni, M. K.; Bhownik, S. J. *J. Am. Chem. Soc.* 1968, *90*, 23. Courtot-Coupez, J.; Le Demezet, M. *Bull. Soc. Chim. Fr.* 1969, 1033. [v] See ref in u.

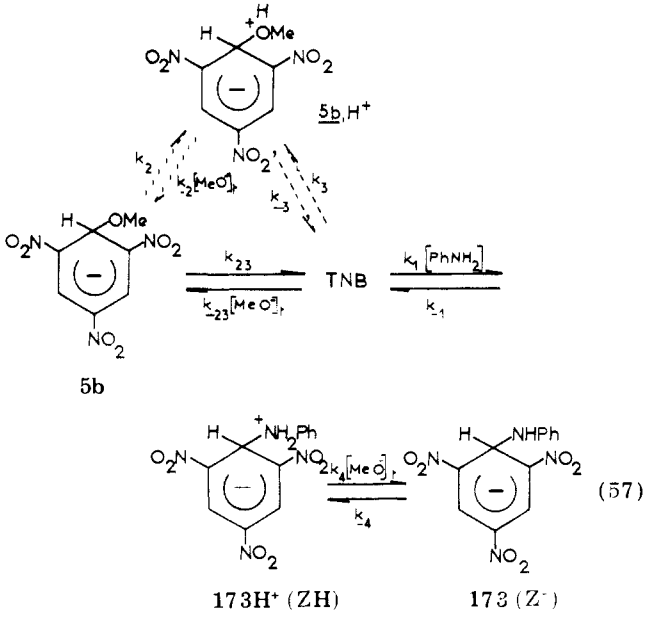
MeOH solutions rich in Me_2SO, Buncel et al. have shown that in the presence of MeO^- ion a rapid reaction occurs to give the TNB-MeO^- complex **5b** which then undergoes a slow reversible conversion to the anilide complex **173**.[343,345] A similar conversion of **5b** into **173**



5b

173

occurs when the reaction is performed by using the potassium salt of **56** and aniline as the reactants. Equation 56 describes the reversible formation of **173**. The apparent equilibrium constant K for this overall reaction was measured from equilibrium absorbance data in 90:10 mol % Me_2SO–MeOH (≃95% Me_2SO by volume): K = 23.2 L mol^{-1} at 25 °C.[345] Kinetic measurements in this medium showed that reaction 56 is first order in aniline but of complex order in **5b**. In addition, the rate of conversion of **5b** into **173** decreases on the addition of MeO^-. *The results are consistent with the dissociative mechanism of eq 57 in which the*



5b

173H⁺ (ZH) 173 (Z⁻)

interconversion of free TNB and the zwitterionic anilide complex ***173H⁺*** *(ZH) constitutes the rate-determing step.*[345] They ruled out a displacement mechanism or a dissociative mechanism involving anilide ion as the nucleophile.[343,345] Although the intermediacy of the protonated complex **5bH⁺** in the reaction scheme (dashed arrows in eq 57) cannot be rigorously excluded on a kinetic basis, several arguments make it extremely unlikely.[345] On the basis of eq 57, the conversion of **5b** into **173** is governed by eq 58 where $[\mathbf{5b}]_t$ and $[\mathbf{5b}]_e$ are the concentrations of **56** at time t and at equilibrium and $[MeO^-]_t$ is the free MeO^- concentration at time t.

$$-\frac{d[\mathbf{5b}]_t}{dt} = \frac{K_{23}k_1[PhNH_2] + K_{-4}k_{-1}}{[MeO^-]_t}([\mathbf{5b}]_t - [\mathbf{5b}]_e) \quad (58)$$

Substituting $[MeO^-]_t$ for its value $K_{23}^{1/2}[\mathbf{5b}]_t^{1/2}$, eq 58 may be written as eq 59 with the rate constant k

$$-\frac{d[\mathbf{5b}]_t}{dt} = \frac{k}{[\mathbf{5b}]_t^{1/2}}([\mathbf{5b}]_t - [\mathbf{5b}]_e) \quad (59)$$

$$k = \frac{K_{23}k_1[PhNH_2] + K_{-4}k_{-1}}{K_{23}^{1/2}} \quad (60)$$

being given by eq 60 where the various rate and equilibrium coefficients are formally defined by eq 57. While eq 58 clearly shows that addition of MeO^- must result in an inhibition of the rate of conversion, eq 59 leads to the approximate law of eq 61 in the early stages

$$-\frac{d[\mathbf{5b}]_t}{dt} \simeq \frac{k}{[\mathbf{5b}]_0^{1/2}}([\mathbf{5b}]_t - [\mathbf{5b}]_e) \quad (61)$$

$$k_{obsd} \simeq \frac{k}{[\mathbf{5b}]_0^{1/2}} \quad (62)$$

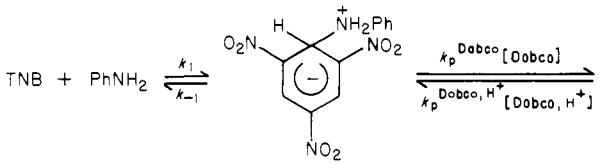
of the reaction where $[\mathbf{5b}]_t^{1/2} \simeq [\mathbf{5b}]_0^{1/2}$. Under such conditions, the observed first-order rate constant k_{obsd} derived in experiments carried out at a given $PhNH_2$ concentration but different initial concentrations of **5b** should obey eq 62. In agreement with this equation, a plot of log k_{obsd} vs. log $[\mathbf{5b}]_0$ was found to be linear with a slope −0.51. Equation 59 also predicts an increase in k_{obsd}, i.e., in $k/[\mathbf{5b}]_t^{1/2}$, and hence an increase in the slope of a first-order plot as the reaction proceeds to equilibrium and $[\mathbf{5b}]_t$ decreases. The observed kinetic behavior is in complete accord with this expectation.[345]

173 also forms from TNB and aniline in the presence of a tertiary amine (Et_3N or Dabco).[346,362] A kinetic and equilibrium study of reaction 63 has been carried out

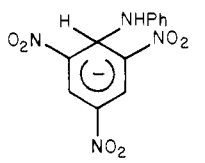
$$TNB + PhNH_2 + Dabco \rightleftarrows \mathbf{173} + Dabco, H^+ \quad (63)$$

$$K = \frac{[\mathbf{173}][Dabco,H^+]}{[TNB][Dabco][PhNH_2]} \quad (64)$$

in Me_2SO solution. The equilibrium constant K, defined by eq 64, is ≃ 1.7 L mol^{-1} at I = 0.1 M Et_4NCl and ≃ 8 L mol^{-1} at I = 0.5 M (25 °C). This dependence of K on the ionic strength will be discussed later (section IX). Kinetic experiments show that the forward reaction is first order in aniline, TNB, and Dabco while the reverse reaction is first order in **173** and Dabco,H^+. The results are in accord with the mechanism of eq 65 where the deprotonation of the zwitterion **173H⁺** occurs by the sole action of Dabco and is the rate-determining step.[346] The various parameters of eq 65 have been derived (see Table XXIV) by assuming that the deprotonation of ZH by Dabco is essentially diffusion controlled with $k_p^{Dabco} \simeq 10^9$ L mol^{-1} s^{-1}. This assumption was based on the fact that the proton transfer from ZH to Dabco should be largely thermodynamically favored: $K_a^{ZH} > K_a^{PhNH_3^+} > K_a^{Dabco,H^+}$. Not surprisingly, a high k_{-1} value (> 10^7 s^{-1}) is found, accounting for the situation $k_{-1} > k_p^{Dabco}[Dabco]$ and the proton transfer ZH ⇌ Z^- being rate limiting under the experimental conditions. The



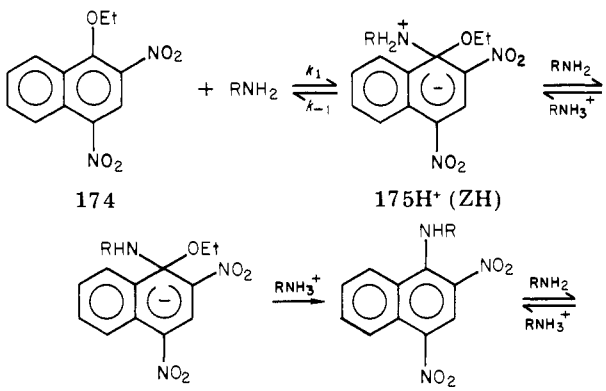
173H⁺ (ZH)



173 (Z^-) (65)

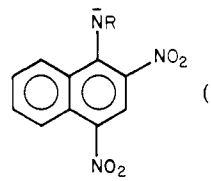
k_1 and K_1 values are respectively $\simeq$ 1 L mol^{-1} s^{-1} and $\simeq 10^{-7}$ L mol^{-1} (Table XXIV).[346]

c. Naphthalene Complexes. Orvik and Bunnett[340] were able to determine rate and equilibrium parameters for the formation of **175a** and **175b** in Me_2SO (see Table XXV). These complexes rapidly form as transient species in the substitution reactions of 2,4-dinitro-1-ethoxynaphthalene **174** with *n*-butylamine and *tert*-butylamine to give the corresponding naphthylamines (eq 66). Recent flow-NMR studies have unambiguously confirmed the structure of **175a** as well as that of similar complexes.[180,358-360] The constancy of the equilibrium constant K_c (eq 67) at various concentrations of amine and alkylammonium ion shows that the intermediate complex exists predominantly as the anionic complex **175**, in accord with findings for the TNB complexes. The formation of **175** is not base catalyzed, indicating that formation of the zwitterion ZH and not the proton transfer step ZH $\rightleftharpoons$ Z^- is rate-limiting in this process ($k_{-1} << k_p$).[495] Conversion of **175** into the products is the rate-determining step of the overall reaction. It is first order in butylammonium ion but independent of amine concentration. This substantiates the mechanism of base catalysis of the substitution reaction as general acid catalysis of ethoxide departure from the conjugate base Z^- of the σ-complex intermediate. *This study has provided the first direct evidence for the correctness of the two-step mechanism proposed by Bunnett for S_NAr reactions.*[3,4]



174 175H⁺ (ZH)

175a, R = *n*-Bu
b, R = *t*-Bu (Z^-)



(66)

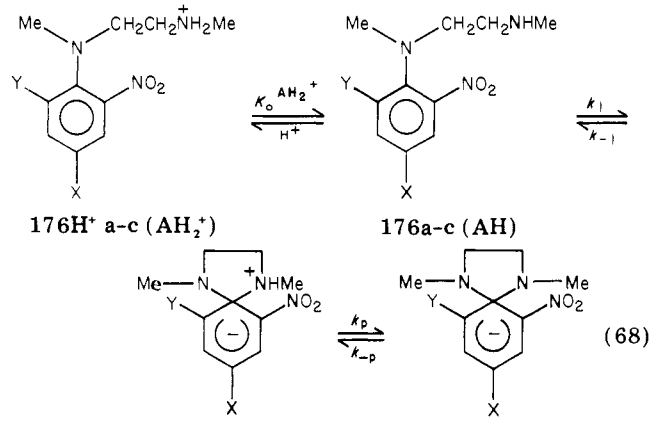
$$K_c = \frac{[175][RNH_3^+]}{[174][RNH_2]^2} = K_1 \frac{K_a^{ZH}}{K_a^{RNH_3^+}} \qquad (67)$$

TABLE XXV. Kinetic and Thermodynamic Parameters for the Formation and Decomposition of the Naphthalene Complexes 175 in Me_2SO

	175a-*n*-butylamine[a,b]	175b-*tert*-butylamine[a,c]
k_1, L mol^{-1} s^{-1}	31.8[f]	0.51
k_{-1}, s^{-1} [d]	5.9	490
K_1, L mol^{-1} [e]	5.4	1.02×10^{-3}
K_c, L mol^{-1}	540[g]	0.074

[a] Rate and equilibrium constants as defined by eq 66 and 67. [b] t = 25.4 °C. [c] t = 25 °C. [d] Calculated from data of ref 340 by assuming $K_a^{ZH}/K_a^{RNH_3^+} \simeq 10^2$; see discussion. [e] $K_1 = k_1/k_{-1}$. [f] $\Delta H_1^{\ddagger}$ = 24.2 kJ mol^{-1}; $\Delta S_1^{\ddagger}$ = −134 J mol^{-1} K^{-1}. [g] ΔH° = −80 kJ mol^{-1}; ΔS° = −213 J mol^{-1} K^{-1}.

d. Spiro Complexes. Equation 68 is representative of the reversible formation of the spiro complexes **177**.[342,344] Although the reaction is intramolecular, eq 68 resembles eq 50. The situation therefore differs from the one prevailing in comparing intra- and intermolecular additions of oxygen or sulfur bases. The conversion of *N,N'*-dimethyl-*N*-picrylethylenediamine **176a** into **177a** represents *the first reaction where rate-limiting proton transfer was observed in the formation of an amine complex.*[342] Formation of **177a** is quantitative at pH $\geq$ 12 in aqueous solution. Kinetics of the interconversion of **176a** and **177a** are characterized by one single relaxation time under all experimental conditions in the pH range 7.6–10.5. $1/\tau$ not only depends strongly on pH, but at pH $\leq$ 9.5 on the chemical nature and the concentration of the buffer as well as on the substrate concentration. A typical feature is the curvilinear dependence of $1/\tau$ on buffer concentration, indicating a change in rate-determining step as the buffer concentration is increased. This change was shown to be from rate-limiting proton transfer between ZH and Z^- at low concentrations to rate-determining nucleophilic attack at high concentrations.[342] The kinetic data have been analyzed in terms of eq 69–71, where k_p^S, k_p^{OH}, k_{-p}^S, and $k_{-p}^{SH^+}$ are defined as before (see eq 39 and 40). The $k_p^{B_i}$'s are the rate constants for deprotonation by any general base present in the solution, including the buffer base as well as Z^- and AH, whereas the $k_{-p}^{B_iH^+}$'s refer to the protonation by general acids such as the buffer acid,



176H⁺ a-c (AH_2^+) 176a-c (AH)

177H⁺ a-c (ZH) 177a-c (Z^-) (68)

(a) X = Y = NO_2; (b) X = CF_3, Y = NO_2; (c) X = NO_2, Y = H

$$\frac{1}{\tau} = \frac{k_1 k_p}{k_{-1} + k_p} \frac{K_a^{AH_2^+}}{K_a^{AH_2^+} + [H^+]} + \frac{k_{-1} k_{-p}}{k_{-1} + k_p} \quad (69)$$

$$k_p = k_p^S + k_p^{OH}[OH^-] + \sum_{i=1}^{n} k_p^{B_i}[B_i] \quad (70)$$

$$k_{-p} = k_{-p}^S + k_{-p}^{SH^+}[H^+] + \sum_{i=1}^{n} k_{-p}^{B_iH}[B_iH] \quad (71)$$

AH_2^+, and ZH. $K_a^{AH_2^+}$ is the acid dissociation constant of the protonated amine.

On the basis in particular of the limiting situations encountered at low and high buffer concentrations, the different rate and equilibrium constants of eq 69–71 were determined, including those for deprotonation of ZH and protonation of Z^- by the basic and acid forms of the buffers, respectively (B_i = phosphate, Tris, borate, and carbonate).[342] The results are listed in Table XXVI together with those for the formation of the related complexes **177b** and **177c** which also occurs through eq 68.[344] However, owing to the lower stability of these complexes, the kinetic experiments have been carried out in 70% Me_2SO–30% water and 80% Me_2SO–20% H_2O.

2. Effect of Structures on Rates and Equilibria

a. Complexes of Aliphatic and Alicyclic Amines. Spiro Complexes. Amine expulsion from the TNB zwitterions **172H$^+$** occurs at somewhat higher rates with secondary amines than with primary amines. This is consistent with a greater steric strain in ZH with secondary amines.[347] The k_{-1} values are all very high ($\geq 1.5 \times 10^5$ s^{-1} in 10% dioxane and 30% Me_2SO, $\geq 2 \times 10^4$ s^{-1} in Me_2SO) and responsible for the observation of rate-limiting deprotonation of ZH under certain conditions.[347,356] The rate constants k_1 for nucleophilic attack on TNB follow the familiar pattern for S_NAr reactions, with the secondary aliphatic or alicyclic amines being better nucleophiles than primary amines.[347,356] Combination of the effects on k_1 and k_{-1} leads to somewhat higher stabilities for the ZH complexes **172H$^+$** formed from secondary amines, but due to a compensating effect by K_a^{ZH}, the stabilities of the anionic complexes **172** ($K_1 K_a^{ZH}$) are all of the same order of magnitude in the aqueous solvents.[347] The result is that for a given amine concentration and pH approximately the same fraction of TNB is converted into Z^- regardless of the nature of the amine. Going from 30% Me_2SO–70% H_2O to Me_2SO causes a 10^3-fold increase in K_1 for ZH formation in the *n*-butylamine and piperidine systems.[356] As generally found for Meisenheimer 1:1 complexes, this increase reflects increases in values of k_1 and decreases in values of k_{-1}.

A comparison of the rate constants k_{-1} for expulsion of amines with those of expulsion of alkoxide RO^- ions shows that for a given basicity amines and RO^- ions have comparable leaving-group abilities from TNB complexes. However, in marked contrast with the situation for RO^- nucleophiles where, e.g., MeO^- ion departure from the TNB complex **5b** is $\simeq 5 \times 10^3$ times faster than dioxolane ring opening of the corresponding spiro complex **134a**, the k_{-1} value for ring opening of **177a,H$^+$** is of the same order as those for amine expulsion from **172H$^+$**.

TABLE XXVI. Rate and Equilibrium Constants for Formation and Decomposition of Spiro Complexes Resulting from Intramolecular Attack of an Amino Group in Water and Water–Me_2SO Mixtures[a]

complex	177a	177b	177c	177c	186a	189	186c	186d	186e	186f
% Me_2SO	0[b]	70[c]	70[c]	80[c]	0[b]	0[b]	0[d]	0[d]	0[d]	0[d]
t, °C; ref	25; 342	20; 344	20; 344	20; 344	25; 364	25; 364	60; 406	60; 406	60; 406	60; 406
k_1, s^{-1}	1.20×10^3	1.7×10^3	4	6.25	9.8×10^4	4.6×10^4	8.2×10^4	5.15×10^6	4.85×10^6	10^6
k_{-1}, s^{-1}	1.93×10^5	1.18×10^6	2.4×10^6	4.3×10^5	1.2×10^5	9.3×10^5	2.1×10^7[h]	2.35×10^8[h]	3.16×10^8[h]	7×10^8[h]
K_1	6.21×10^{-3}	1.44×10^{-3}	1.7×10^{-6}	1.47×10^{-5}	0.82	4.9×10^{-2}	3.9×10^{-3}[i]	2.18×10^{-2}[i]	1.53×10^{-2}	1.43×10^{-3}[i]
K_a^{ZH}	2.29×10^{-7}	3.25×10^{-8}	1.33×10^{-9}	5×10^{-10}	2.2×10^{-6}	7.5×10^{-7}				
$K_a^{AH_2^+}$ (EtH_2^+)	4.6×10^{-7}[e]									
k_p^{OH}, L mol^{-1} s^{-1}	2.2×10^{-9}	6.30×10^{-9}			3.2×10^{-9}					
k_p^S, s^{-1}	5.2	4.2×10^7	4.2×10^7[f]	4.2×10^6	5.2×10^9[g]	2.7×10^9	5×10^9[j]	5×10^9[j]	5×10^9[j]	5×10^9[j]
k_{-p}^S, s^{-1}	445	1×10^{-3}	2.5×10^{-2}	1.04×10^{-4}	48	70				
k_p^S, s^{-1}	1.35×10^4	930	38	14.3	4.3×10^4	9×10^3				
$k_{-p}^{SH^+}$, L mol^{-1} s^{-1}	5.90×10^{10}	2.86×10^{10}	2.86×10^{10}[f]	2.86×10^{10}[f]	2.10×10^{10}	1.20×10^{10}				

[a] Rate and equilibrium constants as defined by eq 68, 70, 71, and 79. [b] I = 0.5 M NaCl. [c] 0.5 M Me_4NCl; $K_s = 7.85 \times 10^{-19}$ in 70% Me_2SO, $K_s = 1.29 \times 10^{-20}$ in 80% Me_2SO; see: Achassi-Sorkhabi, H.; Halle J. C.; Terrier, F. *J. Chem. Res.* 1978, (S), 108; (M) 1371. [d] I = 1 M NaCl. [e] Statistically corrected. [f] Assuming $k_p^{OH} = 4.2 \times 10^7$ and $k_{-p}^{SH^+} = 2.86 \times 10^{10}$ as for 177b. [g] Assumed to be the same as for 177a. [h] Calculated from the ratios k_p^{OH}/k_{-1} of ref 406 by assuming $k_p^{OH} = 5 \times 10^9$. [i] $K_1 = k_1/k_{-1}$. [j] Assumed value.

Regardless of the amine, the complexes **172H**$^+$ are about 100 to 400 times more acidic than the parent $RR'NH_2^+$. Similarly the statistically corrected K_a^{ZH} value for the spiro complex **177a,H**$^+$ is 200 times greater than the corresponding $K_a^{AH_2^+}$ value. This is in accord with the strong electron-withdrawing character of the trinitrocyclohexadienylide moiety, despite the negative charge.[26,321,361] The increase in the acidity of ZH relative to AH_2^+ is still of a factor of 10 in the case of the trifluoromethyl derivative **177b,H**$^+$.

More significantly, a negatively charged dinitronaphthyl moiety has been found to exert almost the same acidifying effect as a picryl moiety on an alkylammonium proton.[364] This result is of interest in that it allows good estimates of the k_{-1} values for amine expulsion from the naphthyl complexes **175H**$^+$. By use of the values of the ratios $k_{-1}K_a^{RNH_3^+}/K_a^{ZH}$ determined by Orvik and Bunnett[340] and on assumption of $K_a^{ZH}/K_a^{RNH_3^+} \simeq 10^2$, k_{-1} values of 5.9 and 490 s^{-1} are calculated for the *n*-butylamine and *tert*-butylamine systems in Me_2SO, respectively. Even though these values are underestimated by a factor of 2 or 3, they are remarkably low compared to the k_{-1} values for the TNB complexes in the same solvent ($k_{-1} = 2.3 \times 10^4$ s^{-1} for the butylamine complex **172b,H**$^+$)[356] and in accord with the absence of rate-limiting proton transfer in the formation of **175a** and **175b**.[340] Interestingly the low k_{-1} values for **175H**$^+$ are coupled with low k_1 values ($k_1 = 31.8$ L mol^{-1} s^{-1} for **175a,H**$^+$ as compared with $k_1 = 4.5 \times 10^4$ L mol^{-1} s^{-1} for **172b,H**$^+$ at 25 °C) and an appreciable thermodynamic stability (Table XXV). In fact, **175a,H**$^+$, a naphthyl complex, is 2.7 times more stable than **172b,H**$^+$, a picryl complex. This points out a situation which is somewhat reminiscent of the contrasting behavior between oxygen-bonded 1,1 and 1,3 complexes (see section IIB2). Adducts like **175H**$^+$ which result from amine addition at a substituted alkoxy bearing carbon would form and decompose more slowly, but would have a higher stability, than analogues arising from amine addition at an unsubstituted carbon. Steric factors associated with the bulky *tert*-butyl group are responsible for both the lower k_1 and K_1 values and the greater k_{-1} value found for formation and decomposition of **175b,H**$^+$ relative to those for **175a,H**$^+$.[340]

b. Aniline vs. Aliphatic and Alicyclic Amine Complex Formation The rate and equilibrium constants k_1 and K_1 for formation of the aniline complex **173H**$^+$ are about 10^4 and 10^7 times smaller, respectively, than the corresponding parameters for formation of the complexes **172H**$^+$. While this result is consistent with the much lower basicity of aniline compared to that of aliphatic and alicyclic amines, it provides a clear explanation of why TNB and aniline do not react to yield a σ complex in the absence of a strong base like MeO^- or Dabco.[345,346] The failure to obtain reaction 72 cannot

$$\text{TNB} + 2\text{PhNH}_2 \overset{K_1}{\rightleftharpoons} \mathbf{173H}^+ + \text{PhNH}_2 \overset{K_p}{\rightleftharpoons} \mathbf{173} + \text{PhNH}_3^+ \quad (72)$$

be attributed to the second step. **173H**$^+$ is a stronger acid than anilinium ion: $K_a^{ZH}/K_a^{PhNH_3^+}$ is found to be $\simeq 10^{4.346}$ Under such conditions deprotonation of ZH by aniline should be a thermodynamically favored process. Also, the proton transfer must be fast.[296,365] It follows from this observation that *the absence of a reaction according to eq 72 has essentially its origin in the unfavorable thermodynamic factor associated with formation of* ***173H***$^+$. In fact, K_1 is so small in reaction 72 that in spite of the relatively large equilibrium constant K_p associated with the second step, the overall equilibrium is disfavored, and complex formation does not occur. The effect of adding a stronger base, like Dabco, is then to increase the equilibrium constant for deprotonation of **173H**$^+$ to the extent that the overall reaction becomes feasible. This effect may be easily understood by reference to eq 73 in which B

$$\mathbf{173H}^+ + \text{B} \overset{K_p}{\rightleftharpoons} \mathbf{173} + \text{BH}^+ \quad (73)$$

is either $PhNH_2$ or Dabco. The equilibrium constant for this deprotonation process is given by $K_p = K_a^{ZH}/K_a^{BH^+}$. Hence, the ratio of the K_p values for the aniline and Dabco systems is $K_a^{Dabco,H^+}/K_a^{PhNH_3^+} \sim 10^{4.346}$ Thus, the equilibrium transformation of **173H**$^+$ to the anionic complex **173**, being directly related to the basicity of the abstracting amine, is favored in the Dabco system by a factor of $\simeq 10^{4.346}$

When the formation of **173** through eq 57 and 65 are compared, it is found unexpectedly that the deprotonation of **173H**$^+$ is rate limiting in the Dabco system in Me_2SO and not in the MeO^- system in 95% Me_2SO–5% MeOH (v/v). In this latter case, typical kinetic experiments have been conducted with free MeO^- concentrations in the range 2×10^{-4} to 2.54×10^{-3} M. Assuming an upper limit for $k_p^{MeO^-}$, i.e., $\simeq 10^{10}$ L mol^{-1} s^{-1}, this leads to $k_p^{MeO^-}[MeO^-]$ values in the range 2×10^6 to 2.6×10^7 s^{-1} and, since the k_{-1} value in 95% Me_2SO–5% MeOH is at least equal to that in pure Me_2SO, i.e., $\simeq 10^7$ L mol^{-1} s^{-1}, to a situation where the requirement for rapid proton transfer ($k_{-1} << k_p$) is not met. Deprotonation of **173H**$^+$ should be therefore at least partially rate limiting, in disagreement with the experimental observation. This anomaly probably arises from an overestimate of k_p^{Dabco} which was assumed to be $\simeq 10^9$ L mol^{-1} s^{-1} [346] since the proton transfer of ZH to Dabco is largely thermodynamically favored. However, as pointed out below, the rate constants for the deprotonation of typical ZH-type Meisenheimer complexes by amines are usually depressed by a factor of 100 or more due to steric hindrance[347,356] (vide infra). Thus a more realistic estimate for k_p^{Dabco} in the aniline reaction would be $\simeq 10^7$ L mol^{-1} s^{-1},[347,356] which would make $k_{-1} \simeq 10^5$ s^{-1} and be consistent both with a rapid proton transfer step in the MeO^- system and a rate-limiting proton transfer in the Dabco system. Support for this estimate of k_p^{Dabco} is that it would also make the ratio $K_a^{173H^+}/K_a^{PhNH_3^+} \simeq 10^2$ (instead of 10^4), bringing it close to the ratios $K_a^{172H^+}/K_a^{RR'NH_2^+}$ found for the other amine TNB complexes.[347] General conclusions regarding the relative reactivities of aniline and aliphatic or alicyclic amines towards TNB are not affected by changes in evaluations of the parameters of eq 65 brought about by this new k_p^{Dabco} value (see Table XXIV). However, the fact that k_{-1} for **173H**$^+$ about equals k_{-1} for **172H**$^+$ is puzzling in view of the large difference in basicity between aniline and the aliphatic or alicyclic amines.

Reaction 65 has been studied by using deuterated aniline $PhND_2$ instead of $PhNH_2$.[366] The isotope effect on the equilibrium constant K (eq 64) as well as on the observed rates for the forward and reverse processes are small: $K^H/K^D = 0.90$; $k_f^H/k_f^D = 1.12$; $k_r^H/k_r^D = 1.25$

TABLE XXVII. Typical Proton Transfer Rates for the Reactions of Eq 68 and 78

$$ZH + B^- \underset{k_{-p}^{BH}}{\overset{k_p^B}{\rightleftharpoons}} Z^- + BH$$

ZH (solvent)	BH	pK_a^{BH}	pK_a^{ZH}	$10^{-6} \times k_p^B$, L mol^{-1} s^{-1}	k_{-p}^{BH}, L mol^{-1} s^{-1}
177a,H$^+$ [a,b] (H_2O)	phosphate	6.28	6.64	20	4.6×10^7
	tris	8.06		10	3.8×10^5
	176 (AH)	8.65		100	10^6
	borate	8.71		6	5.1×10^4
183a,H$^+$ [a,c] (H_2O)	phosphate	6.28	5.7	8	1.9×10^6
	tris	8.06		16	6.4×10^4
186H$^+$ [a,c] (H_2O)	phosphate	6.28	6.1	9.8	7×10^6
	tris	8.06		8	9.4×10^4
177b,H$^+$ [d] (70% Me_2SO)	*p*-cyanophenol	9.24	7.49	5.7	1×10^5
	o-bromophenol	10.58		10.2	8.3×10^3
	p-chlorophenol	11.54		6.9	6.1×10^2
	phenol	12.48		7.3	74
	benzimidazole	13.01		7.2	22
	indazole	14.52		7.5	0.7

[a] t = 25 °C; I = 0.5 M NaCl. [b] Reference 342. [c] Reference 364. [d] t = 20 °C; I = 0.5 M Me_4NCl; ref 344.

(f = forward; r = reverse). It has been concluded that such small isotope effects are typical for any S_NAr reaction where deprotonation of a zwitterion like ZH is rate-limiting.[366]

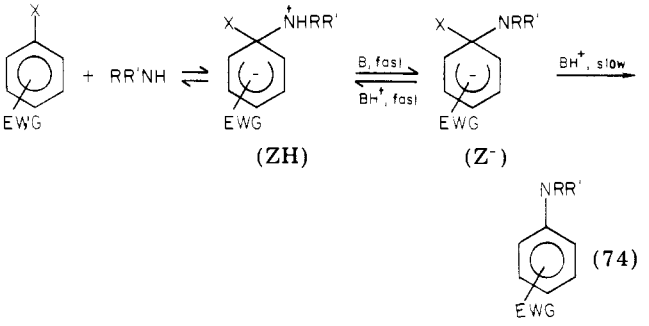
3. Proton Transfer Rates

The study of reactions 50 and 68 has yielded especially important information in regard to solvent and steric effects on proton transfer rates.[342,344,347] The rate constant $k_{-p}^{SH^+}$ for protonation of Z^- by H^+ has been measured in the case of the spiro complexes **177**.[342,344] It is 5.9×10^{10} L mol^{-1} s^{-1} in aqueous solution (t = 25 °C)[342] and 2.86×10^{10} L mol^{-1} s^{-1} in 70–80% Me_2SO (t = 20 °C).[344] It is thus evident that Me_2SO does not affect the diffusion-controlled character of the reaction.[344] In contrast, the rate of deprotonation of ZH by OH^- is essentially close to the diffusion-controlled limit in aqueous solution and in 10% dioxane ($k_p^{OH} = 5 \times 10^9$ L mol^{-1} s^{-1} at 25 °C),[347] but it is reduced about 10-fold in 30% Me_2SO and 100- to 1000-fold in 70–80% Me_2SO.[344] This decrease in k_p^{OH} in the presence of Me_2SO as cosolvent reflects either intramolecular hydrogen bonding of the acidic ammonia proton to an *o*-NO_2 group in ZH or intermolecular hydrogen bonding of this proton to the oxygen of Me_2SO.[347,367] Inasmuch as this hydrogen bond would have to be broken prior to the ZH···OH^- encounter complex formation, this would have in both cases a rate-retarding effect on the proton transfer which otherwise would be diffusion controlled.[347,367]

Some rates of deprotonation of ZH by bases other than OH^-, particularly amines, are abnormally low compared to that by OH^- in aqueous solution.[347] k_p^{Am} for the TNB-dimethylamine complex **172c,H$^+$** is thus about 500 times smaller than k_p^{OH}, i.e., about 100-fold lower than expected for a reaction between an NH acid and a N base which is thermodynamically favored by 2 pK units. Such rate reductions have been interpreted in terms of a steric effect.[347] In contrast to k_p^{OH}, the k_p^B and k_p^{Am} rate constants are not significantly dependent upon the Me_2SO content in aqueous solution.[344,347] Typical values of k_p^B and k_p^{Am} are around 10^7 L mol^{-1} s^{-1} (see Tables XXIV and XXVII) for bases whose pK_a is such as to make the proton transfer thermodynamically favored by at least two pK units. In accord with other reports,[365,368,369] proton transfers involving some amines, like piperidine, are appreciably slower in Me_2SO than in aqueous solution.[356]

4. Relevance of the Results to the Mechanism of S_NAr Reactions Involving Amine Nucleophiles

Considerable interest has been focused on the observation of base catalysis in S_NAr reactions with amine nucleophiles and its significance.[4,17–19,22] Until recently, the most familiar mechanism for these reactions has been the one shown in eq 74 and known as the SB-GA



(74)

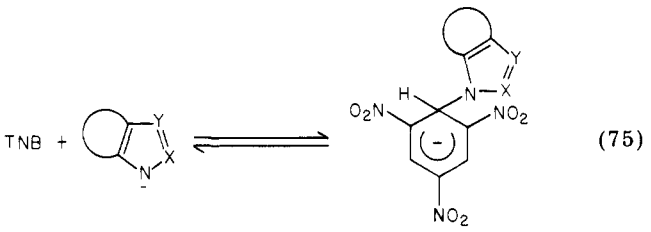
(specific base–general acid) mechanism.[340,370,371] It involves a rapid equilibrium deprotonation of the zwitterionic σ-complex ZH followed by rate-limiting concerted general acid (BH) catalyzed leaving group departure from the anionic σ-complex Z^-. Formulation of this mechanism was based on the assumption that proton transfers between normal acids and bases are always very fast.[296] It became generally accepted after Orvik and Bunnett[340] obtained direct evidence that ethoxide departure is in fact rate limiting and general acid catalyzed in the reaction of **174** with *n*-butylamine and *tert*-butylamine in Me_2SO (supra vide).

The results just discussed clearly point out that the observation of general base catalysis in S_NAr reactions with amines may be associated with rate-limiting deprotonation of the zwitterion ZH rather than with a SB-GA mechanism. For a comprehensive discussion of the conditions where each of these situations may be expected to prevail, the reader is referred to two recent and excellent reviews by Bernasconi.[18,19] One should note, however, that a number of other reactions are now known to involve a rate-limiting diffusion-controlled

proton transfer step.[150,372-375] Also noteworthy is that base catalysis in reactions 74 was originally assumed by Bunnett to be a consequence of rate-limiting deprotonation of ZH.[376] However, this interpretation was later rejected on grounds that deprotonation of ZH should be very rapid.[296]

B. Complexes from Heterocyclic Amines

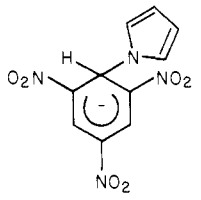
Pyrrolide, imidazolide, pyrazolide, and indolide ions react with TNB in Me_2SO or acetonitrile to give the nitrogen-bonded σ-complexes **178** according to eq 75.[350,351] In most cases, subsequent conversion of **178**



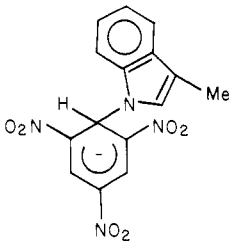
(75)

178

X = Y = C-R; X = N, Y = C-R; X = C-R, Y = N



179



180

into carbon-bonded σ complexes occurs[350,351] (see section VID). However, the adducts **179** and **180** could be isolated as their crystalline potassium salts in the TNB–pyrrole and 3-methylindole systems.[350,351] The high stability of **179** and **180** is reflected in the low values of the second-order rate constant k^{H^+} for their H^+-catalyzed decomposition in aqueous solution: $k^{H^+}_{179} = 1$ L mol^{-1} s^{-1}; $k^{H^+}_{180} = 91$ L mol^{-1} s^{-1} at 25 °C.[351] The exact mechanism of the reactions is currently under investigation.

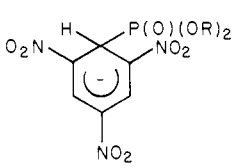
C. Complexes from Phosphorus Bases

A number of phosphorus compounds (alkyl phosphites, phosphoramidous esters, dialkyl phosphorofluoridites) form σ complexes with activated aromatics or heteroaromatics (5-nitropyrimidines).[378-385] The reactions with alkyl phosphites have been the most studied. While dialkyl phosphites behave like secondary amines and give anionic σ complexes like **181**, trialkyl phosphites yield relatively stable zwitterionic adducts. TNB and its tris(trifluoromethylsulfonyl) analogue **8** thus add $P(OEt)_3$ to form **183a** and **183b**, respectively, in Me_2SO.[381,383] Kinetic and thermodynamic parameters for these reactions (eq 76) are given in Table XXVIII.[381,383] Both **183a** and **183b** have a higher stability than amine zwitterions ($K_1 = 9$ L mol^{-1} for the TNB–piperidine complex). In accord with the results obtained for the methoxide analogues, **183b** is more stable than **183a**. However, it decomposes appreciably faster than **183a**. This would result from a greater weakening of the P^+–C bond by the more electron-

TABLE XXVIII. Kinetic and Thermodynamic Parameters for Triethyl Phosphite Complexes 183a and 183b in Me_2SO (t = 25 °C)

	183b[a]	183a[b]
k_1, L mol^{-1} s^{-1}	0.43	1.81×10^{-3}
k_{-1}, s^{-1}	6.2×10^{-4}	2.6×10^{-5}
K_1, L mol^{-1}	693	70
$\Delta H_1^{\ddagger}$, kJ mol^{-1}	29.7	70.2
$\Delta S_1^{\ddagger}$, J mol^{-1} K^{-1}	-150	-63
$\Delta H_{-1}^{\ddagger}$, kJ mol^{-1}	27.2	46.8
$\Delta S_{-1}^{\ddagger}$, J mol^{-1} K^{-1}	-213	-175.5
ΔH°, kJ mol^{-1}	2.5	23.4
ΔS°, J mol^{-1} K^{-1}	63	112.5

[a] Reference 383. [b] Reference 381.



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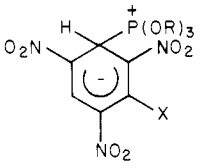
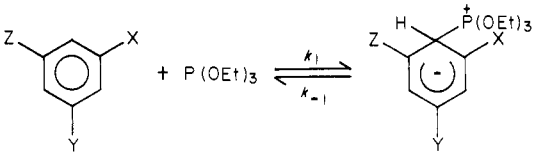


182, X = OMe, Me, $PO(OMe)_2$

R = Me, Et, Pr



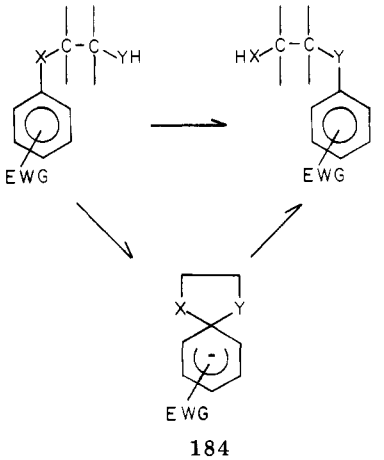
(76)

TNB **8** X = Y = Z = NO_2 **183a**
X = Y = Z = SO_2CF_3 **183b**

withdrawing SO_2CF_3 group.[383] Addition of alkyl phosphites to 1-X-2,4,6-TNB like TNA, TNT, or 1-(dimethoxyphosphinyl)-2,4,6-TNB occurs exclusively at C-3 to give **182**. Steric hindrance to the approach of the bulky phosphorus nucleophile is regarded to be responsible for the absence of reaction at C-1.[384]

V. Smiles Rearrangements—Unsymmetrical Spiro Complexes

Smiles rearrangements (eq 77) of activated aromatic substrates are typical intramolecular S_NAr reactions.[386-393] Most often, the displacement is by Y^-



(77)

184

rather than by YH, and thus the presence of a strong base is usually required. However, when YH is an amino group (NH_2 or NHR), a base may or may not be necessary for the reaction to proceed. The carbon chain joining X and Y may be saturated or part of an aro-

TABLE XXIX. Rate and Equilibrium Constants for Formation and Decomposition of Spiro Complexes Resulting from *N*-(2-Hydroxyethyl)-*N*-methylanilines or Naphthylamines in Water-Me_2SO Mixtures[a]

			186b			
complex % Me_2SO	186a 0[b]	189 0[b]	2[c,d]	50[c,e]	80[c,f,g]	85[c,f,h]
Kk_2^{OH}, L mol^{-1} s^{-1}	1300[i]	415[i]	4.56	19.9	1.42×10^4[j]	8.6×10^4
k_4^{OH}, s^{-1}	0.035	0.034	929	332	26[j]	9
KK_{-2}^{OH}, L mol^{-1}	3.7×10^4[i]	1.2×10^4[i]	4.92×10^{-3}	5.98×10^{-2}	545[j]	9550
k_2, s^{-1}	2.8×10^{-3}	1×10^{-3}				
k_{-2}, s^{-1}	9.5×10^{-7}	3.2×10^{-7}				
$K_{-2} = k_{-2}/k_2$	3.4×10^{-4}	3.2×10^{-4}				
k_4^{AcOH}, L mol^{-1} s^{-1}	0.294	0.146				
k_{-4}^{AcO}, L mol^{-1} s^{-1}	7.7×10^{-6}	2.92×10^{-6}				

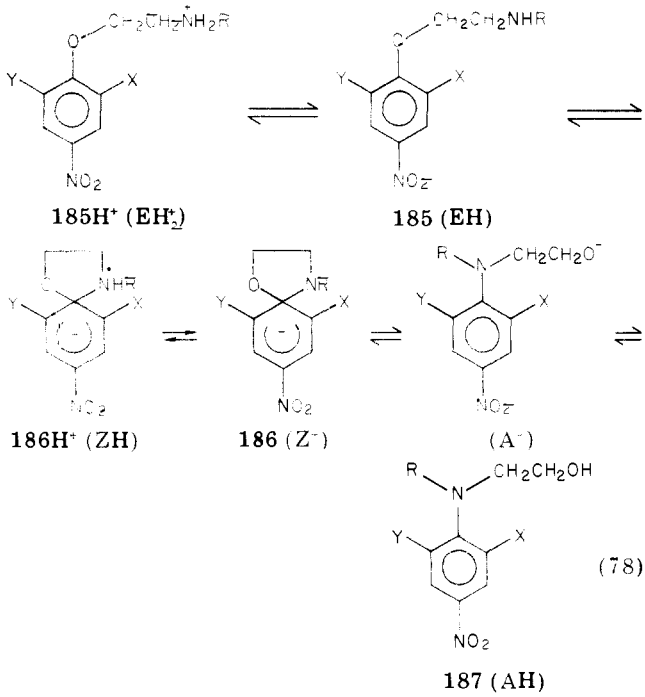
[a] Rate and equilibrium constants as defined by eq 79 with $K = K_a^{AH}/K_s$; t = 25 °C. [b] I = 0.5 M KCl; ref 364; 186a = 156 (see Section IIIA). [c] Reference 65. [d] I = 1 M KOH/KCl. [e] I = 0.5 M KOH/KCl. [f] I = 0.1 M Me_4NOH/Me_4NCl. [g] K = 13.5 L mol^{-1}. [h] K = 43 L mol^{-1}. [i] Calculated from data of ref 364 with $K_s = 1.96 \times 10^{-14}$. [j] At I = 0.1 M KOH/KCl: Kk_2^{OH} = 3020; k_4^{OH} = 53; KK_{-4}^{OH} = 57.

matic system. In general, the rearrangement goes through the formation of the intermediate spiro complex **184**.[181,364,377,386-410] This section is concerned with reactions in which the formation of such unsymmetrical complexes can be investigated by kinetic methods.

A. Complexes with an Oxazolidine Ring

1. *N*-Alkyl-β-aminoethyl Nitroaryl and Naphthyl Ethers

a. **Picryl and 2,4-dinitronaphthyl ethers.** Equation 78 is representative of an intramolecular S_NAr displacement of an alkoxide ion by an amino group. A



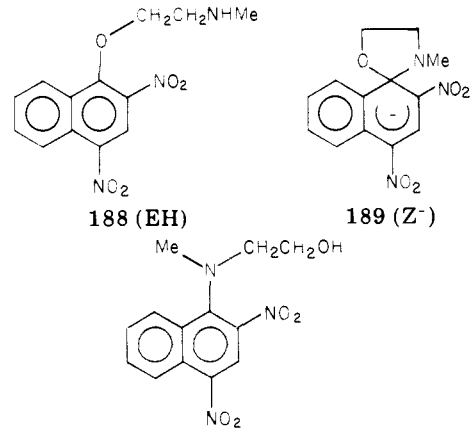
185H$^+$ (EH$_2^+$) 185 (EH)

186H$^+$ (ZH) 186 (Z$^-$) (A$^-$)

187 (AH) (78)

(a) X = Y = NO_2; R = Me (**186a** = **156**); (b) X = NO_2, Y = H, R = Me; (c) X = Y = R = H; (d) X = Y = H, R = Me; (e) X = Y = H, R = Et; (f) X = Y = H, R = *i*-Pr

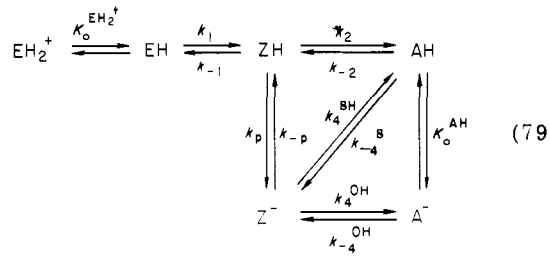
complete kinetic analysis of the picryl and naphthyl systems has been made by Bernasconi in aqueous solution.[364] Conversion of the ethers (EH) **185a** and **188** into the picramide and naphthylamine derivatives (AH) **187a** and **190** occurs in two distinct stages, characterized by two relaxation times. The first is very rapid; it involves equilibrium deprotonation of EH_2^+ (the hydrochloride salt of EH) followed by intramolecular nucleophilic attack by the NHMe group to form the zwitterion (ZH) which is then deprotonated to form the



188 (EH) 189 (Z$^-$)

190 (AH)

more stable anionic complex Z$^-$. The second stage is relatively slow and involves the conversion of Z$^-$ into the final product AH by three concurrent routes as depicted in the complete reaction scheme of eq 79.

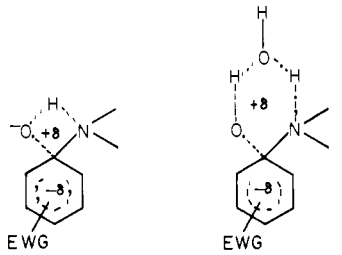


(79)

Most of the rate and equilibrium parameters of the different steps in eq 79 were evaluated by combining the SF and TJ techniques (Tables XXVI and XXIX). The system $EH_2^+ \rightleftarrows EH \rightleftarrows ZH \rightleftarrows Z^-$ associated with the first relaxation time shows features similar to those described for the ethylenediamine derivatives **176**; k_p and k_{-p} are defined by eq 70 and 71, respectively. Despite a virtually diffusion-controlled deprotonation of ZH by OH^- (k_p^{OH} = (3-5) × 10^9 L mol^{-1} s^{-1} at 25 °C), the proton transfer between ZH and Z$^-$ is partially rate limiting. This is again a consequence of high k_{-1} values for **186aH**$^+$ and **189H**$^+$ which make $k_{-1} >> k_p$ at low pH and low buffer concentrations. The zwitterions ZH are also substantially more acidic than their parents EH_2^+ ($\Delta pK > 2$) due to the electron-withdrawing character of the picryl and 2,4-dinitronaphthyl cyclohexadienylide moieties.[364]

The conversion of Z$^-$ into AH occurs via the routes $Z^- \rightleftarrows A^- \rightleftarrows AH$, $Z^- + BH \rightleftharpoons AH + B$ and $Z^- \rightleftharpoons ZH \rightleftarrows AH$. The first involves C-O bond breaking in Z$^-$ fol-

lowed by rapid protonation of the negative oxygen of A^-; it is simply the reverse of the most general scheme described for spiro complex formation from the ethylene glycols analogues **133a** and **135a** (eq 14) with $k_4^{OH} = k_{-1}$, $k_{-4}^{OH} = k_1$, $K_a^{AH} = K_a^{GOH} = KK_s$. As expected, the stability of Z^- relative to AH, as measured by the $K_a^{AH}K_{-4}^{OH}$ values, is higher for the picryl than for the naphthyl system.[364] The second route, $Z^- + BH \rightleftarrows AH + B$, is only general-acid-catalyzed C-O bond-breaking in Z^- which leads directly to AH, presumably via a concerted process. This is again a reaction discussed in section IID1c for the dioxolane analogues. As observed for the latter, the catalysis is relatively weak and has been detected only for the acetic acid-acetate buffer. The third route (k_2, k_{-2}) is typical of the systems at hand. It is the direct conversion of ZH into AH which may occur via a concerted intramolecularly acid catalyzed leaving group departure with a transition state such as **191** or **192**.[364]



191 192

b. 2,4-Dinitro- and 4-Nitrophenyl Ethers. Deprotonation of ZH was also found to be rate limiting in the conversion of the 4-nitrophenyl ethers **185c-f** into the 4-nitroanilines **187c-f** in aqueous solution.[397,406] In agreement with the diminished activation of the phenyl ring in these systems, the k_{-1} values for decomposition of the zwitterions **186H**$^+$ are $> 10^8$ s^{-1}, i.e., 10^3 times greater than the k_{-1} values for the picryl and naphthyl analogues. The overall conversion of the 2,4-dinitrophenyl ether **185b** into **187b** has not been studied.[65] However, the formation of the spiro complex **186b** has been investigated according to the $AH \rightleftarrows A^- \rightleftarrows Z^-$ pathway. The stability of **186b** is very low in aqueous solution but strongly increases on transfer to Me_2SO (Table XXIX). Kinetic experiments in 80 and 85% Me_2SO have provided not only the rate constants Kk_{-4}^{OH} ($K = K_a^{AH}/K_s$) and k_4^{OH} for formation and decomposition of **186b** but also the K values for ionization of the OH group of **187b** (AH).[65] The stability of **186b**, as measured by the KK_{-4}^{OH} value, is considerably less than that of its dioxolane analogue **134d**. This is the result of an important ground-state resonance stabilization of the parent aniline **187b**.

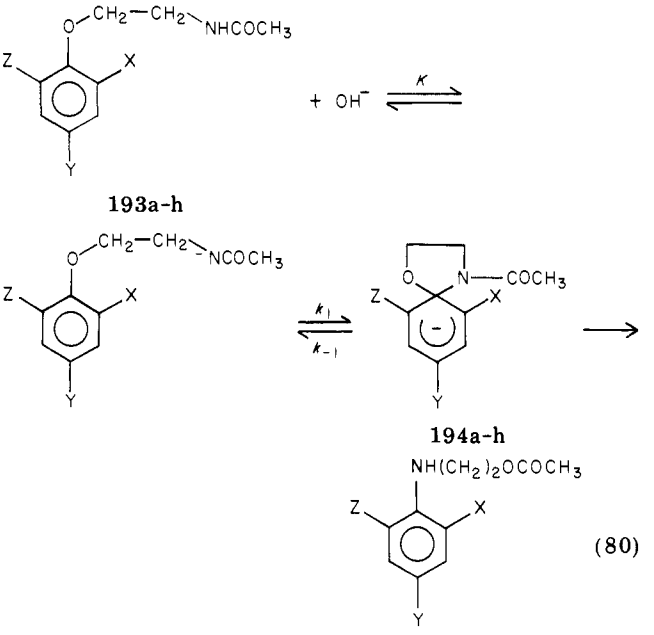
2. *Activated β-(Acetylamino)ethyl Phenyl and Pyridyl Ethers*

In aqueous Me_2SO, the ethers **193a-h** undergo a base-catalyzed Smiles rearrangement with simultaneous migration of the acetyl group to give the anilines **195a-h** as the major products (eq 80).[395,400,404] With the exception of the 2-methyl-4-nitro- and 4-nitrophenyl ethers **193d** and **193e**, all compounds **193** yield the spiro complexes **194** in an initial and rapid step.[400,404] Equilibrium and kinetic data have been determined for formation of **194b** and **194h**, by using the SF technique

TABLE XXX. Rate and Equilibrium Constants for the Spiro Complexes 194h, 194b, and 197a[a]

	96% Me_2SO-4% H_2O[b]		H_2O[c]
	194h	194b	197a
KK_1, L mol^{-1}			8×10^3
K, L mol^{-1}	93	131	$\simeq 0.1$[d]
K_1	46	10.7	8×10^4
Kk_1, L mol^{-1} s^{-1}			1.3×10^4
k_1, s^{-1}	599	118	1.3×10^5
k_{-1}, s^{-1}	12	11	2.2

[a] Rate and equilibrium constants as defined by eq 80 or 81. [b] Reference 400; $I = 0.1$ M $KClO_4$; $t = 25$ °C. [c] Reference 329 at 25 °C. [d] Estimated value; see ref 329.



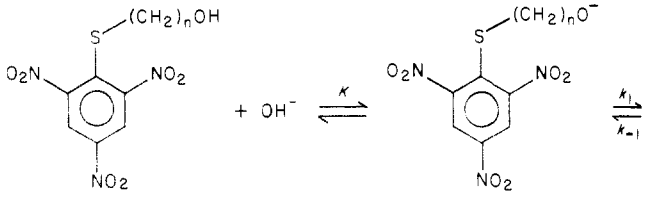
(80)

(a) X = Y = NO_2, Z = H; (b) X = Br, Y = NO_2, Z = H; (c) X = CN, Y = NO_2, Z = H; (d) X = Me, Y = NO_2, Z = H; (e) X = Z = H, Y = NO_2; (f) X = Z = NO_2, Y = H; (g) X = Y = NO_2, Z = Me; (h) X = aza, Y = NO_2, Z = H

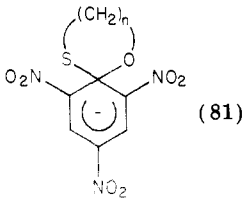
in 96% Me_2SO-4% H_2O (Table XXX).[400] Formation of other complexes was too fast to be measured. The rates of rearrangement are markedly dependent upon steric factors in the ortho positions.[400,404] 4-Nitropyridyl and 4-nitrophenyl ethers **193h** and **193e** rearrange most rapidly. The 2,6-disubstituted ethers **193f** and **193g** rearrange most slowly.[404]

B. Complexes with an Oxathiolane Ring

In the presence of aqueous base cyclization of 1-[(2-hydroxyethyl)thio]-2,4,6-TNB to the spiro complex **197a** (eq 81) is followed by irreversible decomposition to ethylene sulfide and picrate ion.[329] The KK_1 value for formation of **197a** is 4.5×10^3 times lower than that for formation of its dioxolane analogue **134a**. Possible factors accounting for the reduced stability of **197a** are (a) lower polarity of the C-S bond relative to the C-O bond which will disfavor nucleophilic attack at C-1, (b) lower stabilization of an alkoxy-thioalkoxy substitution relative to a dialkoxy substitution at the sp^3 carbon, and (c) increasing steric compression in the complex on replacement of oxygen by sulfur.[329] Only indirect evidence has been obtained for the spiro complex **197b** in



196a, $n = 2$
196b, $n = 3$



(81)

197a
197b

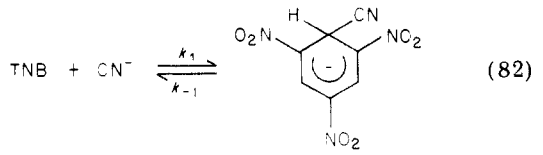
the Smiles rearrangement of 1-[(3-hydroxypropyl)-thio]-2,4,6-TNB.[402]

VI. Carbon-Bonded σ Complexes

Numerous carbon-bonded σ complexes have been characterized. They result from a large variety of carbon nucleophiles which range from carbanions of carbonyl derivatives[12,13] and other carbon acids[12,13] to simple ions like cyanide ions[411-415] or ambident ions like phenoxide,[284-288,416,417] indolide, pyrrolide, or imidazolide ions.[350,351] Amidines,[354,418] enamines,[419] and a number of organometallic compounds[420-425] are also efficient carbon nucleophiles. While the structural aspects of carbon complexes are well documented and have been recently reviewed,[12,13] there are relatively few comprehensive kinetic and thermodynamic studies of their formation and decomposition. The difficulty of generating most of the nucleophiles under conditions suitable for such studies is a major factor responsible for this situation. The ambident or tautomeric character of numerous carbon nucleophiles also makes such studies more difficult because it greatly enhances the complexity of the addition process.

A. Cyanide Complexes

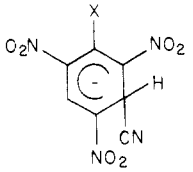
Cyanide ions easily add to TNB in a number of solvents to give the complex **198** (eq 82).[34,90,411-415] For the most part, equilibrium and kinetic studies have been carried out in alcohols (Table XXXI). With lower alcohols, reaction 82 is complicated by the alcoholysis



(82)

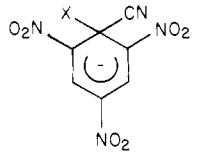
198

of CN^- which yields the corresponding lyate RO^- ion. In fact, formation of the 1:1 alkoxide-TNB complex **5** competes with that of **198** in EtOH and PrOH.[90] Changing the solvent from MeOH to *t*-BuOH greatly enhances k_1 and K_1 and results in significantly more negative $\Delta H_1°$ and $\Delta S_1°$ values.[34] This has been rationalized by the proposal that desolvation of the small CN^- ion is much greater in MeOH or EtOH than in *t*-BuOH. Interestingly, $\Delta G_1°$ and log k_1 values correlate well with Dimroth's solvent polarity parameter E_T[426] and the K_1 value in *t*-BuOH is comparable to those measured in dipolar aprotic solvents like acetone or $CHCl_3$.[34,90,411] The reactions of TNA and TNT with CN^- ion in *i*-PrOH yield exclusively the 1,3-complexes **199a** and **199b** which have stabilities of the same order as that of **198**.[412] In contrast, both **199a** and **200a** form

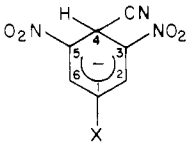


199a
199b
199c

X = OMe
X = Me
X = CHO

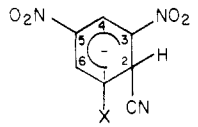


200a
200b
200c

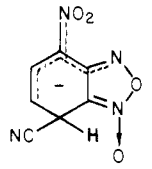


201a
201b

X = CN
X = COOMe



202a
202b



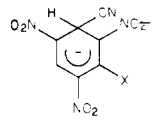
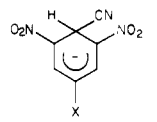
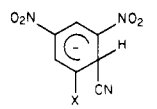
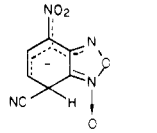
203

in $CDCl_3$ where **200c** is the only observable trinitrobenzaldehyde complex. Isomeric addition of CN^- to 3,5-dinitrobenzonitrile and 1-methoxycarbonyl-3,5-DNB occurs to give both **201** and **202**.[414] The reactions exhibit the same features as those encountered in the MeO^- and OH^- systems (section IIB1c), both complexes forming with similar rates but the 2-complexes **202** being thermodynamically favored. Rate and equilibrium constants have been recently reported for the 4-nitrobenzofuroxan complex **203** in *i*-PrOH.[415] All cyanide complexes have a much higher stability than expected on the basis on the hydrogen basicity of CN^-. For instance, in EtOH, where EtO^- is about 10^6 times more basic than is CN^- ion,[90] the stability of **198** is one order of magnitude greater than that of the TNB-ethoxide complex **5c**.

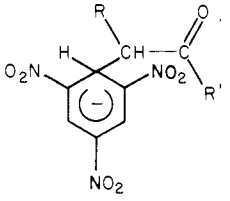
B. Enolate Complexes

Activated aromatics and heteroaromatics react with enolate carbanions of ketones,[11-13,103,212,427-439] aldehydes,[440] keto esters,[429,435] esters,[135,429,435,441-443] amides,[13,444] or compounds like creatinine[446-448] to form complexes of general structure **204**, also called Janowsky complexes.[11-13] Many of such complexes have, for many years, been important in a variety of pharmaceutical color tests.[445] The reaction is usually characterized by a two-step process, as described by eq 83 and 84, in which the carbanion is generated in a fast equilibrium prior to the rate-determining addition step (B = NR_3, OH^- or RO^-). When complexes **204** have a potential nucleophilic site γ to the tetrahedral ring carbon, as those of type **205** (R′ = CH_2R''), intramolecular cycli-

TABLE XXXI. Kinetic and Thermodynamic Parameters for Formation and Decomposition of Cyanide σ Complexes at 25 °C[a,b]

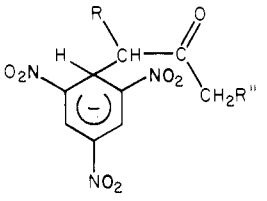
	Cpx	X	solvent	k_f, L mol^{-1} s^{-1}	k_d, s^{-1}	K, L mol^{-1}	activation and thermodynamic parameters;[c] conditions and comments[d]	ref
	198	H	$CHCl_3$	225	6.7×10^{-4} [e]	3.35×10^5	isnc	411
			CH_3COCH_3			1.44×10^5	isnc	411
			MeOH			39	isnc; $\Delta H^\circ \simeq 0$; $\Delta S^\circ = 30$	34
			EtOH			1265	isnc; $\Delta H^\circ = -32.6$; $\Delta S^\circ = -36$; cd	34
				442	0.042	1.05×10^4	isnc	90
			PrOH			1470	isnc; $\Delta H^\circ = -29.7$; $\Delta S^\circ = -42$	34
				932	<0.01	$>9 \times 10^4$	isnc	90
			i-PrOH	2450	0.245[e]	10^4	isnc; $\Delta H^\circ = -29.7$; $\Delta S^\circ = -23$; cd	34, 90
				2450	0.048	5.1×10^4	isnc; $\Delta H_f^\ddagger = 49$; $\Delta S_f^\ddagger = -5$; $\Delta H_d^\ddagger = 78.7$; $\Delta S_d^\ddagger = 11.7$; $\Delta H^\circ = -29.7$; $\Delta S^\circ = -16.7$	412
			BuOH			2020	isnc; $\Delta H^\circ = -32.6$; $\Delta S^\circ = -44$; cd	34
			t-BuOH			5×10^5	isnc; $\Delta H^\circ = -65$; $\Delta S^\circ = -105$; cd	34
				1.06×10^5	2.5	4.24×10^4	isnc	90
	199a	OMe	*i*-PrOH	344	0.031[e]	1.12×10^4	isnc; $\Delta H_f^\ddagger = 38.9$; $\Delta S_f^\ddagger = -47.6$; $\Delta H_d^\ddagger = 42.2$; $\Delta S_d^\ddagger = -113.6$; $\Delta H^\circ = -3.3$; $\Delta S^\circ = 66$	412
	199b	Me	*i*-PrOH	32.6	0.002	2.01×10^4	isnc; $\Delta H_f^\ddagger = 49.3$; $\Delta S_f^\ddagger = -39.3$; $\Delta H_d^\ddagger = 69.8$; $\Delta S_d^\ddagger = -53.5$; $\Delta H^\circ = -20.5$; $\Delta S^\circ = 14.2$	412
	201a	CN	$MeOH-Me_2SO$ 28:72	721	4.28×10^{-3}	1.68×10^5	isnc	414
	201b	COOMe	$MeOH-Me_2SO$ 28:72	142.5	7.2×10^{-3}	1.98×10^4	isnc	414
	202a	CN	$MeOH-Me_2SO$ 28:72	259	5.4×10^{-4}	4.8×10^5	isnc	414
	202b	COOMe	$MeOH-Me_2SO$ 28:72	57.5	4.5×10^{-4}	1.28×10^5	isnc	414
	203		*i*-PrOH	274	<0.01	$>2.74 \times 10^4$	isnc; $\Delta H_f^\ddagger = 36.8$; $\Delta S_f^\ddagger = -75.7$	415

[a] Rate and equilibrium constants as defined by eq 82 or similarly to eq 10. [b] Ph_4AsCN, Et_4AsCN, or NaCN. [c] Enthalpies in kJ mol^{-1}, entropies in J mol^{-1} K^{-1}. [d] See Table I for abbreviations. [e] Calculated as $k_d = k_f/K$.



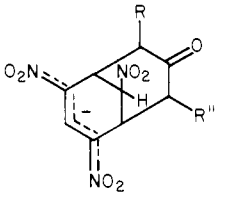
204

(a) R = COOMe, R' = OMe
(b) R = CN, R' = OMe
(c) R = H, R' = C_6H_5
(d) R = H, R' = 4-$MeOC_6H_4$
(e) R = H, R' = 4-$NO_2C_6H_4$
(f) R = H, R' = 4-CNC_6H_4
(g) R = R' = creatinine



205

(a) R = COOMe, R'' = H
(b) R = R'' = H
(c) R = R'' = Me
(d) R = R'' = C_6H_5
(e) R = R'' = cyclopentanone
(f) R = R'' = cyclohexanone
(g) R = R'' = cycloheptanone
(h) R = H, R'' = COOMe



208

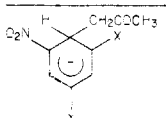
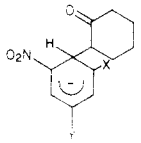
zation may occur to give the bicyclic analogues **208**. Relatively nonacidic ketones (acetone, 3-pentanone, cyclohexanone . . ., but not cyclopentanone) as well as more acidic ketones or ketoesters (acetylacetone, dibenzyl ketone, methyl acetoacetate...) readily form such bicyclic adducts, but the conditions required for their formation in basic solutions differ.[12,13,419,429-431,449-451] If R and/or R' are electron withdrawing or delocalizing (i.e., C_6H_5, COOMe, COMe), H_γ in **205** has an appreciable acidity and cyclization to **208** occurs even with only weak base (i.e., NEt_3).[12,429,452,453] In contrast, if R and R' are hydrogen or alkyl, H_γ is much less acidic and strong base is required to effect the cyclization. In most

$$RCH_2COR' + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\bar{C}H{-}CO{-}R' + BH^+ \quad (83)$$

$$R\bar{C}H{-}CO{-}R' + TNB \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathbf{204\ (205)} \quad (84)$$

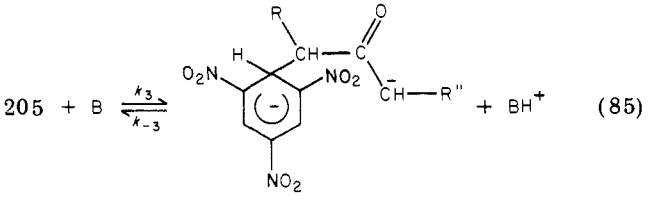
cases, the reaction may be formulated in terms of eq 85-87. A noteworthy exception is when the base is a secondary amine. In this case, the cyclization mechanism involves the formation of enamine intermediates.[12,419] In all systems studied, enolate oxygen attack to give oxygen-bonded complexes or intramolecular

TABLE XXXII. Kinetic and Thermodynamic Parameters for Formation and Decomposition of Ketone Complexes

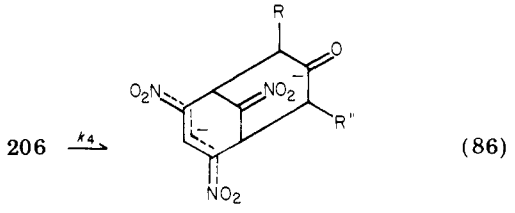
	Cpx	X	Y	solvent	t, °C	K_1k_f,[a] L^2 mol^{-2} s^{-1}	k_d,[a] s^{-1}	K_1K,[a] L^2 mol^{-2}	ref
	205b	NO_2	NO_2	MeOH	25	2.52[b,c]	4×10^{-4} [b,c]	6300[b,c]	87
					25	3.30[d]	8.2×10^{-6} [d]	4×10^5 [d]	435
	210a	$CON(CH_2)_5$	NO_2	MeOH-acetone					
				8.3:91.7	20	0.82[e]	2.86×10^{-6} [e]	2.87×10^5 [e]	433
				18.8:81.2	20	0.077[e]	5.23×10^{-6} [e]	1.47×10^4 [e]	433
				26:74	20	0.012[e]	8.69×10^{-6} [e]	1.38×10^3 [e]	433
	209a	NO_2	$CON(CH_2)_5$	MeOH-acetone					
				8.3:91.7	20	1.57	1.66×10^{-4}	9460	433
				18.8:81.2	20	0.145	3×10^{-4}	480	433
				26:74	20	0.023	5×10^{-4}	46	433
	205f	NO_2	NO_2	MeOH	25	15.2[c,f]	6.88×10^{-4} [c,f]	2.2×10^4 [c,f]	458
					25	16.2[d]	1.76×10^{-4} [d]	9.2×10^4 [d]	435
	210c	$CON(CH_2)_5$	NO_2	MeOH-cyclohexanone					
				25:75	25	0.16	1.30×10^{-4}	1230	434
				50:50	25	0.045	1.70×10^{-4}	265	434
	210d	COOMe	NO_2	MeOH-cyclohexanone					
				25:75	25		9.5×10^{-4}		434
				50:50	25	0.39	2.07×10^{-3}	188.4	434
	210e	CN	NO_2	MeOH-cyclohexanone					
				50:50	25	13.6	1.8×10^{-5}	7.55×10^5	434
	209c	NO_2	$CON(CH_2)_5$	MeOH-cyclohexanone					
				25:75	25	0.12	0.025	4.8	434
	209d	NO_2	COOMe	MeOH-cyclohexanone					
				25:75	25		3.38×10^{-3}		434
				50:50	25	0.34	5.75×10^{-3}	59	434
	209e	NO_2	CN	MeOH-cyclohexanone					
				50:50	25	5.2	2×10^{-3}	2600	434

[a] k_f, k_d, and K represent the rate and equilibrium constants associated with eq 84 or eq 89; K_1 is defined by eq 83. [b] Calculated at 25 °C from data of ref 87; $\Delta H^{\ddagger}(K_1k_f) = 50$; $\Delta S^{\ddagger}(K_1k_f) = -37$; $\Delta H^{\ddagger}(k_d) = 153$; $\Delta S^{\ddagger}(k_d) = 230$; $\Delta H^{\circ} = -103$; $\Delta S^{\circ} = -267$. [c] At 0.1 M acetone or cyclohexanone in MeOH. [d] At 0.75 M acetone or cyclohexanone in MeOH. [e] Data of ref 433 kindly recalculated by the authors. [f] $\Delta H^{\ddagger}(K_1k_f) = 55$; $\Delta S^{\ddagger}(K_1k_f) = -4$; $\Delta H^{\ddagger}(k_d) = 89.5$; $\Delta S^{\ddagger}(k_d) = 29$; $\Delta H^{\circ} = -34.5$; $\Delta S^{\circ} = -33$. [g] Enthalpies in kJ mol^{-1}; entropies in J mol^{-1} K^{-1}.

oxygen attack by the enolate side chain have not been observed.



(85)



(86)

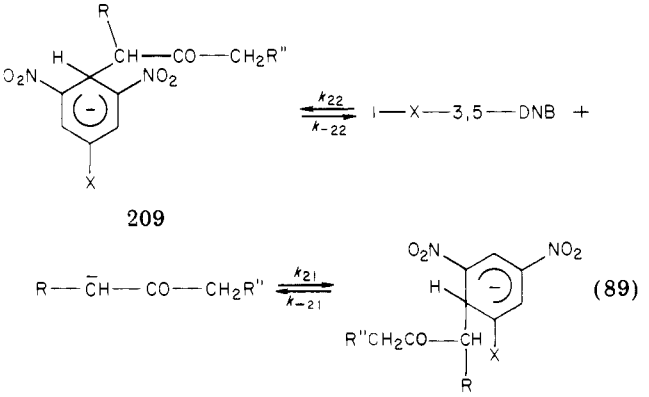
$$207 + BH^+ \xrightarrow{fast} 208 \qquad (87)$$

1. Formation of Complexes 204 and 205. 1:2 Complexes

The kinetics of formation of the TNB-acetone and -cyclohexanone complexes **205b** and **205f** and the TNB-ester complexes **204a**, **204b**, and **205a** have been investigated in MeOH and/or MeOH-Me_2SO mixtures using NaOMe as the base.[87,435,458] The data are summarized in Tables XXXII and XXXIII. In all cases, enolate addition is rate determining. In contrast, in aqueous hydroxide solution where there is a rapid conversion of acetonate ions into diacetone alcohol (eq 88), it is the k_{-5} step which is rate determining in the

$$CH_3COCH_2^- + CH_3CO\,CH_3 \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} CH_3COCH_2C(CH_3)_2O^- \qquad (88)$$

formation of **205b**.[456] Enolate attack occurs concurrently at the 2- and 4-carbons of 1-X-3,5-DNB and 3,5-dinitropyridine.[103,433,434,438,457] The benzene systems with X = $CONC_5H_{10}$, COOMe, CN have been studied in MeOH-acetone and MeOH-cyclohexanone mixtures (eq 89).[433,434] As found for oxygen and cyanide ana-

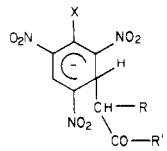
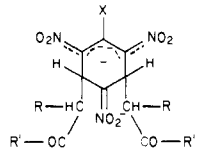
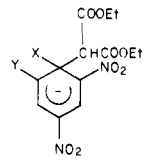


(89)

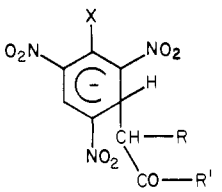
R = R'' = H, (a) X = $CONC_5H_{10}$, (b) X = H
R = R'' = cyclohexanone, (c) X = $CONC_5H_{10}$; (d) X = COOMe; (e) X = CN

logues, **209** and **210** form with relatively similar rates, but the latter complexes which have a NO_2 group para to the sp^3 carbon are thermodynamically favored. Not only the 1,3-complexes **211** but also the diadducts **212** may form prior to the substitution products in the S_NAr

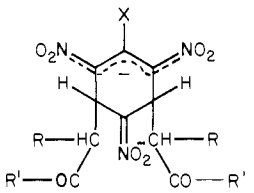
TABLE XXXIII. Rate and Equilibrium Constants for Formation and Decomposition of 1:1 and 1:2 Ester and Keto Ester Complexes at 25 °C

	Cpx	X	Y	R	R'	solvent	k_f,[a] L mol^{-1} s^{-1}	k_d,[a] s^{-1}	K,[a] L mol^{-1}	ref
	205a	H		COOMe	Me	MeOH	5500	470	11.7[b,c]	435
	204b			CN	OMe	MeOH	1.3×10^5	62	1660[b,c]	435
	204a			COOMe	OMe	MeOH	2.5×10^5	20.5	12200[b]	435
	211b	OMe		CN	OMe	MeOH	7600	72	106[b]	441
	211c			COOMe	OMe	MeOH	2.95×10^4	14.2	2090[b]	135
						MeOH-Me_2SO 80:20	8.4×10^4	7.6	11000	135
	211d	Cl		CN	OMe	MeOH	5200	37	140[b]	441
	212e	H		CN	OMe	MeOH	50	0.69	73	435
	212f			COOMe	OMe	MeOH	110	0.40	275	435
	212b	OMe		CN	OMe	MeOH	195	0.25	780	441
	212c			COOMe	OMe	MeOH	1000	0.11	9000	135
						MeOH-Me_2SO 80:20	330	0.37	900	135
	213a	F	H			Me_2SO	6200[d,e]	21.8[d,e]	285[d,e]	442
	213b	Cl	NO_2			C_6H_6-Me_2SO 87.5:12.5	5.8×10^5 [d,f]			443
	213c	Br	NO_2			C_6H_6-Me_2SO 87.5:12.5	2.5×10^5 [d,g]			461

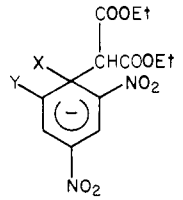
[a] Rate and equilibrium constants as defined by eq 84 or analogous equations for complexes 212 and 213. [b] K_1 values in L mol^{-1}, for deprotonation of the parent esters in MeOH (eq 83 with B = MeO$^-$ and BH$^+$ = MeOH): methyl acetoacetate, 418; methylcyanoacetate, 54; dimethyl malonate, 0.5. [c] K_3 values, in L mol^{-1}, for deprotonation of the complexes in MeOH (eq 85 with B = MeO$^-$, BH$^+$ = MeOH): 205a = 110; 204b = 670. [d] Enthalpies in kJ mol^{-1}; entropies in J mol^{-1} K^{-1}. [e] $\Delta H_f^{\ddagger} = 29$; $\Delta S_f^{\ddagger} = -76$; $\Delta H_d^{\ddagger} = 45$; $\Delta S_d^{\ddagger} = -69$; $\Delta H^{\circ} = -16$; $\Delta S^{\circ} = -7$. [f] $\Delta H_f^{\ddagger} = 9.2$; $\Delta S_f^{\ddagger} = -100$. [g] $\Delta H_f^{\ddagger} = 8$; $\Delta S_f^{\ddagger} = -115$.



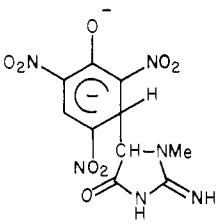
211a, X = OMe, R = H, R' = Me
b, X = OMe, R = CN, R' = OMe
c, X = OMe, R = COOMe, R' = OMe
d, X = Cl, R = CN, R' = OMe



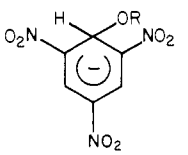
212a, X = OMe, R = H, R' = Me
b, X = OMe, R = CN, R' = OMe
c, X = OMe, R = COOMe, R' = OMe
d, X = Cl, R = CN, R' = OMe
e, X = H, R = CN, R' = OMe
f, X = H, R = COOMe, R' = OMe



213a, X = F, Y = H
b, X = Cl, Y = NO_2
c, X = Br, Y = NO_2



214



5a, R = H
b, R = Me

reactions of TNA and picryl chloride with acetone, methyl cyanoacetate, and dimethyl malonate carbanions in acetone or MeOH-Me_2SO.[135,441,459,460] In contrast, the transient species observed in the substitution reactions of picryl chloride, picryl bromide, and 2,4-dinitrofluorobenzene with diethyl sodiomalonate in benzene–Me_2SO mixtures were assumed to be the 1,1-complexes **213**.[442,443,461] Confirmation of these species as the corresponding 1,3- (or 1,5-) complexes might be, however, more consistent with general observations (section IIB3c). 2,4-Dinitrophenyl and 2,4-dinitronaphthyl phenyl ethers also add acetonate ions to the unsubstituted 3- (or 5-) carbons.[467-469] The reaction of creatinine with an alkaline solution of sodium picrate to form the complex **214** (the Jaffe reaction) is noteworthy in that its mechanism is reported to be temperature dependent. At 25 °C, the rate-determining step is attack of the creatinine anion on picrate, but at 35 °C, it is deprotonation of creatinine, at least at high picrate concentrations.[455]

In formation of all ketone complexes of Table XXXII, the enolate anions are generated by an unfavorable thermodynamic equilibrium in solvents where the equilibrium constant K_1, which refers to the mixture of the keto and enol forms of the parent ketones and is therefore an apparent equilibrium constant, is not known. On the basis of estimates of 10^{-6} and 10^{-4} L mol^{-1} for the K_1 values of acetone and cyclohexanone, respectively, in MeOH,[435] values of the order of 6×10^9 and 2×10^8 L mol^{-1} are derived for the equilibrium constants K_2 associated with formation of **205b** and **205f** in this solvent. Such values are considerably higher than those expected from the difference in the hydrogen basicity between MeO$^-$ and ketonate ions (K_2 = 23 L mol^{-1} for the TNB-MeO$^-$ complex **5b**).[78] More significantly, the ester complexes in Table XXXIII all derive from carbanions less basic than MeO$^-$. However, they are more stable or of the same stability as their methoxide 1:1 or 1:2 analogues. These results emphasize the remarkable stability of enolate complexes, especially those of ketone complexes. Many such adducts

TABLE XXXIV. Rates of Decomposition of the Acetone Complex 210b of 1,3-DNB in Various Solvents at 25 °C[a]

solvent	$10^6 k_{-2}$, s^{-1}
acetone	2.6
HMPT	3.3
H_2O	15.3
t-BuOH	27.2
ethylene glycol	94
EtOH	158
MeOH	195

[a] Ref. 462.

TABLE XXXV. Rate Constants for the Uncatalyzed (k_{-2}) and H^+-Catalyzed Decompositions of Various TNB-Ketone Complexes in Water[a]

ketone	Cpx	k^{H^+}, L mol^{-1} s^{-1}	$10^4 k_{-2}$, s^{-1}
acetophenone, 4-OMe	204d	0.43	1.08
4-H	204c	0.25	2.27
4-CN	204f	0.17	19.50
4-NO_2	204e	0.17	26.60
cyclopentanone	205e	0.0057	
diethyl ketone	205c	0.025	
acetone	205b	0.026	
cycloheptanone	205g	0.093	
cyclohexanone	205f	0.160	

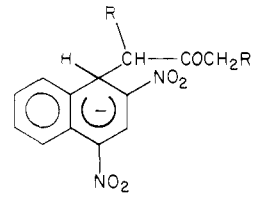
[a] Reference 464; t = 30 °C; I = 1 M KCl.

are, in fact, isolable as very stable crystalline salts, including those in the dinitrobenzene series.[13]

Another striking illustration of the high stability of ketone complexes is the observation of very low rates for their uncatalyzed (k_{-2}) decomposition (Tables XXXIV and XXXV).[87,433-435,458,462-464] For example, the k_{-2} values for the TNB- and 1,3-DNB-acetone complexes **205b** and **210b** are equal to 8.2×10^{-6} and 1.9×10^{-4} s^{-1}, respectively, at 25 °C in MeOH as compared with a k_{-2} value of 305 s^{-1} for **5b**.[435,462] In aqueous solution, the *p*-nitroacetophenone complex **204e**, with the highest k_{-2} value of all the TNB complexes studied, decomposes spontaneously (4×10^3)-fold more slowly than the hydroxide complex **5a**.[464] This is because the formation of departing enolate requires both carbon–carbon bond cleavage and concomitant rehybridization from sp^3 to sp^2, as well as substantial solvent reorganization. These are the same phenomena responsible for the well-known very low rates of carbon acid deprotonation and enolate protonation.[464-466]

Similarly, the H^+-catalyzed decomposition of the adducts is very slow. The k^{H^+} values for the acetophenone complexes **204c-f** are in the range of 0.17–0.43 L mol^{-1} s^{-1} in water whereas that for **5a** is close to the diffusion-controlled limit (section IIB1a). Clearly, the protonated hydroxyl group in the acid-catalyzed decomposition of **5a** is a much better leaving group than the protonated ketone moiety in **204** or **205**, since the positive charge promoting bond cleavage is directly on the departing atom in **5a** but two atoms removed in **204** or **205**.[464] The aforementioned hybridizational changes and solvent reorganization occurring during the uncatalyzed decomposition of **204** and **205** also play a major role in the acid-catalyzed decomposition.

The relative thermodynamic stabilities of some ketone complexes of TNB, 1,3-dinitronaphthalene (DNN), and 1,3,6,8-tetranitronaphthalene (TTNN) have been accurately estimated from calorimetric measurements of their heats of formation ΔH_R in Me_2SO, using NEt_3 as the base reagent.[35,36] The ΔH_R values thus determined are the sum of the enthalpy changes ΔH_1 and ΔH_2 associated with reactions 83 and 84. In Table XXXVI, the data in a given column refer to the reactions of the same ketone (same ΔH_1) with the three aromatics, so that the differences in ΔH_R reflect those in ΔH_2. For the acetone, diethyl ketone, and cyclohexanone complexes, the increase in stability in going from DNN to TNB to TTNN is roughly similar and in general accord with what has been found for hydroxy and methoxy complexes (see section IIB). In contrast, the ΔH_R values reveal a much greater stability of the cyclopentanone complexes **215c**, **205e**, and **216c** relative



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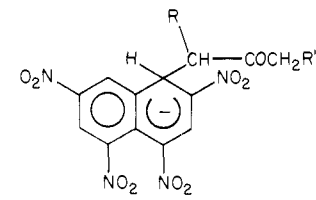


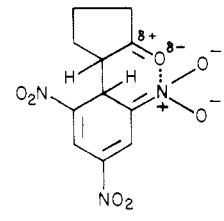
216

(a) R = R'' = H; (b) R = R'' = Me; (c) R = R'' = cyclopentanone; (d) R = R'' = cyclohexanone

to the other ketone complexes. This is especially evident in the cyclopentanone–TNB complex **205e** which is much more stable in the cyclopentanone series than expected. Combining the ΔH_R values for acetone and cyclopentanone complexes thus leads to a value of -92.4 kJ mol^{-1} for the enthalpy ΔH_{exch} associated with the acetone–cyclopentanone exchange reaction of the TNB complexes (eq 90) as compared with ΔH_{exch} values of

205b + cyclopentanone → **205e** + acetone (90)

-16.3 and -16.7 kJ mol^{-1} for the DNN and TTNN complexes. The abnormally high stability of **205e** has been accounted for by a conformation of the complex in which the carbonyl oxygen is favorably located for a stabilizing interaction with the positively polarized nitrogen of an adjacent NO_2 group, as shown in structure **217**. Such an interaction, which would explain the



217

particularly low k^{H^+} value found for **205e**,[464] is supported by ^{13}C and ^1H NMR data.[36,464]

2. Formation of Bicyclic Complexes 208

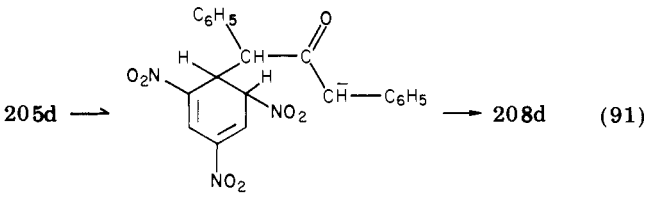
The kinetics of conversion of complexes **205** into bicyclic nitropropene nitronates **208** has been thoroughly studied only for the case of the TNB–dibenzyl ketone system (R = R'' = C_6H_5) in Me_2SO, in the presence of excess NEt_3.[452,453] While the formation of **205d** is complete within a few seconds, that of **208d** is half-complete in about 50 min. The cyclization rate is first order in NEt_3, negative nonintegral order (between -1 and 0) in $NHEt_3^+$, increased by increasing ionic strength, and zero order in dibenzyl ketone. These results fully support the mechanism outlined in eq

TABLE XXXVI. Enthalpies of Formation of Some Ketone Complexes in Me_2SO[a]

	acetone		diethyl ketone		cyclopentanone		cyclohexanone	
aromatics	Cpx	ΔH_R, kJ mol^{-1}	Cpx	ΔH_R, kJ mol^{-1}	Cpx	ΔH_R, kJ mol^{-1}	Cpx	ΔH_R, kJ mol^{-1}
DNN	215a	-9.6	215b	-11	215c	-26	215d	-5.9
TNB	205b	-21.3	205c	-19	205e	-114	205f	-39.3
TTNN	216a	-101	216b	-71.5	216c	-118	216d	-78.6

[a] References 35 and 36 at 25 °C.

85–87 with the deprotonation of **205d** *not occurring* in a rapid preequilibrium step.[453] This excludes in particular the "least contrived" mechanism of eq 91 in



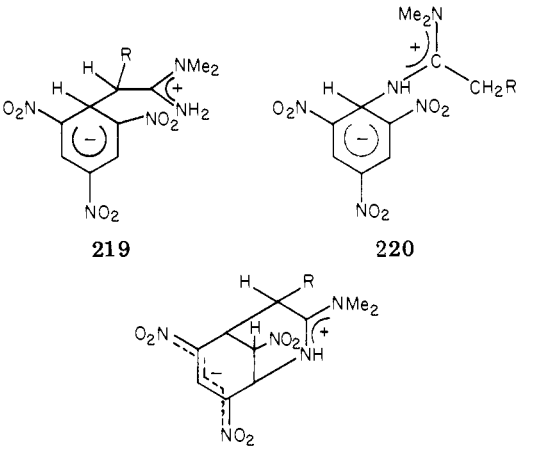
218

which proton transfer from the exocyclic ketonic moiety to the ring in **205d** is followed by intramolecular attack on the resultant dinitrodiene function of **218**. Such a mechanism was initially proposed because it circumvents the necessity of proton abstraction followed by intramolecular nucleophilic attack on a negatively charged species,[11] as described in eq 86. The formation of the TNB-bicyclic adduct **208a** of methyl acetoacetate proceeds similarly to that of **208d** through eq 85–87. However, its precursor is reported to be **205h**, and not the initially formed isomer **205a** in MeOH. In this particular case, **205h** would form as a steady-state intermediate in the overall cyclization process leading from **205a** to **208a**.[435]

The reaction sequence of eq 85–87 exemplifies the second step of a general process which has been termed "meta bridging".[12] It is typical for a number of condensation–cyclization reactions of electron-deficient aromatics with carbanions, even though strong base must be used to achieve the conversion of **205** into **208** when R and R″ are H or electron-donating groups.

C. Amidine Complexes

The reactions of amidines with electron-deficient aromatics such as TNB and polynitronaphthalenes yield different types of products depending on the structure of the parent amidine and the solvent.[354,418,470–473] For α-substituted *N,N*-dimethylacetamidines where the α substituent is alkyl or hydrogen, only the zwitterionic carbon-bonded complexes **219** are obtained in EtOH or Me_2SO.[418] In contrast, when the α substituent is aryl (i.e., C_6H_5), only the bridged complexes **221** can be isolated and these result from cyclization of the initially formed, though undetected, nitrogen-bonded complexes **220**.[354,418] When R = C_6H_5O, both **221d** and the C-bonded complex **219d** form in Me_2SO.[354] Interestingly, while complexes **219** could not be induced to cyclize under a variety of conditions in which the amidine:aromatic ratio was varied in Me_2SO or EtOH solution, in strong base such as OH^- or MeO^- they readily cyclize to **221**.[472,473] A kinetic study of this meta-bridging reaction has been carried out in aqueous solution with the TNB–acetamidine and -propion-

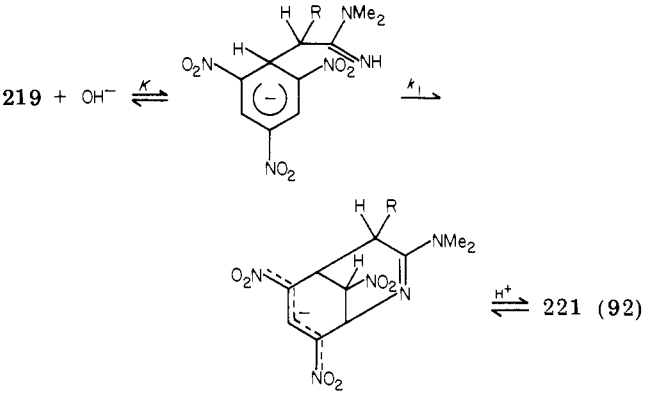


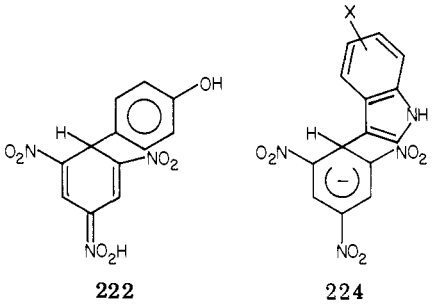
219 220

221

(a) R = H; (b) R = Me; (c) R = C_6H_5; (d) R = C_6H_5O

amidine systems. The results are in accord with a preequilibrium deprotonation of **219a** and **219b** followed by slow cyclization to **221a** and **221b** according to eq 92.[472,473] This mechanism is quite distinct from





222 224

that observed for the **205d** to **208d** conversion in Me_2SO catalyzed by NEt_3. In this latter case, the rates of cyclization and reprotonation are competitive, resulting in a steady-state formation of the dianionic precursor (**206d**) to **208d**.[453] These differences are not unexpected since eq 92 involves proton transfer to and from a nitrogen base while cyclization of **205d** through eq 85 and 86 involves deprotonation of a carbon acid by a weak

TABLE XXXVII. Kinetic and Thermodynamic Parameters for the Ionization of the Zwitterions 219a and 219b and Their Cyclization into the Adducts 221a and 221b at 25 °C, in Aqueous Solution[a]

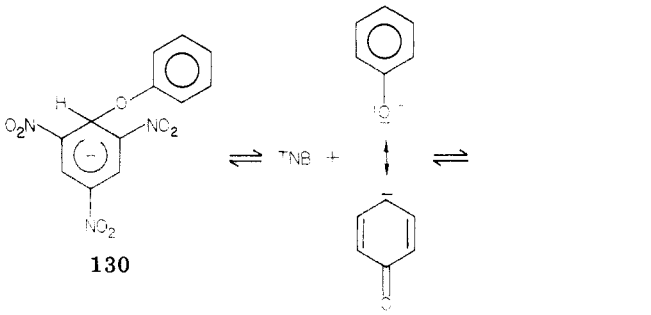
	219a	219b
k_1, s^{-1}	1.51	3.33
K, L mol^{-1}	8.90	13.96
pK_a	12.82	12.62
$\Delta H_1^{\neq}$, kJ mol^{-1}	60.5	64.7
$\Delta S_1^{\neq}$, J mol^{-1} K^{-1}	-37.6	-17.6
ΔH°, kJ mol^{-1}	-9.3	≃0
ΔS°, J mol^{-1} K^{-1}	-13	22

[a] Reference 473; I = 1 M KCl.

base (NEt_3). A very interesting aspect of the results in Table XXXVII is that the amidine moieties in **219a** and **219b** are more basic than those of the parent amidines.[473] This explains why these adducts fail to cyclize in the presence of excess amidine. One should also note that the meta-bridging reaction of amidines leads to a useful synthesis of 6,7-benzomorphans.[474]

D. Other Carbanionic Complexes

Phenoxide ions act as ambident nucleophiles, forming both oxygen- and carbon-bonded complexes with activated aromatics.[283-288,416,417] While the former are most often detected as short-lived species (section IIC), the latter have the high stability typical of C-bonded adducts. The TNB–phenoxide complex **131** is stable in



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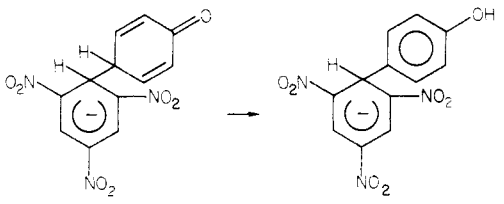


223 131

acidic media where it is readily converted into the nitronic acid **222**. The pK_a of **222** is of the order of -1 in aqueous H_2SO_4.[287] Deprotonation of the enolate-type **223** intermediate is rate limiting in the formation of the 1-naphthoxide–TNB adduct in MeOH–Me_2SO mixtures.[417] Formation of the C-bonded complexes **224** follows that of the N-bonded complexes (see section IVB) in reactions of TNB with indolide ions having a free 3-position. Adducts **224** decompose very slowly in aqueous acidic solution: k^{H^+} is equal to 1.8×10^{-4} and 4×10^{-2} mol^{-1} s^{-1} for the 5-nitroindole– and indole–TNB complexes, respectively, at 25 °C.[351] Addition of 2,4,6-trinitrobenzylanion to the 3-position of TNT results in the formation of the C-bonded complex **52** (see section IIB3b). Rate and equilibrium parameters for this reaction are given in Table XII.

VII. Effect of Structure on Complex Stability

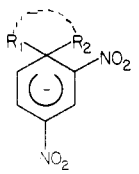
Preceding sections have emphasized several correlations between structure and stability. It is clear that the nature of the aromatic or heteroaromatic nucleus, the number and kind of nitro and/or other electron-withdrawing groups, the substituted or unsubstituted character of the site of nucleophilic attack, as well as steric effects adjacent to this position, and the nature of the entering nucleophile are important factors affecting thermodynamic stabilities of σ complexes. The influence of these various factors has been pointed out in specific instances in sections II–VI. An attempt is now made to draw general quantitative conclusions. In the benzene and naphthalene series, there has been some effort to estimate the influence of some structural changes on complex stability in terms of free energy values.[11,35,133] These estimates are based on the ΔG *values obtained from equilibrium constant determinations* and on *the assumption that, when the formation of two closely similar complexes C and C′ is considered, the difference* $\delta\Delta G$ in *the free energies of complex formation is essentially a reflection of the difference in the free energies of C and C′*. In other words, the difference in the free energies of the reactants forming C and C′ would have a negligible effect on the relative stabilities of these complexes. Although such an approximation may not be warranted, eq 93,

$$\delta\Delta G = RT \ln (K_C/K_{C'}) \qquad (93)$$

where K_C and $K_{C'}$ are equilibrium constants for the formation of C and C′, has been useful in providing free energy contributions $\delta\Delta G$ associated with a benzo fusion and the presence of various substituents in different ring positions.[11,35,133] The information accumulated on the formation of methoxy and *gem*-dimethoxy complexes has been a primary source for such calculations. The data are summarized in Table XXXVIII. The aim of this section is to focus on these calculations, to critically review the limits of their validity, and to show the necessity of reevaluating data previously derived.

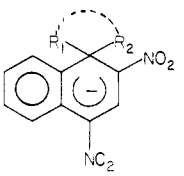
A. Effect of Benzo Fusion and Methoxy Substitution

Comparison of **225** and **226** has been made to assess the free energy contribution of the added aromatic ring (benzo fusion) to the stabilization of complexes.[11,133] When the equilibrium constants for formation of **225a** and **226a** in MeOH, **225b** and **226b** in MeOH, and **225c** and **226c** in H_2O and MeOH (references and data in Tables I, VI, XIII, and XIX) are compared, rather consistent $\delta\Delta G$ values of 29.3, 30.1, and 30.9 kJ mol^{-1} are obtained.[133] By use of the recently reported K_C ($=KK_{-4}^{OH}$)[65,364] values for **225d** and **226d** in H_2O (see Table XXIX), a $\delta\Delta G$ value of ≃ 35 kJ mol^{-1} is derived.



(11i) = 225 (25g) (134d) (186b)

(a) R_1 = H, R_2 = OMe
(b) R_1 = R_2 = OMe
(c) R_1 = R_2 = -OCH_2CH_2O-
(d) R_1 = R_2 = -$NMeCH_2CH_2O$-



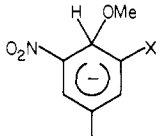
226 = (72c′) (70a) (136a) (189)

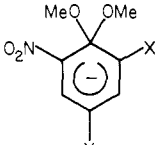
TABLE XXXVIII. Relative Stabilizing Powers of Benzo Fusion and Substituents in Benzene and Naphthalene Series

	$\delta\Delta G$, kJ mol^{-1}		
		previous estimations	
effect of	this work	ref 133	ref 11
benzo fusion	−33	−30	−29.3
1-OMe	−17.5	−17.5	
2-NO_2	−42[a]	−43	−37.6
3-NO_2	−21.7	−21.7	
4-NO_2	−48[c]	−88	−125
5-NO_2	−12.1	−12.1	−11.7
6-NO_2	−12.1	−12.1	
7-NO_2	−15	−15	−15.9
8-NO_2	−10	−10	
2-SO_2CF_3	−46.7[b]		
4-SO_2CF_3	−58[c]		
2-aza	−45[a]		
4-aza	−43[c]		
2-CN	−34[a]	−35	
4-CN	−37.5[c]	−77.3	
2-SO_2Me	−32.5[a]		
4-SO_2Me	−35[c]		
4-CHO	−36.5[c]		
2-COOMe	−21.5[a]	−25	
4-COOMe	−27.8[c]	−67.7	
2-CF_3	−23.2[a]	−26	
4-CF_3	−25[c]	−66.5	
2-Cl	−22[b]	−23.4	
4-Cl	−9.5[c]	−50.6	

[a] Estimated by comparing 229 to 225a. [b] Estimated by comparing 230 to 225b. [c] Estimated by comparing 232 to 231.

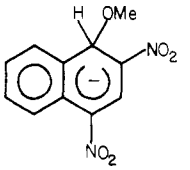
Dewar has calculated that the difference in resonance energy between benzene and a cyclohexadienylide ring is 41.8 kJ mol^{-1} whereas that between naphthalene and an analogous C-1 complex is 8.36 kJ mol^{-1}.[475] The difference in these two values (i.e., 33.5 kJ mol^{-1}) is remarkably close to the experimentally measured $\delta\Delta G$ values due to benzo fusion. It thus appears that a stabilizing contribution of $\simeq$ 33 kJ mol^{-1} may be safely assigned to this latter.[133] Comparison of the stabilities of the benzene complexes **227** and **228** in MeOH or

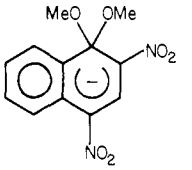




(5b) = 227 (a) X = Y = NO_2 228 = (13a)
(11a) (b) X = CN, Y = NO_2 (25b)
(11b) (c) X = CF_3, Y = NO_2 (25c)
(11d) (d) X = COOMe, Y = NO_2 (25d)
(10a) (e) X = NO_2, Y = CN (13c)

MeOH–Me_2SO mixtures (see Tables I, III, and VI) yields $\delta\Delta G$ values in the range 16.7–18.8 kJ mol^{-1} for the additional stabilization by a methoxy group covalently attached to the 1-position. The methoxy group in the precursors of **228a–e** is sterically crowded. The free energy contribution thus measured reflects both release of steric compression which occurs upon formation of **228a–e** and greater stabilization of double methoxy substitution relative to a monomethoxy substitution on the sp^3 carbon of a complex.[9,11,52,78] Interestingly, comparison of **225a** and **225b** provides a $\delta\Delta G$ value of only 10 kJ mol^{-1}. This is because formation of **225b** involves much less relief of steric strain than that of its substituted analogues **228a–e**.[31] In contrast, comparing **226a** and **226b** in MeOH–Me_2SO mixtures provides a $\delta\Delta G$ value of 17.5 kJ mol^{-1}.

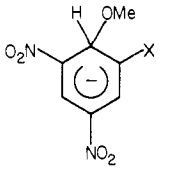


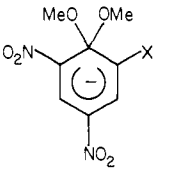


226a (=72c') **226b** (=70a)

B. Effect of Electron-Withdrawing Substituents

The free-energy contribution of ortho substituents is best calculated by comparing the monomethoxy complexes **229** and **225a** (see Table I) rather than the 1,1-

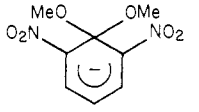




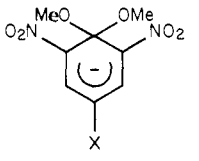
(5b) = 229 X = NO_2 230 = (13a)
(11a) X = CN (25b)
(11c) X = SO_2Me
(11d) X = COOMe (25d)
(11b) X = CF_3 (25c)
X = SO_2CF_3 (25a)
X = Cl (25e)

dimethoxy complexes **230** and **225b** (see Table VI). Due to the differences in the steric factors associated with the formation of **230** and **225b**, the $\delta\Delta G$ values obtained in the second comparison are all higher by $\simeq$ 8 kJ mol^{-1} than those obtained in the first comparison. The effect assigned to the *o*-NO_2 group (42 kJ mol^{-1})[133] is consistent with the difference in stabilization energy predicted by composite molecule calculations, or Miller's empirical method, between a 2,4-dinitro and a 2,4,6-trinitrocyclohexadienylide ring.[7,11]

Two earlier estimates of the stabilizing effect of a *p*-NO_2 group have yielded $\delta\Delta G$ values of 125[11] and 88 kJ mol^{-1}.[133] Both of these values were based on comparisons involving the complex **231**. However, the



231 (=13j)



232 (=13a-i; X = NO_2, SO_2CF_3, CN, SO_2Me, CHO, COOMe, CF_3, Cl)

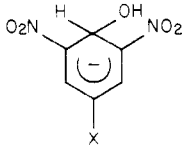
reported equilibrium constant of 10^{-19} assigned to **231**[11,133] is not suitable for eq 93 because it was a K_a value,[141] as defined by eq 5, and not a K_1 value, as defined by eq 2 (see section IIA). Using the correct K_1 value for **231** in MeOH (7.5×10^{-5} L mol^{-1})[56] and comparing with that for **228a** (=**13a**; K_1 = 17 000 L mol^{-1})[113] yield a $\delta\Delta G^{4\text{-}NO_2}$ of 48 kJ mol^{-1}. This is considerably lower than those previously calculated. However, in agreement with theoretical predictions,[11,26,27] it is greater than that for an *o*-NO_2 group: $\delta\Delta G^{4\text{-}NO_2} - \delta\Delta G^{2\text{-}NO_2} \simeq$ 6 kJ mol^{-1}. In terms of the effect on the equilibrium constant, this means that a *p*-NO_2 group is about 12

times as effective as an o-NO_2 group in stabilizing a complex. This result looks quite reasonable when compared with the experimental observation.

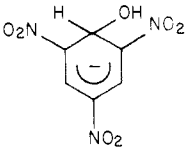
The effect of other para substituents has been estimated by comparing complexes **232** and **231**. As can be seen in Table XXXVIII, all the $\delta\Delta G$ values thus obtained are lower by $\simeq$ 40 kJ mol^{-1} than those previously derived from various comparisons, necessitating the use of $\delta\Delta G^{4\text{-}NO_2}$ = 88 kJ mol^{-1} as a reference.[133] In the naphthalene series, the effect of adding a NO_2 group at the 5-, 6-, 7- and 8-positions has been evaluated by comparing appropriate pairs of complexes in Table XIII.[133] The additional stabilization effect of these groups is considerably less than for NO_2 groups directly bonded to the ring which undergoes nucleophilic attack.

C. Reliability of the Results

It has been pointed out throughout the review that, other factors remaining constant, the order of Meisenheimer complex stabilities parallels the electron-withdrawing power of the substituents attached to the ring(s). Another general observation is that complex stability is more sensitive to changes in substituents para to the site of nucleophilic attack than ortho to it, the stability being particularly affected when a p-NO_2 group is removed or replaced by another substituent. The $\delta\Delta G$ values in Table XXXVIII reflect these observations. However, the assumption that differences in reactant free energies do not appreciably govern relative stabilities of C and C′ must be kept in mind. For example, kinetic experiments have provided evidence that conjugation between the 1-OMe and 4-NO_2 groups is important in TNA (see structures **17a**, **17b**, in section IIB2a) and result in greater ground-state stabilization of this compound relative to other 4-X-2,6-DNA (most especially 2,6-DNA).[52,56,78] On this basis, one might expect the free energy contribution of the 4-NO_2 group to be somewhat underestimated by comparing **231** and **228a** through eq 93. Surprisingly, when $\delta\Delta G^{4\text{-}NO_2}$ = 48 kJ mol^{-1} is used as the reference, assuming additivity of free energy contributions and comparing the complexes **232** (X $\neq$ NO_2) with their trinitro analogue, $\delta\Delta G$ values remarkably consistent with those directly determined by comparing **232** and **231** are obtained for the 4-SO_2CF_3, CN, SO_2Me, CHO, COOMe, CF_3, and Cl groups. Comparison of the hydroxy complexes **10a′** and **10b′** with the TNB complex **5a** in 50:50



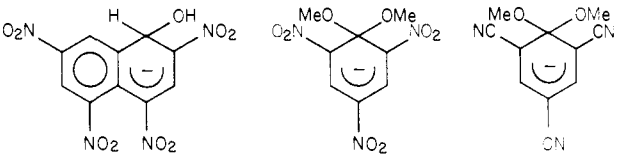
10a′, X = CN
10b′, X = CF_3



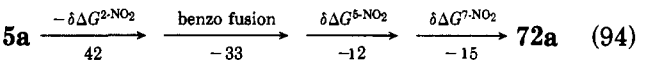
5a

H_2O-Me_2SO (see Table I) also yields similar $\delta\Delta G^{4\text{-}X}$ values for X = CN and CF_3. This is a noteworthy result since steric and resonance factors are reduced in the precursors of these complexes.

More generally, the $\delta\Delta G$ values of Table XXXVIII have been used to predict Meisenheimer complex stability. Fair to good agreement between experimentally determined and predicted relative free energies of stabilization was found for more than 100 pairs of benzene and naphthalene complexes. Schemes like those outlined in eq 94 and 95 were used. In these latter examples, the predicted ratios K^{72a}/K^{5a} and K^{13a}/K^{32} obtained from eq 93 are 1400 and 4.4 × 10^4, respectively, while those directly measured are 2950 and 4.25 × 10^4, respectively. One should note that most earlier comparisons[35,133] are not affected by changes in the individual $\delta\Delta G$ values assigned to the para substituents. Though surprising, the remarkable consistency of the results tends to confirm the hypothesis that ground-state effects are in most cases unimportant in determining the relative thermodynamic stabilities of structurally similar complexes.[11,133] It also supports the additivity of the $\delta\Delta G$ values attributed to structural changes.[35,133] This is further substantiated by the observation of satisfactory relationships between the log K for complex formation and the corresponding substituent constants σ_S obtained from summation of appropriate individual substituent constants.[133] Equation 93 is therefore useful in estimating unknown stabilities and reactivities of polysubstituted arenes. Similar treatments should be applicable to heteroarenes. However, the available data are yet too limited to allow statistically valid predictions.



72a **13a** **32**



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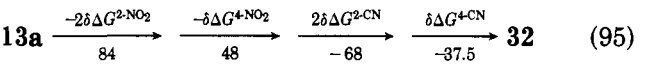
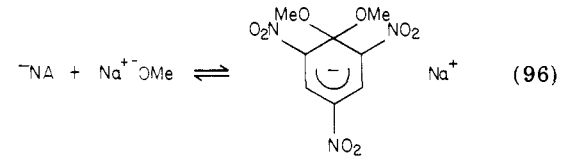


(95)

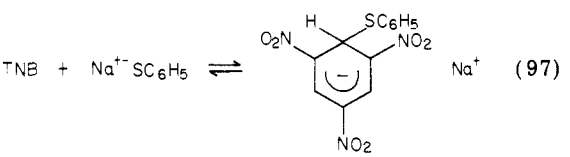
VIII. Solvent Effects

When solvent effects in Meisenheimer complex chemistry are considered, an essential feature is undoubtedly the ability of dipolar aprotic solvents, especially Me_2SO, to greatly enhance the stability of 1:1 complexes. Calorimetric studies have provided insights into the origin of this effect for the reactions of TNA with sodium methoxide to give **13a** (eq 96) and of TNB



(96)

13a



(97)

166a

with sodium thiophenoxide to give **166a** (eq 97) in MeOH-Me_2SO mixtures.[37-39] The heats of formation ΔH_R of **13a** and **166a** and the heats of transfer ΔH_T of the starting materials (TNA, TNB, NaOMe, $NaSC_6H_5$) and complexes have been determined over a wide range

TABLE XXXIX. Heats of Reaction and Heats of Transfer for the TNA-Sodium Methoxide System in MeOH-Me_2SO Solutions at 25 °C[a]

% Me_2SO (v/v)	ΔH_R[b] (TNA + NaOMe)	ΔH_T[b] (TNA)	ΔH_T[b] (NaOMe)	ΔH_T[b] (13a)	ΔG_R[b] (TNA + NaOMe)	ΔS_R[c] (TNA + NaOMe)	$\Delta G_T^{\ddagger}$[b]
0	-20.30	0	0	0	-24.12	12.75	0
10	-26.80	-3.80	2.5	-7.8	-28.30	5.06	0.042
20	-29.17	-4.60	5.43	-8.02	-30.05	2.92	-0.21
30	-35.10	-5.18	9.20	-11.08	-32.35	-10.24	-0.38
50	-43.05	-6.02	16.30	-14.17			
60	-49.32						
70		-7.19	29.26				
80	-63.95	-8.07	34.45	-17.18			
95.4	-85.70	-7.56	44.48	-28.34			

[a] References 37 and 38. [b] kJ mol^{-1}. [c] J mol^{-1} K^{-1}.

TABLE XL. Heats of Reaction and Heats of Transfer for the TNB-Sodium Thiophenoxide System in MeOH-Me_2SO Solutions at 20 °C

% Me_2SO (v/v)	ΔH_R[b] (TNB + $NaSC_6H_5$)	ΔH_T[b] (TNB)	ΔH_T[b] ($NaSC_6H_5$)	ΔH_T[b] (166a)	ΔG_R[b] (TNB + $NaSC_6H_5$)	ΔS_R[c] (TNB + $NaSC_6H_5$)
0		0	0		-1.55	
10	-15.42	-2.67	4.26	0	-4.05	-38.83
20	-17.60	-3.43	2.30	-4.89	-5.93	-39.87
30	-17.18	-3.85	2.38	-4.80	-8.40	-29.93
40	-21.36	-3.18	-0.17	-10.87	-10.45	-37.20
50	-22.90	-3.97		-17.14	-12.75	-34.70
60	-27.67	-3.18	-8.36	-25.37	-15.60	-41.30
70	-29.68	-3.30	-10.07	-29.26	-18.68	-37.53
80	-31.43	-3	-11.16	-31.77	-20.56	-37.11
95	-37.41	-3.80	-13.63	-41	-26.80	-36.24
100	-41.50	-3.13			-27.71	-47.11

[a] Reference 39. [b] kJ mol^{-1}. [c] J mol^{-1} K^{-1}.

of MeOH–Me_2SO mixtures. They are listed in Tables XXXIX and XL together with the free energy and entropy changes ΔG_R and ΔS_R. In the TNA-NaOMe system, the free energies and entropies of transfer ΔG_T and ΔS_T of both reactants and the complex as well as the free energy of transfer $\Delta G_T^{\ddagger}$ of the transition state are also available in the Me_2SO concentration range of 0–30%.[38] The transfers of both TNA and **13a** are enthalpy controlled, as is the transfer of NaOMe. The latter is remarkable in that $\Delta S_T^{NaOMe} \simeq 0$, i.e., $\Delta G_T^{NaOMe} \simeq \Delta H_T^{NaOMe}$. Interestingly, the free energy of the transition state is essentially insensitive to solvent. The overall reactions to give **13a** and **166a** are both enthalpy controlled. In fact, changes in ΔG_R exactly parallel those in ΔH_R for the formation of **166a**, the reaction being isoentropic, except in 100% Me_2SO.[39]

On the basis of these data, the solvent effect on the thermodynamics of reactions 96 and 97 is nicely illustrated by Figure 9. The most striking feature is that the heat of reaction between TNA and NaOMe to give **13a** becomes considerably more exothermic on transfer from MeOH to Me_2SO than does the heat of reaction between TNB and $NaSC_6H_5$ to give **166a**. Going from MeOH to Me_2SO therefore results in a much greater increase in the equilibrium constant K for formation of **13a**[38] than in that for formation of **166a**.[39] The reason for this is obvious. On the one hand, the heats of transfer of **13a** and **166a** as well as those of TNA and TNB are of the same order of magnitude. Since the two complexes as well as the two precursor aromatics are quite similar in structure, this is to be expected. On the other hand, the heat of transfer of $NaSC_6H_5$ is exothermic while that of NaOMe is strongly endothermic. In reaction 97, both reactants and product are becoming more stable as the Me_2SO concentration increases. ΔH_R is negative only because the increase in the stability of **166a** is greater. In reaction 96, the enormous increase in ease of formation of **13a** in Me_2SO is due not only to the increased stabilization of this complex but also to the decreased stabilization of the nucleophile. In fact, the latter predominates.

The results are fully consistent with well-known differences in hydrogen-bonding power of protic and dipolar aprotic solvents and the ability of the latter to stabilize large polarizable anions.[477,478] In this regard, comparison of ΔH_T values for NaOMe, $NaSC_6H_5$, and the complexes **13a** and **166a** is meaningful. In all cases, the cation is Na^+, and its contribution will be the same in each case, so the observed differences in ΔH_T must be due to the anions. For **13a** and **166a** which have a highly delocalized negative charge, ΔH_T is quite negative. The increased stabilization of **13a** and **166a** contributes about 28 and 41 kJ mol^{-1}, respectively, to the increased heats of reaction in 95% Me_2SO. For the less polarizable, less delocalized thiophenoxide, ΔH_T values are still negative but significantly smaller in absolute magnitude than those of **13a** and **166a**. For the small, "hard" in HSAB theory,[335,479] MeO^- ion which is a strong hydrogen-bond acceptor, ΔH_T is largely positive ($\simeq$ 45 kJ mol^{-1} in 95% Me_2SO), reflecting the expected decrease in solvation of this ion on going from MeOH to Me_2SO.[477]

The above data for reactions 96 and 97 provide a good frame of reference for understanding the effect of Me_2SO on the stability of other Meisenheimer complexes. In this regard, the much greater increase in K for **13a**[38] than for **166a**[39,95] on transfer from MeOH to Me_2SO is essentially a reflection of differences in ΔH_T values of NaOMe and $NaSC_6H_5$. This suggests that the ability of Me_2SO to enhance the thermodynamic sta-

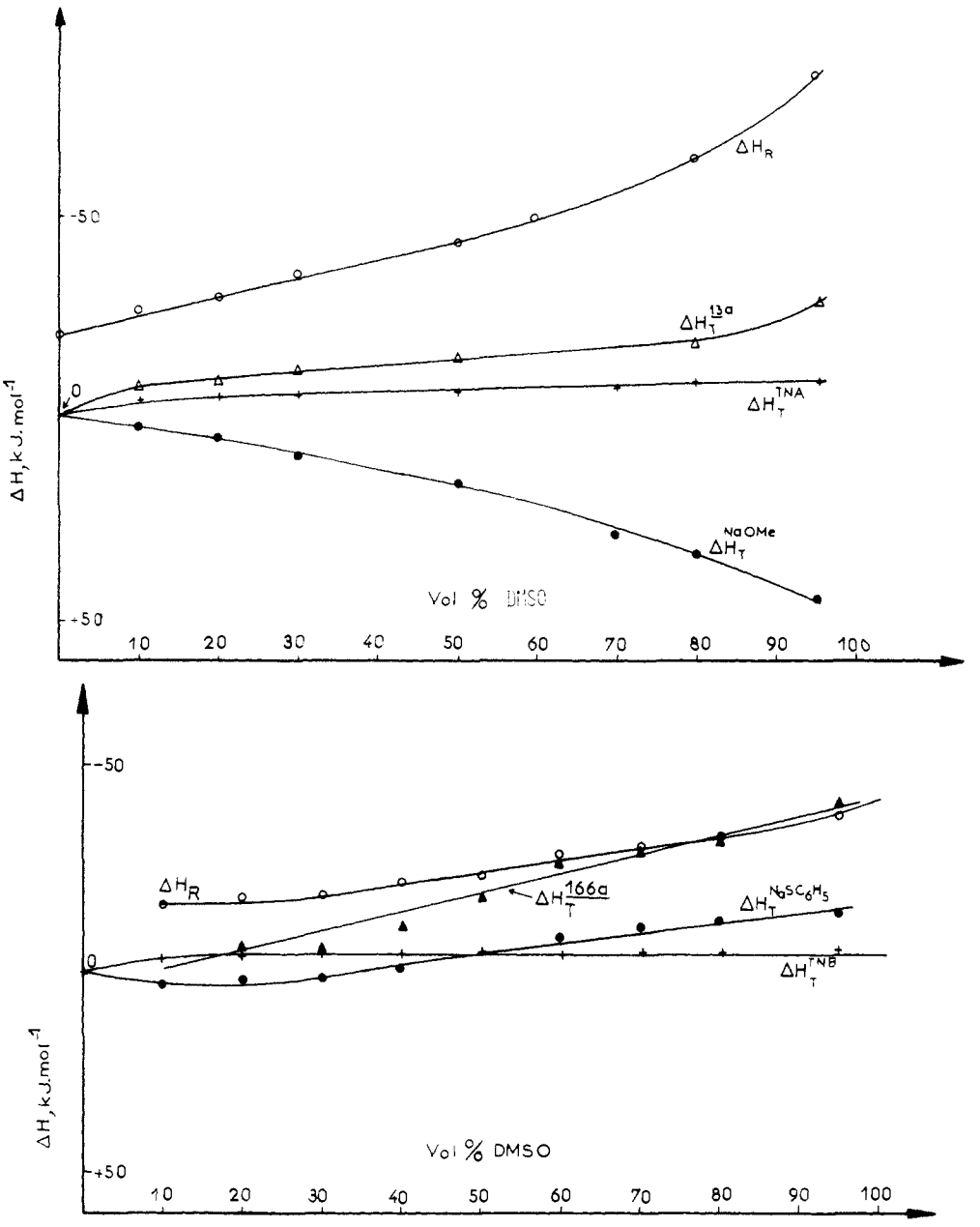


Figure 9. (a) Heats of reaction (ΔH_R) and heats of transfer (ΔH_T) for the TNA–sodium methoxide system (1,1-complex formation) in MeOH–Me_2SO solutions at 25 °C.[37,38] (b) Heats of reaction (ΔH_R) and heats of transfer (ΔH_T) for the TNB–sodium thiophenoxide system in MeOH–Me_2SO solutions at 20 °C.[39]

bility of complexes formed from similarly activated substrates but different nucleophiles should depend primarily on the nature of these nucleophiles. Experimental observations confirm this expectation. It is generally observed that log plots of the equilibrium constant K for complex formation vs. the mole fraction of Me_2SO are all linear for a variety of reactions.[56,288,319] Even though such linear plots are probably fortuitous, it is noteworthy that the slopes can differ widely. In the TNB and TNA series, much higher slopes are thus observed with hydroxide, alkoxide, or sulfite complexes (>10) than with phenoxide (4.9) or thiophenoxide (4.6) complexes.[56,82,288,319] This trend is well consistent with the notion that small or doubly charged (i.e., OH^-, RO^-, and SO_3^{2-}) ions are much more susceptible to destabilization by Me_2SO than the large and polarizable $C_6H_5O^-$ and $C_6H_5S^-$ ions.[477,478]

Another interesting comparison is between complexes formed from the reactions of a given nucleophile with different activated aromatics. However, only data for hydroxide and methoxide complexes of substituted dinitrobenzenes and dinitroanisoles are available.[56,159] As mentioned in section IIB, the effect of Me_2SO on complex stability is very similar in each of these series. This is simply because destabilization of OH^- and MeO^- is so important in determining the ΔH_R values for formation of the various complexes that it completely overshadows the effect of the differences in the ΔH_T values of the aromatics and complexes.

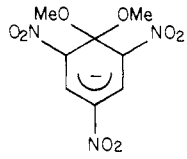
In all systems studied, the effect of Me_2SO on the stability of 1:1 complexes is the result of an increase in the rate constant of formation k_f and a decrease in the rate constant of decomposition k_d.[32,53,54,56,160,288,319] The relative contributions of the changes in k_f and k_d to changes in K are governed by relative differences in stabilization of the reactants, complexes, and respective transition states on going from MeOH to Me_2SO. The data of Table XXXIX provide a clear explanation of

this phenomenon in the case of the TNA-MeO^- system.[38] Since the free energy of the corresponding transition state is essentially unaffected by the solvent, it is apparent that changes in k_f and k_d parallel, respectively, the destabilization of the reactants, in fact that of MeO^-, and the increased stabilization of **13a**. Just as for log K, the dependence of log k_f and log k_d on N_{Me_2SO} is generally linear,[56,288,319] the slopes of the plots being primarily dependent on the nucleophile. This is illustrated in Figure 3 which refers to the reactions of MeO^- with a number of 4-X-2,6-dinitroanisoles (section IIIB2a). Such linear correlations have proven very useful in estimating rate and equilibrium parameters not directly measurable in water or MeOH.[56,288,319]

In contrast, with 1:1 complexes, the stability of 1:2 complexes decreases on transfer from protic to dipolar aprotic solvents.[305] This is consistent with destabilization of such anions which bear at least two relatively localized negative charges and are therefore poorly solvated by Me_2SO.

IX. Electrolyte and Micellar Effects

Salt effects on σ-complex formation and decomposition processes have been reported for a number of systems, but in only in a few cases have these been conducted in a systematic fashion. Fendler et al. have studied the effect of various inert electrolytes on the decomposition of **13a** in aqueous solution at 25 °C (eq 98).[480,481] Lithium perchlorate and lithium chloride

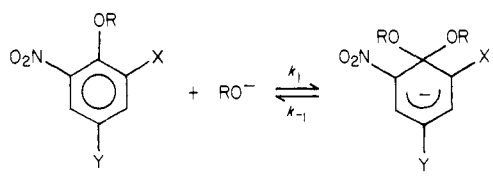


$$Na^+ \xrightarrow{k_{-1}} \text{TNA} + \text{NaOMe} \qquad (98)$$

13a

enhance whereas all the other electrolyte investigated decrease the rate of decomposition of **13a**. The reactivity order $LiClO_4 > LiCl > NaNO_3 > NaCl > NaBr > Me_4NCl > NaClO_4 > KCl > Na_2SO_4 > p\text{-}MeC_6H_4SO_3Na$ arises from a smaller destabilization of the initial state (**13a**) than of the transition state. It is essentially the reverse of that found for the reactions of anionic nucleophiles with 2,4-dinitrohalogenobenzenes in which the rate-determining step is the formation and not the decomposition of the intermediate σ complex.[482]

An important observation relating to salt effects is the finding that ion pairing affects the equilibrium formation of 1,1-dialkoxy complexes in alcohols (eq 99).[30,57,59,60,119-121,123] Intensive studies of this effect have



$$+ RO^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \qquad (99)$$

been made in MeOH where the measured equilibrium constant K_c for formation of **233** (R = Me) depends to some extent on the nature of the cation and the base concentration.[114,119-121] This is illustrated by Figure 10

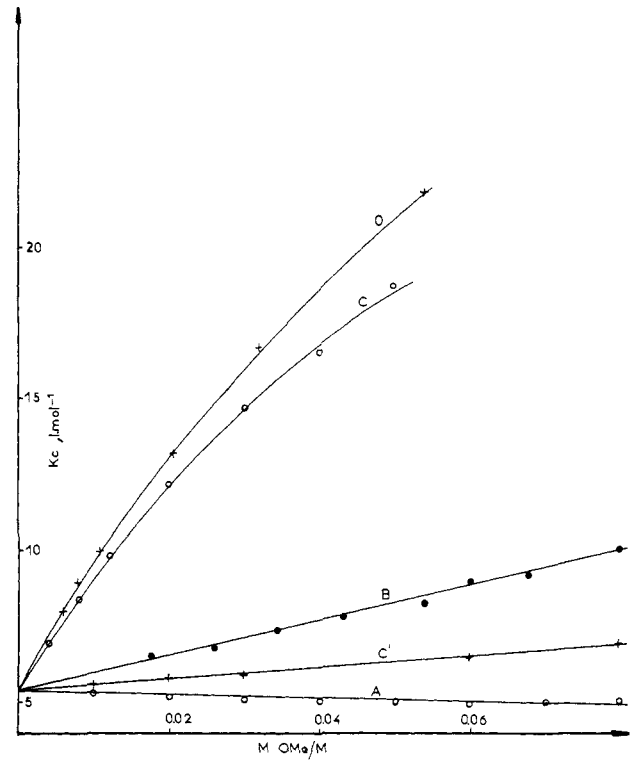
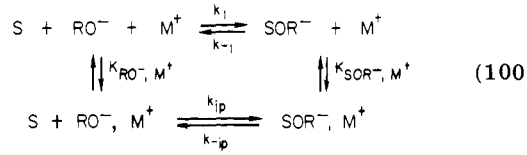


Figure 10. variation of the equilibrium constant K_c with base concentration for formation of the 1,1-dimethoxy complex of 4-methoxycarbonyl-2,6-dinitroanisole with the following methoxides: (A) lithium; (B) tetra-*n*-butylammonium; (C) sodium; (C′) NaOMe with 18-crown-6-ether; (D) potassium. t = 25 °C.[120,123]

which refers to 4-methoxycarbonyl-2,6-dinitroanisole.[120] With *n*-Bu_4NOMe as the base, one observes an increase in K_c which is much less pronounced than with KOMe or NaOMe while with LiOMe the effect is reversed, a slight decrease in K_c being observed with increasing methoxide concentration. Significantly, addition of small concentrations of Ba^{2+} and Ca^{2+} results in much larger variations[121] while addition of crown ethers causes only small changes in K_c.[123] For a given cation, the effect of increasing the base concentration is also strongly dependent on the structure of the parent anisole. Crampton has proposed the ion association scheme of eq 100 (R = Me) to account for these results.



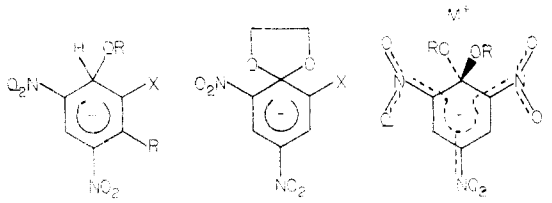
$$\begin{array}{ccc} S + RO^- + M^+ & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & SOR^- + M^+ \\ \Updownarrow K_{RO^-,M^+} & & \Updownarrow K_{SOR^-,M^+} \\ S + RO^-,M^+ & \underset{k_{-ip}}{\overset{k_{ip}}{\rightleftharpoons}} & SOR^-,M^+ \end{array} \qquad (100)$$

In terms of this scheme, ion association will affect the measured equilibrium constant so that K_c is given by eq 101 where K_1 is the thermodynamic equilibrium

$$K_c = \frac{K_1(1 + K_{SOR^-,M^+}[M^+])}{1 + K_{RO^-,M^+}[M^+]} \qquad (101)$$

constant in terms of free ions (eq 2 in section IIA). In agreement with the observed trends in K_c, analysis of the data shows that for $M^+ = K^+$, Na^+, or *n*-Bu_4N^+, the complexes **233** (R = Me) are stabilized by ion-pair formation to a greater extent than MeO^- ion ($K_{MeO^-,M^+} < K_{SOR^-,M^+}$) while the reverse holds for $M^+ = Li^+$. The overall changes in K_c result from increases in the rates of formation and decreases in the rate of decomposition

with increasing the methoxide concentration.[119] The apparent decrease in the rate of decomposition is well predicted by eq 100 since, in dilute solutions where association of MOMe is negligible compared to that of **233**, the observed value is given by $k_{-1}/(1 + K_{SOR^-,M^+}[M^+])$.[119,128] In contrast, the increase in the rate of formation is probably the result of a genuine salt effect.[119,156] However, at high methoxide concentrations, it may also be due to the greater reactivity of the methoxide ion pairs compared to that of free MeO^- ions. In contrast with complexes **233**, those of type **234** (R

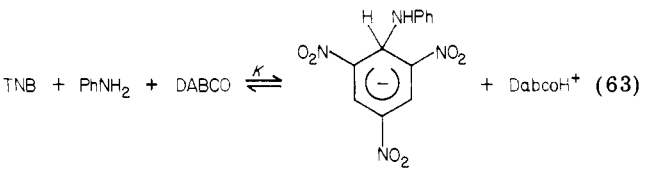


234 235 236

= Me, R′ = H, OMe)[121] and spiro complexes **235**[63] show no evidence for apreciable association with cations in MeOH. On this basis, the tendency of anions **233** to associate would arise from a specific interaction of the cations with the oxygen atoms of the methoxy groups at C_1 and the ortho substituents (X = NO_2, COOMe, Cl) as described in structure **236** (R = Me).[121,123]

Recent studies of the formation of complexes **233** and **234** (R = Et, Pr, *i*-Pr) in EtOH, PrOH, and *i*-PrOH also support the facile formation of associations like **236**.[57,59,60] In these solvents, the rate constants for attack of free and ion-paired RO^- ions on the parents (S) and those for the decomposition of the free and ion-paired complexes were determined. For 1,1-complex formation, the alkoxide ion pairs show in general greater reactivity than free RO^- ions while the ion-paired complexes revert to the reactants less rapidly than their unpaired analogues. In contrast, alkoxide ion pairs are generally less reactive than free RO^- ions toward unsubstituted carbons (see section IIB). Table XLI summarizes some thermodynamic data for sodium alkoxide systems.

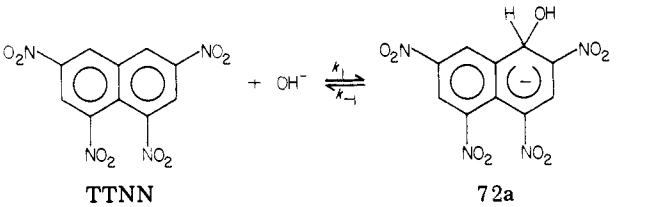
Reaction 63 which involves only uncharged reactants is subject to a large salt effect in the presence of tetraethylammonium chloride in Me_2SO.[363] The corresponding equilibrium constant K (eq 64 in section IVA1b) increases by 340-fold on increasing the Et_4NCl concentration from 0 to 1.2 M. This increase in K results from a 2.5-fold increase in the forward rate constant and a 140-fold decrease in the reverse rate constant. Though in the same direction, much less pronounced changes in these parameters are obtained with Et_4NClO_4. This specific and unusual catalytic effect of Et_4NCl might originate from association of



173

chloride ion with protonated Dabco to yield the $DabcoH^+\cdots Cl^-$ heteroconjugate complex with a consequent decrease in the rate of the reverse reaction.[363]

The cationic micellar hexadecyltrimethylammonium bromide (CTAB) increases, the anionic micellar sodium dodecyl sulfate (NaLS) decreases, and the uncharged polyoxyethylene (15) nonylphenol (Igepal CO-730) does not affect the equilibrium constant for formation of the hydroxyl complex **72a** in aqueous solution.[483] These



TTNN 72a

(102)

effects arise primarily from those on the rate constant of formation k_1. CTAB increases k_1 by a factor of 36, NaLS decreases it by a factor of 43, and nonionic Igepal CO-730 has no appreciable effect. The results resemble those observed in S_NAr reactions of 2,4-dinitrohalobenzenes[484] and are explicable in terms of simple electrostatic interactions. Appreciable catalysis by the cationic micelles results from the incorporation of TTNN into micellar phase resulting in an electrostatically more favorable environment for attack by the incoming OH^- ion. Similarly, rate retardation by anionic NaLS is explicable in terms of repulsion of OH^- from the surface of the micelle–substrate complex.[483] The binding constants between TTNN and CTAB and between TTNN and NaLS are 1.9×10^5 and 3.6×10^3 L mol^{-1}, respectively. As that of the complexes **13a**, **70a**, **70d**, and **136a**, the spontaneous decomposition of **72a** is retarded by cationic and neutral micellar surfactants and almost unaffected by anionic NaLS.[480,481] However, the magnitude of the rate retardation for complex decomposition is markedly dependent on the substrate. Thus, the k_{-1}/k_{-1}^{CTAB} values for **72a**, **13a**, **70a**, **70d**, and **136a** are equal to 2.8, 12, 3, 2, and 660, respectively. For the most part, these ratios reflect differences in destabilization of the various transition states by CTAB.[481,483]

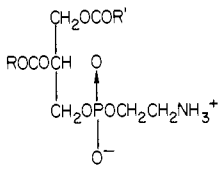
Dodecylammonium carboxylates considerably enhance the rate of decomposition of **13a** and **70a** in benzene (containing 0.05% Me_2SO to dissolve the complexes).[485] In the case of **13a**, k_{-1} in the presence

TABLE XLI. Association Constants of Sodium Ions with Alkoxide Ions (K_{RO^-,Na^+}) and 1,1-Dialkoxy Complexes 233 (K_{SOR^-,Na^+}) at 25 °C

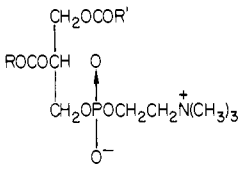
			Y = NO_2; X =				X = NO_2; Y =	
solvent	R	NaOR	COOR	Cl	NO_2	H	COOR	CF_3
methanol	Me	4.9[a]	160[d]	25[d]	70[d]		100[f]	100[f]
ethanol	Et	4.9[b]	3300[d]	270[d]		200[d]		
propanol	Pr	672[c]	1.05×10^4 [e]	1100[e]	1000[e]	1500[e]		
2-propanol	*i*-Pr	1.9×10^4 [a]	1.3×10^5 [d]	1×10^4 [d]		6000[d]		

[a] Barthel, J.; Wachter, R.; Knerr, M. *Electrochim. Acta* 1971, *16*, 723. [b] Barthel, J.; Schwitzgebel, G.; Wachter, R. *Z. Phys. Chem. (Wiesbaden)* 1967, *55*, 33. [c] Barthel, J.; Justice, J. C.; Wachter, R. *Z. Phys. Chem. (Wiesbaden)* 1973, *84*, 113. [d] Reference 59. [e] Reference 60. [f] Reference 123.

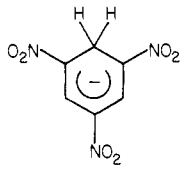
of dodecylammonium benzoate (DABz) aggregates ($k_{-1}^{DABz} = 0.943\ s^{-1}$) is greater by a factor of 6.2×10^4 than k_{-1} in pure benzene ($k_{-1}^{C_6H_6} = 1.5 \times 10^{-5}\ s^{-1}$); for comparison $k_{-1}^{H_2O} = 5.08 \times 10^{-4}\ s^{-1}$. Saturation-type kinetics are, however, observed with respect to both the surfactant and **13a**. The rate enhancement of the decomposition of **13a** and **70a** is explicable in terms of solubilization of these complexes in the polar cavity of the micelles and a mechanism involving proton transfer from the ammonium group on the surfactant to the leaving methoxyl group.[485,486] Phospholipids, like phosphatidylethanolamine **237** and lecithin **238**, also enhance the rate of decomposition of **13a** in benzene.[485] **237** is a better catalyst than DABz because it has a higher capability to transfer protons from its ammonium group. In contrast, lecithin, which cannot transfer proton to **13a**, has a much smaller catalytic effectiveness than DABz or **237**.[485]



237



238



239

The base-catalyzed decomposition of the 1,1-dihydro complex **239** in aqueous solution is unique in that it yields 3,5,3′,5′-tetranitroazoxybenzene as the final product. Bovin serum albumine (BSA) acts as a macromolecular catalyst in accelerating this reaction by a factor of $\sim 10^4$ in the neutral to slightly basic region. At higher pH values (11–12), the base-catalyzed decomposition of **239** is rapid ($t_{1/2} \sim 105$ s at pH 11.5), but in this region where BSA is known to undergo conformational transition rate accelerations due to this protein are eliminated.

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