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# Kinetics and Mechanism of Amidine Meta Bridging of Electron Deficient Aromatics

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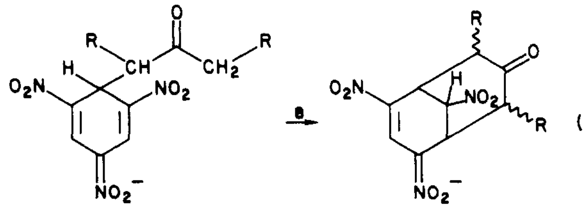
The detailed mechanism of cyclization of carbon bonded amidine $\sigma$ complexes of *sym*-trinitrobenzene has been studied over a large range of sodium hydroxide concentrations, i.e., $5 \times 10^{-3}$–1 M, in aqueous solution. p$K$ values for amidinium functionality in the complexes have been determined, and the temperature dependence of the reactions has been investigated. Implications of the results on the structure of the transition state for meta bridging are considered.

The reaction of amidines with electron-deficient aromatics such as *sym*-trinitrobenzene (TNB), 1,3-di-, 1,3,6-tri-, 1,3,8-tri-, and 1,3,6,8-tetranitronaphthalenes yields various types of products depending on the structure of the amidine.[1,2] For $\alpha$-substituted *N*,*N*-dimethylacetamidines when the $\alpha$-substituent is alkyl or hydrogen, only a single bond is formed between amidine and aromatic to yield adducts like **1a,H$^+$** and **1b,H$^+$**. When the $\alpha$-substituent is aryl, i.e., $C_6H_5$, only bridged adducts like **3c,H$^+$** can be isolated. These result from initially formed nitrogen bonded adducts like **2c,H$^+$**. There is no evidence for formation of carbon bonded adducts like **1c,H$^+$** in these instances.[3] The reasons for this change in reactivity with different $\alpha$-functionality in the amidine have previously been discussed in terms of Scheme I by us.[2]

Interestingly, while structures like **1a,H$^+$** and **1b,H$^+$** could *not* be induced ty cyclize under a variety of conditions in which the amidine:aromatic ratio was varied in $Me_2SO$ or ethanol solution, in strong base such as methoxide they readily cyclize to the bicyclic structures **3a,H$^+$** and **3b,H$^+$**. These products are readily deprotonated to form the corresponding anions **3a** and **3b**. This cyclization exemplifies the second step of a general process which has been termed "Meta Bridging".[4,5] We have previously reported a detailed study of the kinetics and mechanism of this second step for carbon bases, i.e., the cyclization of ketonic complexes generated in situ from ketones and TNB (eq 1).[6,7]



(1)

**Table I. Observed First-Order Rate Constants for the Cyclization of 1a,H$^+$ in Aqueous Solution at Various Temperatures (I = 1 M)**

| | $k_{obsd}$, s$^{-1}$ | | | |
|---|---|---|---|---|
| [OH$^-$], M | $t$ = 10.2 °C | $t$ = 20 °C | $t$ = 30.2 °C | $t$ = 40.1 °C |
| 0.005 | 0.0205 | 0.045 | 0.105 | 0.19 |
| 0.007 | 0.028 | 0.060 | 0.130 | 0.255 |
| 0.008 | 0.033 | 0.068 | 0.145 | 0.295 |
| 0.010 | 0.040 | 0.080 | 0.19 | 0.35 |
| 0.0125 | 0.048 | 0.106 | 0.248 | 0.43 |
| 0.016 | 0.059 | 0.128 | 0.275 | 0.565 |
| 0.025 | 0.084 | 0.204 | 0.43 | 0.78 |
| 0.04 | 0.116 | 0.288 | 0.60 | 1.19 |
| 0.10 | 0.193 | 0.508 | 1.20 | 2.38 |
| 0.20 | 0.275 | 0.594 | 1.42 | 3.30 |
| 0.50 | 0.33 | 0.84 | 1.90 | 4.05 |

**Table II. Observed First-Order Rate Constants for the Cyclization of 1b,H$^+$ in Aqueous Solution at Various Temperatures (I = 1 M)**

| | $k_{obsd}$, s$^{-1}$ | | | |
|---|---|---|---|---|
| [OH$^-$], M | $t$ = 5 °C | $t$ = 15 °C | $t$ = 25 °C | $t$ = 34.5 °C |
| 0.005 | 0.031 | 0.087 | 0.21 | 0.586 |
| 0.008 | 0.041 | | | |
| 0.01 | 0.063 | 0.165 | 0.40 | 0.99 |
| 0.02 | 0.116 | 0.273 | 0.75 | 1.845 |
| 0.03 | 0.128 | | | |
| 0.04 | 0.181 | 0.498 | 1.185 | 2.86 |
| 0.06 | | 0.63 | 1.57 | 3.50 |
| 0.08 | 0.242 | | | |
| 0.10 | | 0.75 | 1.90 | 4.20 |
| 0.15 | 0.37 | 0.95 | 2.30 | 5.20 |
| 0.30 | 0.436 | 1.09 | 2.66 | 5.94 |
| 0.50 | | 1.09 | 3.05 | 6.52 |
| 1 | 0.446 | 1.23 | 3.20 | 7.11 |

Because of the unusual stability of the amidine adducts **1a,H$^+$** and **1b,H$^+$**, we have been able to study the pH and temperature dependence of their cyclization in aqueous solution. The results further clarify the nature of meta bridging processes and provide a more complete picture of the transition state for this interesting type of reaction.

## Results

The adducts **1a,H$^+$** and **1b,H$^+$**, which have visible absorption spectra typical of carbon bonded $\sigma$ complexes ($\lambda_{max}$ 450 and 550 nm)[1-4,8-10] rapidly cyclize to **3a,H$^+$** and

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[2] Bard, R. R.; Strauss, M. J. *J. Org. Chem.* **1976**, *41*, 2421.

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[7] Strauss, M. J.; Schran, H. F., Bard, R. R. *J. Org. Chem.* **1973**, *38*, 3394.

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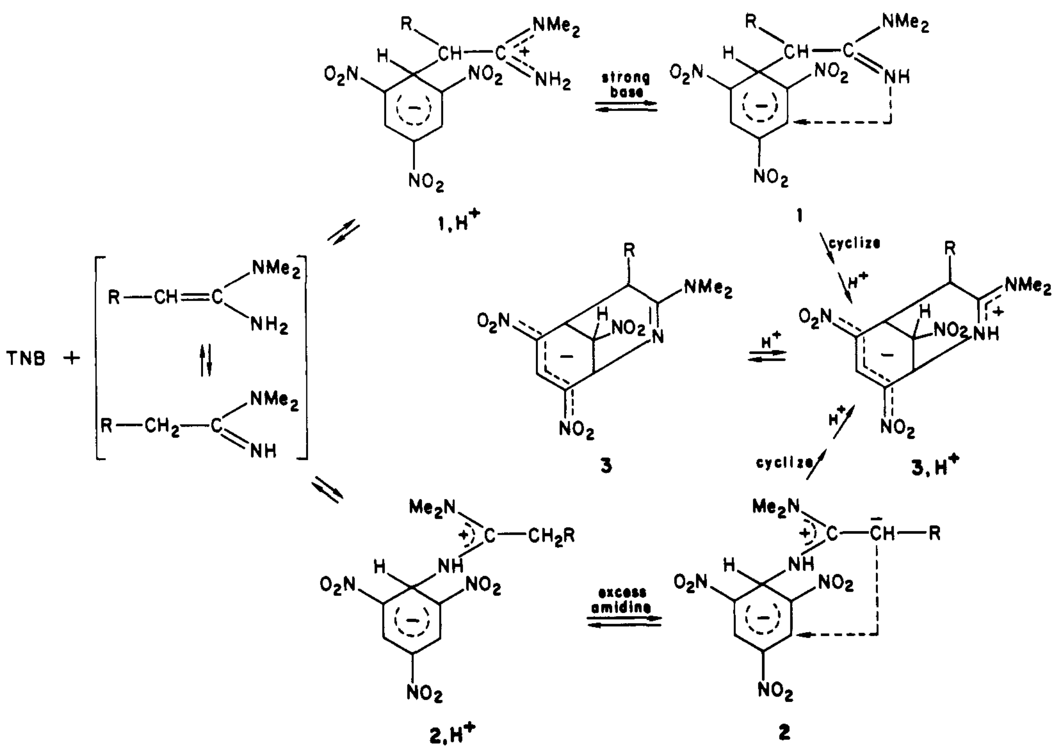
Scheme I[a]



[a] a, R = H; b, R = Me; c, R = $C_6H_5$.

**3b,H**$^+$ in aqueous sodium hydroxide. The structures of **3a,H**$^+$ and **3b,H**$^+$ have previously been confirmed by NMR and elemental analysis.[1,2] These compounds have a visible absorption maximum at 500 nm, characteristic of the nitropropene nitronate function.[1,2,4,5,11] The rates of cyclization of **1a,H**$^+$ and **1b,H**$^+$ at several temperatures were measured by using stopped-flow spectrophotometry by monitoring the disappearance of absorption maxima for these species as a function of time. In all experiments, the hydroxide ion concentration was very large relative to the concentrations of **1a,H**$^+$ and **1b,H**$^+$, assuring pseudo-first-order conditions. The ionic strength was kept constant at 1 M by the addition of appropriate amounts of NaCl. Under these experimental conditions only a single fast process was observed.

The observed rate constants, $k_{\mathrm{obsd}}$, for cyclization of **1a,H**$^+$ and **1b,H**$^+$ are summarized in Tables I and II. For both adducts, $k_{\mathrm{obsd}}$ values are consistent with Scheme II, where $K$ is the equilibrium constant for deprotonation of the amidinium moiety of the zwitterions **1a,H**$^+$ or **1b,H**$^+$ (symbolized by XH in eq 2) and $k_b$ is the rate constant for

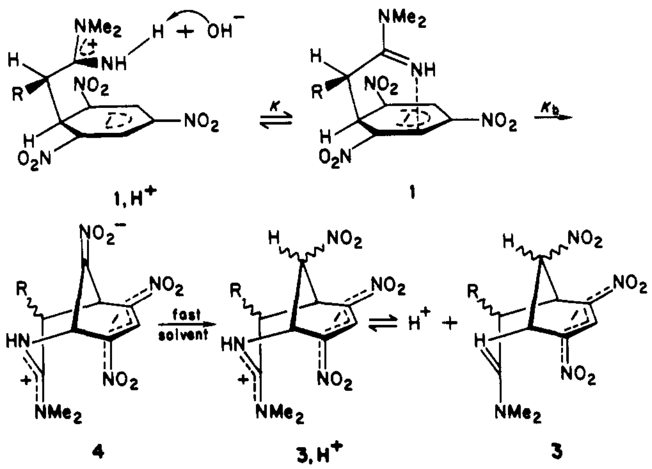
$$K = \frac{[\mathrm{X}^-]}{[\mathrm{XH}][\mathrm{OH}^-]} \qquad (2)$$

$$\mathrm{XH} + \mathrm{OH}^- \underset{(\text{fast})}{\overset{K}{\rightleftharpoons}} \mathrm{X}^- \xrightarrow{k_b} \mathbf{3,H}^+ \qquad (3)$$

$$k_{\mathrm{obsd}} = \frac{k_b K[\mathrm{OH}^-]}{1 + K[\mathrm{OH}^-]} \qquad (4)$$

cyclization of the anionic forms of **1a,H**$^+$ and **1b,H**$^+$, i.e., **1a** and **1b** (symbolized by $\mathrm{X}^-$ in eq 2). From studies of the cyclization of analogous ketonic adducts,[6,7] it is known that the protonation of the unconjugated nitronate function in the initially formed adducts **4a** and **4b** by any general acid, including the solvent, to give **3a,H**$^+$ and **3b,H**$^+$ is fast. On this basis, the cyclization of **1a,H**$^+$ and **1b,H**$^+$ is best formally described by the very simple and classical kinetic scheme formulated in eq 3, with the observed rate constant, $k_{\mathrm{obsd}}$, being given by eq 4.[12] The fact that, depending on pH, the resulting bridged adducts **3a,H**$^+$ and **3b,H**$^+$ may exist partly or completely in their anionic forms **3a** and **3b** does not affect eq 4.

Scheme II[a]



[a] a, R = H; b, R = Me.

Plots of $k_{\mathrm{obsd}}$ vs. $[\mathrm{OH}^-]$ are curved (Figure 1) and approach a plateau at the highest base concentrations when eq 4 reduces to eq 5 because we have $K[\mathrm{OH}^-] \gg 1$.

$$k_{\mathrm{obsd}} = k_b \qquad (5)$$

$$\frac{1}{k_{\mathrm{obsd}}} = \frac{1}{k_b} + \frac{1}{k_b K[\mathrm{OH}^-]} \qquad (6)$$

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[11] Kohashi, K.; Okhura, Y.; Momose, T. *Chem. Pharm. Bull.* **1971**, *19*, 2065.

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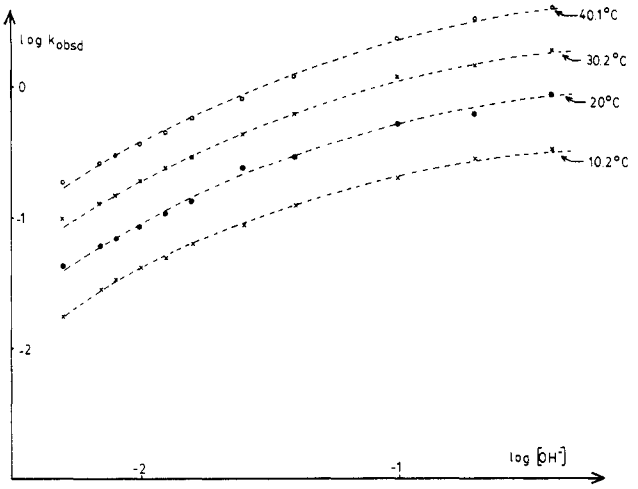

**Figure 1.** Variation of $k_{obsd}$ for the cyclization of **1a,H$^+$** with base concentration at the different temperatures studied in aqueous solution (I = 1 M).

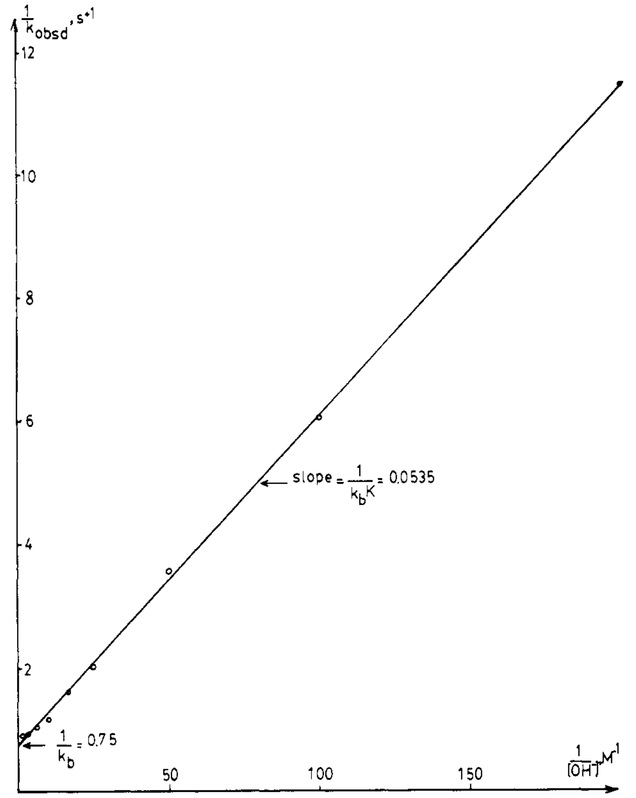

**Figure 2.** Inversion plot according to eq 6 for cyclization of the propionamidine complex **1b,H$^+$** into **3b,H$^+$** at $t$ = 15 °C.

Inversion plots according to eq 6 are linear as shown in Figure 2, and when the intercepts ($1/k_b$) and slopes ($1/k_bK$) are used the values of $k_b$ and $K$ can be obtained. These are summarized in Table III for the different temperatures studied. The $k_b$ value determined at 5 °C for the cyclization of **1b,H$^+$** is in good agreement with that previously determined by conventional spectrophotometric methods at lower pH ($k_b$ = 0.45 s$^{-1}$).[13] Table III also contains the p$K_a$ values for the ionization of the amidinium moiety of **1a,H$^+$** and **1b,H$^+$**. These values have been calculated by means of eq 7 where p$K_w$ is the ionic product of water at ionic strength 1 M and at the different temperatues studied.[14]

$$pK_a = pK_w + pK \qquad (7)$$

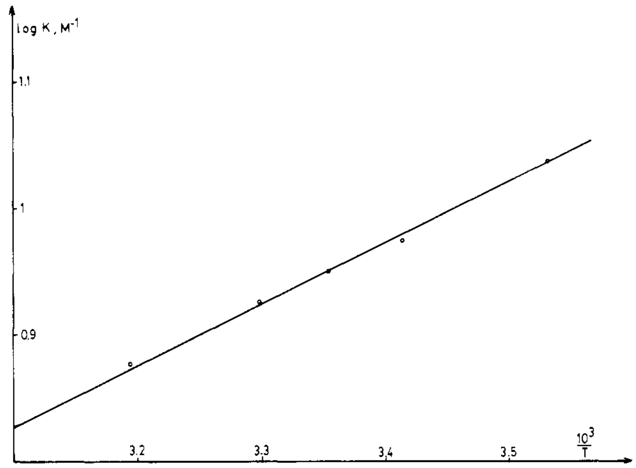

**Figure 3.** Temperature dependence for the equilibrium deprotonation of the amidinium moiety of the acetamidine complex **1a,H$^+$**.

**Table III. Rate and Equilibrium Constants for the Cyclization of 1a,H$^+$ and 1b,H$^+$ at Different Temperatures in Aqueous Solution (I = 1 M)**

| | 1a,H$^+$ | | | | 1b,H$^+$ | | | |
|---|---|---|---|---|---|---|---|---|
| $t$, °C | 10.2 | 20 | 30.2 | 40.1 | 5 | 15 | 25 | 34.5 |
| $k_b$, s$^{-1}$ | 0.4 | 1 | 2.38 | 5.13 | 0.47 | 1.33 | 3.33 | 7.69 |
| $K$, M$^{-1}$ | 10.91 | 9.39 | 8.42 | 7.58 | 14.27 | 14.06 | 13.96 | 14.77 |
| p$K_a$[a] | 13.28 | 12.97 | 12.68 | 12.42 | 13.36 | 12.98 | 12.62 | 12.27 |
| p$K_w$[b] | 14.32 | 13.94 | 13.60 | 13.30 | 14.51 | 14.13 | 13.77 | 13.44 |

[a] Calculated using eq 7. [b] Reference 14.

**Table IV. Kinetic and Thermodynamic Parameters for the Ionization of the Zwitterions 1a,H$^+$ and 1b,H$^+$ and Their Cyclization into the Adducts 3a,H$^+$ and 3b,H$^+$ at 25 °C (I = 1 M)[a]**

| | 1a,H$^+$ | 1b,H$^+$ |
|---|---|---|
| $k_b$, s$^{-1}$ | 1.51 | 3.33 |
| $K$, L mol$^{-1}$ | 8.90 | 13.96 |
| p$K_a$ | 12.82 | 12.62 |
| $\Delta H^‡$, kJ mol$^{-1}$ | 60.5 | 64.7 |
| $\Delta S^‡$, J mol$^{-1}$ K$^{-1}$ | -37.6 | -17.5 |
| $\Delta H°$, kJ mol$^{-1}$ | -9.30 | $\simeq$0 |
| $\Delta S°$, J mol$^{-1}$ K$^{-1}$ | -13 | 22 |

[a] Estimated errors, rate constants ±3%. $\Delta H$ values ±1.5 kJ mol$^{-1}$. $\Delta S$ values ±5 J mol$^{-1}$ K$^{-1}$.

From the temperature dependence of $k_b$, satisfactory Arrhenius plots (not shown) have been obtained, allowing a determination of activation parameters $\Delta H^‡$ and $\Delta S^‡$ for the cyclization processes (Table IV). In the case of the acetamidine system, $K$ decreases with increasing $T$, and in spite of the relatively small changes observed, a plot of log $K$ vs. $1/T$ is linear (Figure 3). This allows calculation of $\Delta H°$ and $\Delta S°$ for the deprotonation of the amidinium moiety of **1a,H$^+$** by hydroxide ion. In the case of the propionamidine system, $K$ is clearly almost temperature independent, suggesting a $\Delta H°$ value close to zero; the corresponding $\Delta S°$ value was then calculated by the expression $\Delta S° = 2.303R \log K$, using the average $K$ value of 14.26 measured for the equilibrium **1b,H$^+$** + OH$^-$ $\rightleftarrows$ **1b** + $H_2O$. All the activation and thermodynamic parameters for the cyclization of the adducts, as well as p$K_a$'s of the amidinium moieties in **1a,H$^+$** and **1b,H$^+$** at 25 °C, are summarized in Table IV.

For the purpose of comparison, we have determined the acidity (p$K_a$) of the amidinium functionality of the parent

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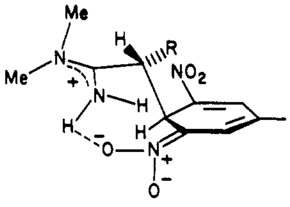
[13] Strauss, M. J.; Terrier, F. *Tetrahedron Lett.* **1979**, 313.

[14] Harned, H. S.; Owen, B. B. "The Physical Chemistry of Electrolyte Solutions"; Reinhold: New York, 1950; p 487.

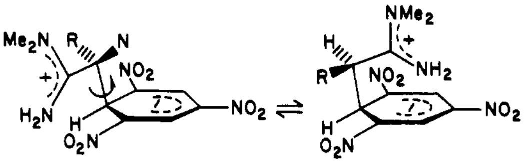
amidines under similar experimental conditions to those used for kinetics ($I$ = 1 M NaCl, $t$ = 25 °C). These values which have been determined by a conventional potentiometric procedure are equal to 12.24 and 11.83 for acetamidine and propionamidine, respectively. Our value for acetamidine compares well with those previously reported in the literature.[15,16]

## Discussion

One very interesting aspect of the data shown in Table IV is that the amidine moieties in the anionic adducts **1a** and **1b** are more basic than those of the parent amidines. The $pK_a$ values are 12.82 and 12.62 for **1a** and **1b**, respectively, as compared with $pK_a$ values of 12.24 and 11.83 for acetamidine and propionamidine, respectively, in aqueous solution at $t$ = 25 °C. While the negative trinitrocyclohexadienate ring in $\sigma$ complexes is known to possess an appreciable electron-withdrawing effect,[3,17-20] which might be expected to diminish amidine basicity in the complex, this is clearly not the predominant effect in this instance. That inductive effect is usually exhibited at the tetrahedral ring carbon[3,17-20] or $\alpha$ to this site (i.e., in enolization of carbanionic complexes[4,6,7]). In the case of the complexes **1a,H**$^+$ and **1b,H**$^+$, one can imagine that the positive amidinium moiety, further removed from the ring junction, may be stabilized by either an ortho nitro group, as shown in structure A, or via solvent H bonding and electrostatic interaction with the trinitrocyclohexadienate ring, as visualized in B. We have assumed the $o$-nitro functionality remains approximately in the plane of the ring for maximum charge delocalization.



A



B

Table IV shows that it is the anionic adduct with the less basic amidine functionality, i.e., **1b**, which cyclizes more rapidly. This unexpected result may have something to do with the conformations of the adducts. We believe that conformation A may be favored for **1a,H**$^+$ and B may be favored for **1b,H**$^+$. While it may not be immediately apparent from structure A, examination of Dreiding models of these complexes reveals that stabilization by an $o$-$NO_2$ group is possible in **1a,H**$^+$ but more difficult in **1b,H**$^+$. In this latter case, significant steric interference between the R = Me group and the $NO_2$ group exists in the conformation of A that allows ortho $NO_2^-$ stabilization of the positive amidinium side chain, so that conformation B is clearly favored.[21] The ionization of **1a,H**$^+$ and **1b,H**$^+$ thus leads to the formation of **1a** and **1b** having different conformations, analogous to A and B, respectively, and in the case of **1b** this conformation is exactly that which would favorably lead to the transition state for cyclization, as shown in Scheme II. In contrast, rotation around the exocyclic C–C bond is required in **1a** before a conformation favorable to cyclization is reached thus accounting for a ratio of $k_b^{1b}/k_b^{1a} > 1$ (=2.20).

Comparison of the enthalpies of activation $\Delta H^{\ddagger}$ for the cyclization step gives some support to the above argument. Table IV shows that $\Delta H^{\ddagger}$ for the cyclization of **1a** is in fact less than that for the cyclization of **1b**, even though **1b** cyclizes *more* rapidly that **1a**. The rate enhancement thus results from a less negative entropy of activation for **1b**: $\Delta S^{\ddagger}_{1b} = -17.5$; $\Delta S^{\ddagger}_{1a} = -37.6$ J mol$^{-1}$ K$^{-1}$. This is exactly what would be expected if the most stable conformation of **1b** was one, i.e., B, which required the least rotation about the exocyclic bond to reach an orientation favorable for cyclization. Also of interest are the $\Delta S°$ values for equilibrium between the protonated and deprotonated forms of the complexes: $\Delta S°_{1a,H^+} = -13$; $\Delta S°_{1b,H^+} = 22$ J mol$^{-1}$ K$^{-1}$. Thus, deprotonation of the amidinium moiety in **1b,H**$^+$ is entropically favored as compared with that of **1a,H**$^+$. This would be so if the amidinium moiety in **1b,H**$^+$ is not stabilized internally by the negative trinitrocyclohexadienate ring to the same extent as in **1a,H**$^+$, but is stabilized substantially by solvent H bonding, resulting in more substantial ordering of solvent structure, as it is possible in B but not in A. This structuring is diminished upon deprotonation, and to a greater extent for **1b,H**$^+$ than for **1a,H**$^+$.

The finding that the amidine moieties of the adducts are appreciably more basic than those of the parent amidines in aqueous solution ($\Delta pK$ ~0.6–0.8) is of interest with respect to the observation that **1a,H**$^+$ and **1b,H**$^+$ could not be induced to cyclize in the presence of excess amidine in $Me_2SO$ or ethanol solution.[1,2] It is well-known that relative acidities may be strongly affected by solvent changes.[22] Thus, it might be that the basicity difference between the adducts and the corresponding amidines increases on transfer from water to $Me_2SO$ or ethanol, making the equilibrium **1a,H**$^+$ (**1b,H**$^+$) + amidine $\rightleftarrows$ **1a**-(**1b**) + amidine,H$^+$ thermodynamically unfavorable. This would account for the necessity of a strong base, i.e., $MeO^-$ or $EtO^-$, to induce the cyclization to **3a,H**$^+$ and **3b,H**$^+$.[1,2]

We have previously discussed geometrical requirements for meta bridging qualitatively[4] and have also speculated on conformational preferences for these adducts from $^1H$ and $^{13}C$ NMR spectroscopic measurements of amidine and related carbanionic complexes.[1,2] The work presented here represents the first mechanistic evidence, deduced from kinetic measurements and temperature dependence studies, that such reactions are indeed quite sensitive to minor structural changes, and that the rate of any specific meta bridging process is sensitive to substituents attached to the bridging fragments.

## Experimental Section

The adducts **1a,H**$^+$ and **1b,H**$^+$ were prepared from the reaction of TNB with the parent amidines in ethanol according to a method previously described.[1] The amidines were also prepared as de-

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(21) In this case, there is also, though to a lesser extent, some steric interference between the R = Me group and the methyl group of the planar amidinium function.

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scribed previously.[1] NaOH solutions were prepared from Titrisol.

Kinetic determinations were made on a Durrum stopped-flow spectrophotometer, the cell compartment of which was maintained to ±0.5 °C. All runs were carried out under first-order conditions with a substrate concentration of about $5 \times 10^{-5}$ M. Rate constants are considered accurate to ±3%.

**Acknowledgment.** The authors thank the North Atlantic Treaty Organization for a grant (NATO Res. 1540) to F.T. and M.J.S. supporting this research.

**Registry No.** **1a**,H$^+$, 56776-17-1; **1b**,H$^+$, 56776-18-2; **3a**,H$^+$, 91631-87-7; **3b**,H$^+$, 91631-88-8.

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# Methanol Attack on Highly Electrophilic 4,6-Dinitrobenzofurazan and 4,6-Dinitrobenzofuroxan Derivatives. A Kinetic Study

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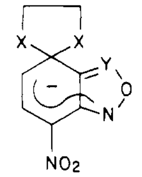
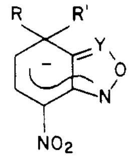
*Received April 10, 1984*

Methanol readily adds to the unsubstituted 7-carbons of 4,6-dinitrobenzofurazan (DNBZ) and 4,6-dinitrobenzofuroxan (DNBF) as well as the methoxy-bearing carbon of 7-methoxy-4,6-dinitrobenzofurazan (MDNBZ) to form the most stable methoxyl $\sigma$ adducts known in this solvent. The formation and decomposition of the adducts are subject to general base and general acid catalysis, respectively, with $\beta$ ($\alpha$) values of ~0.50, indicating a concerted mechanism. The results suggest that methoxide ion behaves as a base catalyst for methanol addition rather than as a nucleophile. The intrinsic rate constants $k_0$ (in the Marcus sense) have been determined for the derivatives. Although the equilibrium constant for methanol addition to MDNBZ is somewhat greater than for addition to DNBZ and DNBF, the $k_0$ value for the latter derivatives is about 10-fold higher than that for MDNBZ. This indicates a higher intrinsic barrier for attack at a methoxy-bearing than at an unsubstituted carbon, in qualitative agreement with previously reported patterns in the benzene series. The high reactivity of DNBZ, DNBF, and MDNBZ toward methanol and other bases, together with the very high stability of the resulting adducts, emphasizes the superelectrophilic character of these electron-deficient aromatics.

There is now convincing evidence that mononitro-2,1,3-benzoxadiazoles and related *N*-oxides, currently known as nitrobenzofurazans and nitrobenzofuroxans, easily react with oxygen, sulfur, and nitrogen nucleophiles to form anionic $\sigma$ complexes.[2–7] Complexes such as **1** and **2** have been fully characterized and isolated as crystalline alkali salts.[3,5,6] Such characterization is of importance with respect to the proposal that the antileukemic properties exhibited by some of these derivatives may be related to their ability to form $\sigma$ complexes with essential cellular SH and/or amino groups.[7]



1, X=O,S
Y=N,N→O



2, R=R'=OMe; R=H, R'=OMe
Y=N, N→O

Kinetic and thermodynamic studies have shown that the electrophilic character of 4-nitrobenzofurazans and benzofuroxans is comparable to that of 1,3,5-trinitrobenzene (TNB).[2,5,6] Since the introduction of a second nitro group must increase this character, the study of dinitro derivatives like 4,6-dinitrobenzofurazan (DNBZ) and 4,6-dinitrobenzofuroxan (DNBF) is of interest. Indeed, the latter compound, which is readily prepared by direct nitration of benzofuroxan[8] is known to behave as a super electrophile and can be used to assess the reactivity of very weak nucleophiles, including potential carbon nucleophiles like enols, anilines, or $\pi$-excessive heterocycles.[6,9–12] Also of interest is that the alkali salts of the formed adducts exhibit very strong explosive properties.[9a,11]

In view of these results, it was surprising to find no report regarding the furazan analogue of DNBF, i.e. DNBZ, in the literature. We have therefore undertaken efforts to synthesize this compound and compare its reactivity toward methanol and methoxide ion with that of DNBF. Following a preliminary communication of the p*K*a values in a recent review,[6] we now report detailed

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