Kinetics of the Reaction of β-Methoxy-α-nitrostilbene with Cyanamide in 50% DMSO−50% Water. Failure to Detect the S_NV Intermediate

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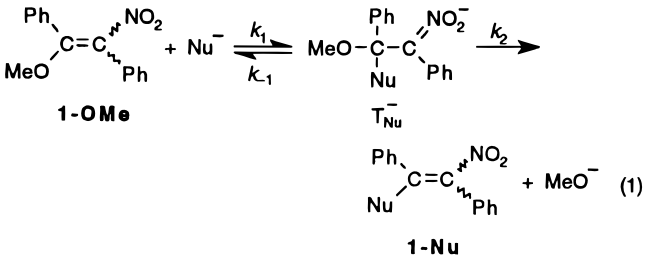
A kinetic study of the reaction of β-methoxy-α-nitrostilbene (**1-OMe**) with cyanamide (CNA) over a pH range from 8.5 to 12.4 shows that it is the anion (CNA^-, $pK_a = 11.38$) rather than the neutral amine that is the reactive species. Attempts at monitoring the reaction with the neutral CNA at low pH were unsuccessful because of competing hydrolysis. It is shown that the nucleophilic reactivity of CNA is abnormally low, probably because of a resonance effect, and that the reactivity of CNA^- is high, higher than that of strongly basic oxyanion because of relatively weak solvation. The high reactivity of both **1-OMe** and CNA^- appeared to constitute favorable conditions conducive to the detection of the S_NV intermediate, as has been the case in the reactions of **1-OMe** with thiolate ions, alkoxide ions, and some amines. However, no intermediate was observed. Reasons for this failure are discussed.

Introduction

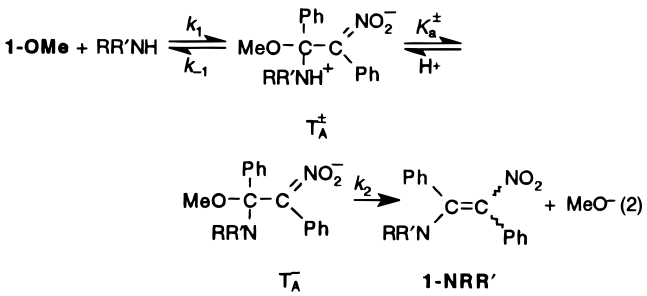
Nucleophilic vinylic substitution (S_NV) reactions[1] continue to offer challenging problems for the mechanistic chemist. Recent research has focused on various limiting situations that pertain to the attachment−detachment two-step mechanism that operates with substrates that are activated by electron-withdrawing groups. One such limiting situation pertains to reactions with substrates that are only weakly activated and have very good leaving groups. In such cases, the intermediate may be too unstable to exist and the reaction becomes a concerted single step substitution.[2,3]

At the other end of the spectrum are reactions of strong nucleophiles with highly activated substrates that have a sluggish leaving group where the intermediate may accumulate to detectable levels.[4,5] A prominent example of this latter situation is the reaction of β-methoxy-α-nitrostilbene (**1-OMe**) with several nucleophiles (eq 1) where the involvement of the tetrahedral intermediate (T^-_{Nu}) has been directly demonstrated by spectroscopic observation, and the rate constants of the various elementary steps (k_1, k_{-1}, and k_2) were amenable to kinetic determination.[4] The nucleophiles that, thus far, have allowed direct detection of the respective intermediates include alkanethiolate ions such as n-PrS^-, $HOCH_2CH_2S^-$, $MeO_2CCH_2CH_2S^-$, and $MeO_2CCH_2S^-$,[4a,b] alkoxide ions such as MeO^- and $CF_3CH_2O^-$,[4d,f] and amines such as $MeONH_2$ and MeONHMe,[4c,e] with all reactions conducted in 50% DMSO−50% water (v/v) at 20 °C.



(1)

The reactions with amine nucleophiles are more complex because they involve two intermediates that are in rapid acid−base equilibrium with each other, eq 2, with the anionic form (T^-_A) being directly observable in some cases. A particularly interesting feature of the reactions of **1-OMe** with amines is that T^-_A was only detectable



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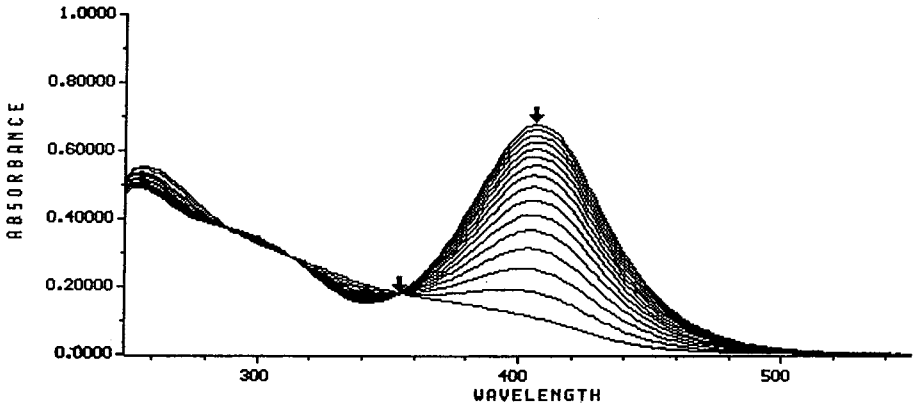
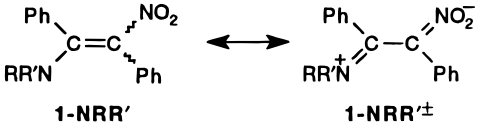


Figure 1. Time-dependent absorption spectra of the reaction of **1-OMe** with CNA^- in 50% DMSO−50% water at 20 °C: $[\mathbf{1\text{-}OMe}]_o = 5 \times 10^{-5}$ M, $[CNA^-] = 6 \times 10^{-3}$ M, pH 10.50. Scans collected every 10 s.

with the weakly basic amines $MeONH_2$ and MeONHMe[4c,e] but not with the much more basic *n*-butylamine, morpholine, piperidine, or pyrrolidine.[6] This finding is rather counterintuitive since one would expect that the chances for T_A^- to accumulate to detectable levels should improve with increasing nucleophilicity and/or basicity of the amine. The observed behavior is the result of the much greater sensitivity of k_2 than k_1 to amine basicity which increases the k_1/k_2 ratio for less basic amines, e.g., from $k_1/k_2 \leq 3.3 \times 10^{-2}$ M^{-1} for piperidine to $k_1/k_2 = 37.3$ for MeONHMe. The strong dependence of k_2 on amine basicity was attributed to an electronic "push" due to transition state stabilization by the developing resonance in the substitution product (**1-NRR′**$^{\pm}$).

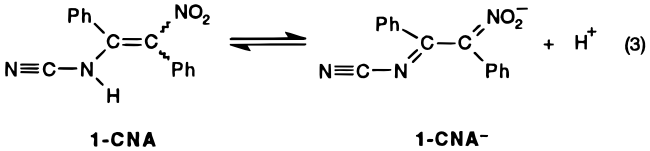


On the basis of the above analysis, one would anticipate that the reaction of **1-OMe** with still less basic amines than $MeONH_2$ or MeONHMe would also yield a detectable intermediate and render the k_1/k_2 ratio even more favorable. In order to test this hypothesis, we investigated the reaction of **1-OMe** with cyanamide, $N{\equiv}C{-}NH_2$ whose $pK_a^{RR'NH^+_2}$ in water is 1.1.[7] We now report that nucleophilic substitution indeed occurs but that the reactivity patterns of cyanamide differ greatly from those of any amine studied thus far and that no intermediate could be observed.

Results

General Features. The reaction of **1-OMe** with $N{\equiv}C{-}NH_2$ (CNA) in 50% DMSO−50% water (v/v) is characterized by a single kinetic process in the pH range 8.5−12.39. Below pH 8.5 the reaction is very slow, and at pH ≤ 6 only hydrolysis of **1-OMe** could be detected. These observations and the kinetic results reported below indicate that the nucleophile is not the neutral amine but its conjugate anion, $N{\equiv}C{-}NH^-$ (CNA^-); the pK_a of CNA, determined potentiometrically, was found to be 11.38.

Time-dependent UV−vis scans of the reaction at all pH values studied show three sharp isosbestic points at 290, 312, and 354 nm (Figure 1), indicating a clean conversion of **1-OMe** to the substitution product without the accumulation of an intermediate. The relatively long λ_{max} of the product (406 nm) is characteristic of an extended π-system, consistent with the *anionic* form of the product, eq 3.



Kinetics. All kinetic experiments were run with a large excess of the amine over the substrate. Clean first-order kinetics were observed. Pseudo-first-order rate constants, k_{obsd}, were measured as a function of CNA concentration at pH 8.50, 9.70, 10.11, 10.60, and 12.39. The k_{obsd} values for substrate depletion (k^S_{obsd}, 342 nm) and for product formation (k^P_{obsd}, 406 nm) were identical within experimental error. Plots of k^S_{obsd} or k^P_{obsd} vs $[CNA^-]$ were linear with pH-independent slopes and negligible intercepts. A representative plot is shown in Figure 2. The average of the slopes is 2.7 ± 0.2 M^{-1} s^{-1}; the intercept is indistinguishable from zero.

Stability of CNA and CNA^-. CNA is known to be relatively unstable in aqueous solution. At pH > 10 CNA reportedly dimerizes to dicyandiamide, while at pH < 8 it hydrolyzes to urea.[8] However, on the time scale of our kinetic experiments, no significant decomposition took place, as determined by ^{13}C NMR experiments in 50% DMSO−50% D_2O. Specifically, the ^{13}C signal of CNA at 119.14 ppm in neutral solution and that of CNA^- at 138.76 ppm at pH > 12.0 remained unchanged for several hours. At pH ≈ 11 where CNA and CNA^- are present at comparable concentrations, dimerization, which presumably occurs by attack of CNA^- on CNA, was observable from the gradual appearance of the imine carbon signal at 164.4 ppm. However, the reaction was too slow to interfere with our rate determinations.

Discussion

CNA^- as the Nucleophile. The fact that the slopes of the plots of k_{obsd} vs $[CNA^-]$ are pH-independent in the

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(7) Soloway, S.; Lipschitz, A. *J. Org. Chem.* **1958**, *23*, 1963.
(8) *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley-Interscience: New York. 1979; Vol. 7, p 291 and references therein.

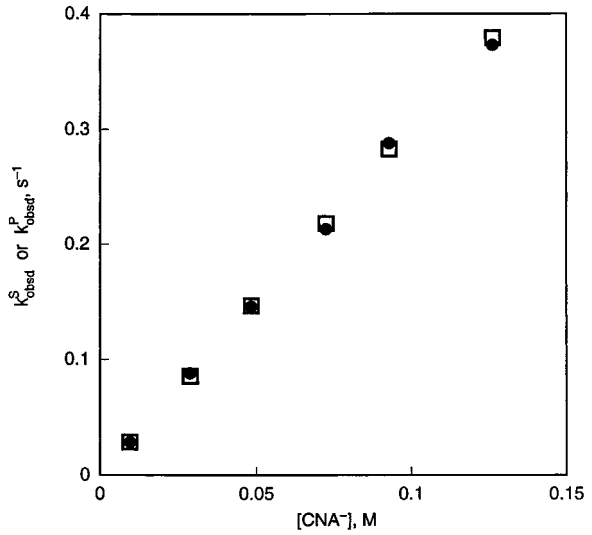


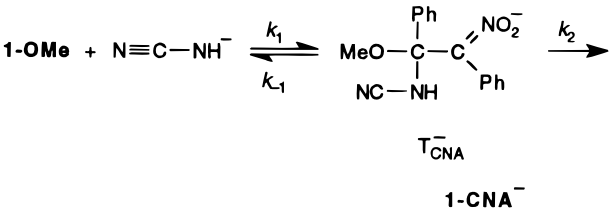
Figure 2. Plots of k^S_{obsd} (●, 342 nm) and k^P_{obsd} (□, 406 nm) vs [CNA⁻] at pH 12.39.

range from 8.5 to 12.39 demonstrates that it is the conjugate base of CNA that acts as the nucleophile. In view of the high acidity of CNA ($pK_a = 11.38$), which means that, even at pH 8.5, there is a significant concentration of CNA⁻, this conclusion is not surprising. The high acidity of CNA is the result of the strong electron-withdrawing effect of the cyano group that presumably stabilizes the anion both inductively and by resonance delocalization (eq 4).

$$N{\equiv}C{-}NH^- \longleftrightarrow {}^-N{=}C{=}NH \qquad (4)$$

One might have expected that the reaction with the neutral CNA as the nucleophile should become significant at very low pH but, due to competition by the hydrolysis of **1-OMe**, this reaction could not be observed. An upper limit for the second-order rate constant for the reaction of CNA (k_1^{CNA}) may be estimated on the basis of $k_1^{H_2O} = 2.37 \times 10^{-5}$ s^{-1} for the hydrolysis in neutral or acidic solution.[12] Assuming that less than 5% aminolysis product was formed even at the highest [CNA] used (0.5 M), one obtains $k_1^{CNA} \leq 2.4 \times 10^{-6}$ M^{-1} s^{-1}.

Mechanism. The simplest reaction scheme that is consistent with our data is shown in eq 5, with T^-_{CNA} being a steady-state intermediate. According to this



(5)

mechanism, the slopes of the plots of k_{obsd} vs [CNA⁻] (2.7 M^{-1} s^{-1}) are given by eq 6; if $k_2 \gg k_{-1}$, slope $= k_1$ while

$$\text{slope} = \frac{k_1 k_2}{k_{-1} + k_2} \qquad (6)$$

for $k_2 \ll k_{-1}$, slope $= K_1 k_2$ with $K_1 = k_1/k_{-1}$. However, the following reasoning suggests that the actual mechanism is more complex. The argument is based on the notion that T^-_{CNA} should accumulate to detectable levels if eq 5 were the correct mechanism.

As discussed in detail elsewhere,[4a,b,c,e] there are two necessary conditions for an intermediate in a two-step reaction to accumulate to detectable levels. The first ("thermodynamic condition") is that the equilibrium between the intermediate and the reactants favors the intermediate, i.e., $K_1[CNA^-] > 1$ in our case. The second ("kinetic condition") is that the rate of formation of the intermediate is faster than its conversion to products, which, for eq 5, means $k_1[CNA^-]/k_2 > 1$. It has been shown that for the reaction of neutral amines with **1-OMe** the thermodynamic condition is amply met at high pH but that the kinetic condition is only fulfilled for weakly basic amines.[9] As alluded to in the Introduction, this is because for highly basic amines the strong electronic push leads to high k_2 values and hence low k_1/k_2 ratios. For weakly basic amines the push is weak, leading to low k_2 values; since k_1 is much less sensitive to the pK_a of the amine ($\beta_{nuc} = \text{dlog } k_1/\text{d}pK_a^{RR'NH^+_2} = 0.25$) than k_2 ($\beta_{push} = \text{dlog } k_2/\text{d}pK_a^{RR'NH^+_2} = 0.71$) this leads to large k_1/k_2 values.[4c,e]

As for CNA⁻, its nucleophilicity and carbon basicity are expected to be at least as high as that of the most nucleophilic neutral amines, and hence, one expects $K_1[CNA^-] \gg 1$; i.e., the thermodynamic condition for detectability of T^-_{CNA} should be met. Regarding the kinetic condition, because of the lower basicity of CNA ($pK_a \approx 1.1$)[10] compared to that of $MeONH_2$ ($pK_a = 4.70$), the basicity of the NCNH-moiety of T^-_{CNA} (eq 5) must also be lower than that of the MeONH moiety in the corresponding T^-_A intermediate of the $MeONH_2$ reaction. Hence, the push in the k_2 step of the CNA⁻ reaction should be even weaker than in the $MeONH_2$ reaction. This should make the k_1/k_2 ratio for the CNA⁻ reaction particularly favorable for the detectability of T⁻ in eq 5. Hence, to explain why T^-_{CNA} was *not* detected, we need to invoke one or several additional pathways from T^-_{CNA} to products that are considerably faster than the k_2 step.

Scheme 1 shows an extended mechanism with a number of such additional possible pathways.

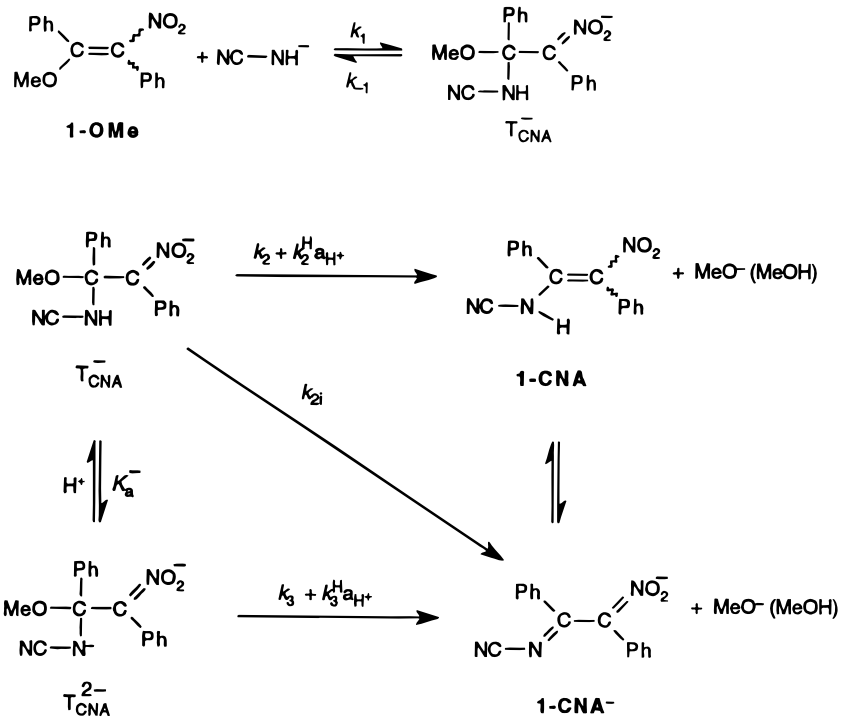
The pathway via the deprotonated intermediate, T^{2-}_{CNA}, should provide a considerable advantage over the k_2 step for two reasons. (1) The pK_a^- of T^-_{CNA} is expected to be comparable to that of CNA since the effect of the negative charge is probably offset by the electron-withdrawing Ph(OMe)C(NO_2^-)Ph moiety; if the $pK_a^{\pm}$ of $T^{\pm}_A$ type intermediates (eq 2) can serve as a guide,[4e] the electron-withdrawing effect of the Ph(OMe)C(NO_2^-)Ph moiety may actually overcompensate for the negative charge. Hence T^{2-}_{CNA} should be the dominant form of the intermediate, at least at high pH. (2) The breakdown of T^{2-}_{CNA} to **1-CNA**⁻ is expected to be much faster than that of T^-_{CNA} because of the strong push provided by the negative charge on the nitrogen atom of T^{2-}_{CNA}. This is similar to the push provided by the negative charge on the

(9) For the reaction of neutral amines, the thermodynamic condition takes on the form $K_1K_a^{\pm}[RR'NH]/a_{H^+} > 1$ ($K_a^{\pm}$ defined in eq 2), while the kinetic condition is the same as for anionic nucleophiles, i.e., $k_1[RR'NH]/k_2 > 1$.

(10) We shall use the pK_a value determined in water.[7] Since pK_a values of protonated amines in 50% DMSO−50% water are typically very nearly the same as in water,[11] this is of little consequence.

(11) Bernasconi, C. F.; Paschalis, P. *J. Am. Chem. Soc.* **1986**, *108*, 2969.

Scheme 1



oxygen of **2** in the hydrolysis of **1-OMe**, which is believed to be responsible for the failure to detect an intermediate in this reaction.[12]

2 **3**

The direct conversion of T^{2-}_{CNA} to **1-CNA**$^-$ (k_{2i}) is also likely to be faster than the k_2 step because of intramolecular acid catalysis of MeO^- departure by the NH proton; acid catalysis of MeO^- departure from T^-_{Nu} type intermediates such as **3** is known to be strong.[4f] For these reasons, H^+-catalyzed pathways ($k_2^H a_{H^+}$, $k_3^H a_{H^+}$) have been included in Scheme 1.[13]

According to this mechanism, with T^-_{CNA} and T^{2-}_{CNA} being treated as steady-state intermediates in rapid acid−base equilibrium with each other, the slopes of the plots of k_{obsd} vs [CNA^-] are given by eq 7. If our

$$\text{slope} = \frac{k_1\left[k_2 + k_{2i} + k_2^H a_{H^+} + \dfrac{K_a^-}{a_{H^+}}(k_3 + k_3^H a_{H^+})\right]}{k_{-1} + k_2 + k_{2i} + k_2^H a_{H^+} + \dfrac{K_a^-}{a_{H^+}}(k_3 + k_3^H a_{H^+})} \quad (7)$$

assumption that the equilibrium of the first step favors T^-_{CNA} is correct, this requires that $k_1 > k_{-1}$. Failure to detect an intermediate then implies that conversion of T^-_{CNA} to products is faster than formation of T^-_{CNA}; i.e., the kinetic condition is not met. It follows that $k_2 + k_{2i} + k_2^H a_{H^+} + (K_a^-/a_{H^+})(k_3 + k_3^H a_{H^+}) \gg k_{-1}$ and hence slope = k_1; i.e., nucleophilic attack is rate limiting.

It should be noted that even if the assumption that $k_1 > k_{-1}$ were incorrect, the conclusion that k_1 is rate limiting would stand. This can be shown as follows. At high pH the $k_2^H a_{H^+}$ and $k_3^H a_{H^+}$ terms must be negligible, as are the k_2 and k_{2i} terms compared to $k_3 K_a^-/a_{H^+}$. This reduces eq 7 to eq 8, showing that the slopes of k_{obsd} vs [CNA^-] can only be pH-independent if

$$\text{slope} = \frac{k_1 k_3 K_a^-/a_{H^+}}{k_{-1} + k_3 K_a^-/a_{H^+}} \quad (8)$$

$k_3 K_a^-/a_{H^+} \gg k_{-1}$ so that slope = k_1. Since the experimental slopes are pH-independent over the *entire* range, they must all be equal to k_1, i.e., the k_1 step is rate limiting in all our experiments.

Reactivity of CNA$^-$. Table 1 presents a summary of rate constants for nucleophilic attack on **1-OMe** by some representative anionic and neutral nucleophiles. The reaction of CNA^- with **1-OMe** is of particular interest because it is the first example of an S_NV reaction with an amide ion for which a rate constant has been determined. CNA^- is seen to be about 4-fold more reactive than $CF_3CH_2O^-$ and OH^-, despite its substantially lower basicity. It should be noted that the difference in the nucleophilicity between CNA^- and the oxyanions would probably be even greater if the electrophile did not have an alkoxy leaving group. This is because in the reactions with the oxyanion nucleophiles there is an extra transition state stabilization by the anomeric effect[14] which enhances their k_1^{Nu} values.[4d,12]

(12) Bernasconi, C. F.; Fassberg, J.; Killion, R. B., Jr.; Schuck, D. F.; Rappoport, Z. *J. Am. Chem. Soc.* **1991**, *113*, 4937.

(13) It is likely that acid catalysis by CNA (k_2^{CNA}[CNA], k_3^{CNA}[CNA]) also contributes to the reaction, but these terms have been omitted from Scheme 1 for clarity.

(14) In the present context, the anomeric effect[15,16] refers to the stabilization exerted by geminal oxygen atoms[17−20] in dialkoxy or alkoxyhydroxy adducts such as T^-_{Nu} (Nu = RO or OH) in eq 1.

(15) Kirby, A. G. *The Anomeric Effect and Related Stereoelectronic Effects of Oxygen*; Springer-Verlag: Berlin, 1983.

Table 1. Summary of Rate Constants for Nucleophilic Attachment of Anionic and Neutral Nucleophiles to 1-OMe in 50% DMSO−50% Water (v/v) at 20 °C[a]

Nu^-	pK_a^{NuH}	$k_1^{Nu^-}$ (M^{-1} s^{-1})	NuH	$K_a^{NuH^+}$[2]	k_1^{NuH} (M^{-1} s^{-1})
$NC-NH^-$ [b]	11.38	2.7 ± 0.2	$NC-NH_2$[b]	ca. 1.1[i]	$<2.4 \times 10^{-6}$
			$MeONH_2$[f]	4.70	7.8×10^{-2}
			n-$BuNH_2$[g]	10.68	1.45
$CF_3CH_2O^-$ [c]	14.0	0.73			
OH^- [d]	17.33	0.69	H_2O[d]	−1.44	8.54×10^{-7} [h]
$HOCH_2CH_2S^-$ [e]	10.56	390			

[a] $\mu = 0.5$ M (KCl). [b] This work. [c] Reference 4d. [d] Reference 12. [e] Reference 4a. [f] Reference 4e. [g] Reference 6. [h] First-order rate constant divided by water concentration. [i] In water at 29 °C, ref 7; pK_a in 50% DMSO−50% water expected to be very similar.

An important and perhaps the main factor responsible for the higher intrinsic nucleophilicity of CNA^- may be its relatively weak solvation. An indication of weak solvation is the rather small increase in the pK_a of CNA from its value in water, 10.27,[21] to that in 50% DMSO−50% water, 11.38. For CF_3CH_2OH the pK_a increases from 12.37 in water[22] to 14.00 in 50% DMSO−50% water[4d] and for H_2O from 15.74 to 17.33[23] for the same change in solvent.

Strongly basic oxyanions and especially OH^- are known to be less nucleophilic than expected on the basis of their pK_a values, a phenomenon attributed to their strong hydrogen-bonding solvation in hydroxylic solvents.[24−26] The reduction in reactivity is the result of the requirement for partial desolvation of the nucleophile and the fact that this desolvation runs ahead of bond formation at the transition state, which increases the intrinsic barrier[27] of the reaction.[28−30] Aryloxide ions and other weakly basic oxyanions whose solvation is weaker than that of strongly basic alkoxide ions are considerably more nucleophilic relative to their pK_a. For example, in the reaction of oxyanions with *p*-nitrothiophenyl acetate in water, the rate constant for OH^- lies approximately 3.6 log units below the straight line Brønsted plot defined by aryloxide ions;[25] in the reaction with *p*-nitrophenyl acetate the negative deviation for OH^- amounts to about 3.1 log units.[25] That solvation is an important factor is also apparent when comparing our results with Bordwell's findings for S_N2 reactions conducted in *pure DMSO*; in this medium solvation is drastically reduced and amide ions are *less* reactive than oxyanions of the same pK_a.[31]

The reduced solvation of CNA^- may, in part, be due to delocalization of the negative charge. If this is the case, the advantage gained from the reduced solvation is apparently greater than the expected reduction in reactivity of CNA^- due to its resonance stabilization (eq 4). Such a reduction in reactivity is expected on the basis of the generally observed phenomenon that the loss of the resonance effect from a reactant runs ahead of bond formation at the transition state, thereby increasing the intrinsic barrier of the reaction.[28−30]

Though more reactive than the oxyanions, CNA^- is far less reactive than the less basic $HOCH_2CH_2S^-$ (Table 1). This reflects the generally very high nucleophilicity of thiolate ions.[25,31] The exalted reactivity of thiolate ions is the combined result of low solvation[25,32] and high polarizability of sulfur.[31c,33]

Reactivity of CNA. The reaction of **1-OMe** with the neutral CNA is too slow to compete with hydrolysis, and only an upper limit of 2.4×10^{-6} M^{-1} s^{-1} can be given for k_1^{NuH}. The following considerations show that this upper limit is lower than expected on the basis of comparisons with reactions of **1-OMe** with other amines. For example, the Brønsted β_{nuc} value calculated based on the reactions of **1-OMe** with CNA and *n*-$BuNH_2$[34] is >0.60, much higher than $\beta_{nuc} = 0.25$ for the reaction of **1-OMe** with piperidine and morpholine.[6] It is unreasonable that β_{nuc} for primary amines would be so much larger than for secondary alicyclic amines; i.e., the high β_{nuc} value indicates that k_1^{NuH} for CNA is abnormally low and that CNA apparently is not part of the Brønsted family of primary amines.

One may estimate a k_1^{NuH} value for a hypothetical primary amine that does belong to the Brønsted family with *n*-$BuNH_2$ and has a pK_a^{NuH} equal to that of CNA. Assuming that β_{nuc} for this family is the same as for secondary alicyclic amines, i.e., 0.25, one calculates a $k_1^{NuH} \approx 5.8 \times 10^{-3}$ M^{-1} s^{-1} based on $k_1^{NuH} = 1.45$ M^{-1} s^{-1} for *n*-$BuNH_2$. This is 2.4×10^3-fold larger than the upper limit estimated for CNA. Our assumption that β_{nuc} for the primary amines is the same as for secondary alicyclic amines is probably an underestimation because in reactions with several other electrophilic olefins one usually finds $\beta_{nuc}(1°) > \beta_{nuc}(2°)$. For example, $\beta_{nuc}(1°) = 0.22$ and

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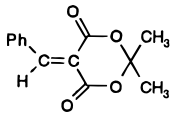
$\beta_{nuc}(2°) = 0.07$ for benzylidene Meldrum's acid, **4**,[36a] $\beta_{nuc}(1°) = 0.22$ and $\beta_{nuc}(2°) = 0.15$ for benzylidene malonodialdehyde, **5**,[36b] or $\beta_{nuc}(1°) = 0.37$ and $\beta_{nuc}(2°) = 0.22$ for benzylidene-1,3-indandione, **6**.[36c] Thus, a $\beta_{nuc}(1°)$ value



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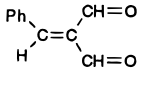

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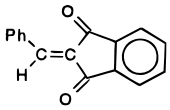
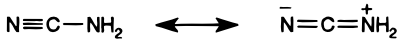


6

on the order of 0.35 to 0.40 is probably more realistic. Based on $\beta_{nuc} = 0.35$, one estimates k_1^{NuH} to be $\sim 6.3 \times 10^{-4}$ M^{-1} s^{-1} for a primary amine of equal basicity as CNA; based on $\beta_{nuc} = 0.40$ one obtains $k_1^{NuH} \approx 2.1 \times 10^{-4}$ M^{-1} s^{-1}. These estimates are still >87 to >260-fold higher than the upper limit estimated for CNA.

One factor that could reduce the reactivity of CNA is resonance stabilization according to eq 9. Evidence for



(9)

such resonance stabilization comes from Raman, microwave, and X-ray data[37] that show the $C-NH_2$ bond (1.34 Å)[37c] to be considerably shorter than in methylamine (1.47 Å) or even in formamide (1.376). The shortening of the $C-NH_2$ bond has been attributed to a combination of a change in hybridization of the C atom and delocalization.[37c]

A reduction in the reactivity of CNA by the resonance effect would again be the result of the loss of the resonance stabilization running ahead of bond formation at the transition state, thereby increasing the intrinsic barrier of the reaction.[28−30] As discussed earlier, in the case of CNA^- this effect is overcompensated by the diminished solvation and hence does not manifest itself in a reduced k_1^{Nu}. In the case of CNA there is no such compensating solvation factor; on the contrary, the zwitterionic character of CNA may lead to enhanced solvation compared to regular primary amines, which would further contribute to the low reactivity.

Conclusions

The reaction of **1-OMe** with CNA shows a behavior that is distinctly different from that of the reactions with other weakly basic amines. These differences can all be attributed to the combined field effect/π-acceptor properties of the cyano group, as follows. (1) The reactivity of the neutral CNA is lower than expected based on its basicity, probably because of resonance stabilization that leads to an increased intrinsic barrier. On the other hand, the reactivity of CNA^- is unusually high, higher than that of strongly basic oxyanions. This is attributed to the reduced solvation compared to that of the oxyanions, an effect that more than offsets the expected increase in the intrinsic barrier resulting from the resonance stabilization of CNA^-. (2) As a result of the high acidity of CNA (inductive and π-acceptor effect), a large fraction of CNA is present as CNA^- and hence the reaction with **1-OMe** occurs exclusively via CNA^-; the reaction with the natural CNA at low pH is too slow to compete with hydrolysis. (3) The intermediate in the CNA^- reaction, T_{CNA}^-, does not accumulate to detectable levels because it is converted to products more rapidly than it forms. The reason for this is the high acidity of the NH proton in T_{CNA}^-, which allows fast conversion to products via the highly reactive dianionic intermediate T_{CNA}^{2-} and/or via intramolecular acid catalysis (Scheme 1).

Experimental Section

Materials. β-Methoxy-α-nitrostilbene (**1-OMe**) was available from a previous study.[4e] Cyanamide (CNA) purchased from Sigma was purified by sublimation under high vacuum, mp 42−45° (lit.[38] mp 42−45 °C). The dimer of CNA, Dicyandiamide (DCDA), was obtained from a solution containing 7.0 M CNA and 3.5 M NaOH in D_2O upon standing overnight. The white crystals were characterized by melting point (uncorrected mp 196−201 °C (lit.[39] mp 208 °C), ^{13}C NMR (found δ (D_2O) 164.16, 121.20 (lit.[40] δ (DMSO-d_6) 162.62, 118.29)); (+)-FAB MS[41] (*m*/*z* 85, $[M + H]^+$ ion). β-*N*-Cyanamino-α-nitrostilbene (**1-CNA**) was obtained by reaction of **1-OMe** with CNA in 50% DMSO−50% water, i.e., the same conditions as for the kinetic experiments. The product was isolated by HPLC (Hypersil reversed phase column, isocratic 50% acetonitrile) and characterized by (+)-FAB MS: *m*/*z* 265, $[M + H]^+$ ion. A ^{13}C NMR spectrum of **1-CNA** could not be obtained due to the low concentration of the sample ($<10^{-5}$ M). Triethylamine and *N*-methylmorpholine were refluxed over sodium metal for at least 5 h and then fractionally distilled under argon. Acetic acid was used without purification. DMSO was refluxed over CaH_2 and then fractionally distilled under vacuum. Water was obtained from a Millipore water purification system.

Solutions: pH and pK_a Measurements. Preparation of solutions and pH measurements were as described before.[4e] The pK_a of CNA was obtained potentiometrically from a plot of pH vs log[CNA^-]/[CNA] whose slope was 1.04 ± 0.02 and intercept yielded pK_a = 11.38 ± 0.02.

Kinetics. Kinetic studies were conducted in 50% DMSO−50% water at 20 °C, at a constant ionic strength of 0.5 M (KCl). Typical substrate concentrations were on the order of 10^{-5} M. Reactions in the pH range 9.70−10.60 were run on a Hewlett-Packard 8452A diode array spectrophotometer. Substrate depletion and product formation were monitored simultaneously at 342 and 406 nm, respectively. Reactions at pH 8.50 were conducted on a Perkin-Elmer Lambda 2 spectrophotometer and monitored only at 406 nm. At pH 12.39, an Applied Photophysics stopped-flow spectrophotometer was used, and the kinetics were followed at both analytical wavelengths.

MS and NMR Spectra. Mass spectra were obtained on a VG 7070E magnetic sector high-resolution mass spectrometer. The instrument was set to FAB ionization mode, both with positive- and negative-ion detection. Glycerol and *n*-butylamine were used as matrices. The ^{13}C NMR spectra of CNA and the dimer were recorded on a 250 MHz Bruker instrument in D_2O. Samples at high pH were prepared by adding NaOH to the D_2O solution. Transients were acquired every 3 s to allow enough time for relaxation of the quaternary carbons. At least 900 transients were collected for each spectrum.

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