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Mechanism of Elimination from (1-Anilino-1-cyanoethyl)benzene Promoted by Sodium Methoxide in Methanol

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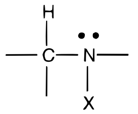
Introduction

Extensive studies on the imine-forming elimination reactions have revealed that the reactions are much more facile than the corresponding alkene-forming eliminations and proceed via E2-central or E1-like transition states.[2] For MeONa-promoted eliminations from $ArCH_2N(OSO_2Ar)R$, a competing E2 and $(E1)_{ip}$ mechanism was also reported.[3] All of these studies utilized **1**, in which the leaving group is attached to the nitrogen. Accordingly, many of the characteristics of the imine-forming eliminations have been attributed to the weaker strength of the N−X bond and greater C=N bond energy than those involved in the corresponding alkene-forming eliminations.

In contrast, little is known about the imine-forming eliminations from **2**, in which the leaving group is attached to the carbon. Since C−X and N−H bonds are stronger than N−X and C−H bonds, respectively,[4,5] eliminations from **1** are expected to be more exothermic than those from **2**. On the other hand, the N−H bond is more acidic than the C−H bond.[6,7] Hence, if the acidity of the *β*-proton is more important, the latter should react at a faster rate. However, the relative importance of these two opposing factors on the imine-forming eliminations has not been investigated in detail.



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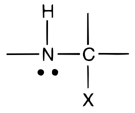

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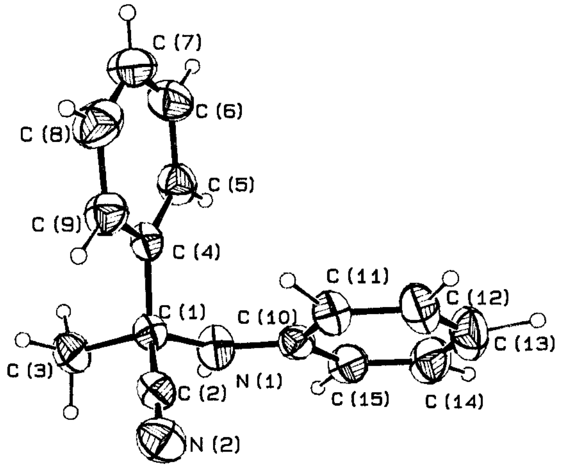
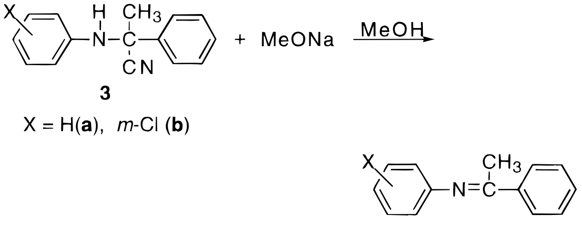


Figure 1. ORTEP representation of the (1-anilino-1-cyanoethyl)benzene structure.

It has been reported that the pyrolytic elimination of (1-anilino-1-cyanoethyl)benzene proceeds at 210 °C to afford *N*-phenylacetophenonimine in high yield.[8] The result is somewhat surprising considering the facility of the imine-forming elimination reactions. In order to add to the meager store of information available concerning imine-forming eliminations from **2**, we have investigated the reactions between (1-anilino-1-cyanoethyl)benzenes **3** with MeONa in MeOH (eq 1). We have determined the X-ray structure of the reactant and measured the reaction rates. The mechanism of the reactions is assessed by the use of the transition state parameters. The results of these studies are reported here.



3

X = H(**a**), *m*-Cl (**b**)

4

(1)

Results and Discussion

(1-Anilino-1-cyanoethyl)benzenes **3** were synthesized by reacting aniline, acetophenone, and NaCN by the literature method.[8] The X-ray structure of **3a** reveals that the two phenyl groups are nearly orthogonal to each other, and the dihedral angle between the N−H and the C−CN bonds is 105.2° (Figure 1), which is close to 90°, which is the most unfavorable angle for elimination reactions.[9] Therefore, the high temperature required for the pyrolytic elimination from **3a** may in part be ascribed to the unfavorable dihedral angle.

Reaction of **3a** with MeONa in MeOH produced only *N*-phenylacetophenonimine. Rates of eliminations from **3** were followed by monitoring the increase in the absorption at 243−244 nm. Rate constants for MeONa-promoted eliminations from **3** are listed in Table 1. The second-order rate constant $k_2 = 2.81 \times 10^{-4}\ M^{-1}\ s^{-1}$ at 40.0 °C for MeONa-promoted elimination from **3a** is approximately 130-fold smaller than $k_2 = 3.65 \times 10^{-2}\ M^{-1}\ s^{-1}$ for MeONa-promoted eliminations from *N*-chloro-*N*-methylbenzylamine at 39.0 °C.[10] Although a direct comparison of these rate constants may not be very meaningful because the two reactions proceed by different mechanisms (*vide infra*), the slower rate of **3a** can

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[1] (a) Korea University. (b) Sook Myung Women's University.

[2] Hoffman, R. V.; Bartsch, R. A.; Cho, B. R. *Acc. Chem. Res.* **1989**, *22*, 211−217.

[3] Cho, B. R.; Pyun, S. Y. *J. Am. Chem. Soc.* **1991**, *113*, 3920−3924.

[4] Bond energies for C−H, C−Cl, CH_3−OH, N−H, N−Cl, and CH_3N−OH are 85, 80, 80, 62, 90, and 50, respectively,[5] indicating that the N−H and C−X bonds are stronger than the C−H and N−X bonds.

[5] Dean, J. A. *Handbook of Organic Chemistry*; McGraw-Hill: New York, 1987; pp 3-13−3-37.

[6] The pK_a values of HCl, HCN, $C_6H_5NH_2$, and $C_6H_5CH_3$ in DMSO are 1.8, 12.9, 30.6, and 43, respectively.[7] Although the corresponding values determined in MeOH are not available in the literature, the relative acidities may be assumed to be nearly the same in both solvents.

[7] Bordwell, F. G. *Acc. Chem. Res.* **1986**, *21*, 456−463.

[8] Dew, E. N.; Richie, P. D. *Chem. Ind.* **1969**, 51−52.

[9] Bartsch, R. A.; Zavada, J. *Chem. Rev.* **1980**, *80*, 453−494.

[10] Bartsch, R. A.; Cho, B. R. *J. Am. Chem. Soc.* **1979**, *101*, 3587−3591.

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Table 1. Second-Order Rate Constants for Eliminations from $XC_6H_4NHC(CN)(CH_3)C_6H_5$[a] Promoted by MeONa in MeOH

X	T, °C	[MeONa]	10^4k_2, M^{-1} s^{-1} [b,c]
H	40.0	1.00	2.91 ± 0.01
H	40.0	0.510	2.75 ± 0.01
H[d]	40.0	0.640	2.50 ± 0.02
H	50.0	1.00	6.28 ± 0.05
H	60.0	1.00	14.9 ± 0.1
m-Cl	40.0	1.00	8.13 ± 0.01
m-Cl	40.0	0.760	7.66 ± 0.01

[a] [Substrate] = $(2-3) \times 10^{-5}$ M. [b] $k_2 = k_{obs}$/[MeONa]. [c] Average and standard deviation for two or more kinetic runs. [d] The base–solvent was MeONa–MeOD.

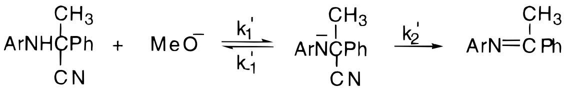
Table 2. Transition State Parameters for Eliminations from $ArCH_2N(Cl)CH_3$ and $ArNHC(CN)(CH_3)Ph$ Promoted by MeONa in MeOH

	$ArCH_2N(Cl)CH_3$[a]	$ArNHC(CN)(CH_3)Ph$
rel rate	130	1
k_H/k_D	6.0 ± 0.1	<2.5[b]
ρ	1.52 ± 0.06	1.1 ± 0.1
$\Delta H^‡$, kcal/mol	16.6 ± 0.1	16.3 ± 0.9
$\Delta S^‡$, eu	−12.1 ± 0.3	−22.7 ± 1.6

[a] Reference 10. [b] Estimated from $k_2^{MeOH}/k_2^{MeOD} = 1.1$ and the maximum solvent isotope effect (see text).

at least in part be attributed to the poor leaving group ability of CN and the unfavorable dihedral angle.[11]

The reactions are second order as indicated by the pseudo-first-order kinetics and nearly identical k_2 values for 2- to 4-fold variations in base concentration (Table 1). Therefore, all but bimolecular mechanism can be ruled out. In addition, the rate of β-protium exchange was much faster than the elimination reaction (see Experimental Section). This result clearly establishes that the reaction proceeds by the $(E1cB)_R$ mechanism, in which the preequilibrium deprotonation is followed by the rate-limiting elimination (eq 2).



$$ArNH\overset{CH_3}{\underset{CN}{C}}Ph + MeO^- \underset{k_1'}{\overset{k_1'}{\rightleftharpoons}} Ar\overset{-}{N}\overset{CH_3}{\underset{CN}{C}}Ph \xrightarrow{k_2'} ArN{=}\overset{CH_3}{C}Ph \quad (2)$$

The primary isotope effect was estimated from the rate ratio, $k_2^{MeOH}/k_2^{MeOD} = 1.1$, for reactions of **3a** with MeONa in MeOH and MeOD. Since the N–H bond must be completely converted into N–D in MeOD before the elimination reaction takes place (*vide supra*), this value includes both the primary isotope effect and the medium effect. For MeONa-promoted deprotonation reaction in MeOH, the maximum solvent isotope effect has been estimated to be $K_D/K_H = 2.5$.[13] Hence, the primary isotope effect value for this reaction should be less than 2.5 (Table 2). The small isotope effect value is in good agreement with the $(E1cB)_R$ mechanism, in which the proton transfer occurs before the rate-limiting step.[14] The Hammett ρ value of 1.1 calculated with the rate data for **3a** and **3b** provides additional support for this mechanism (Table 2). An electron-withdrawing substituent would increase the acidity of the N–H bond to enhance the equilibrium constant for the first step. On the other hand, it should also stabilize the negative charge developed at the nitrogen atom to decrease the rate of elimination. A combination of these two opposing factors should give rise to a small ρ value, as observed.[15] The activation parameters calculated for this reaction are also in accord with this interpretation. The enthalpies of activation for eliminations from **3a** and *N*-chloro-*N*-methylbenzylamine are the same despite the poorer leaving group and unfavorable dihedral angle in the former (*vide supra*). This result underlines the importance of the acidity of the β-proton in determining the activation enthalpy. In contrast, the entropy of activation for **3a** is more negative than that for the latter by approximately 11 eu. Since more solvent reorganization would be required to solvate the more carbanionic transition state, the entropy of activation should be more negative. Hence, the large difference in rates results from an entropic factor.

In conclusion, the reactions of **3** with MeONa in MeOH proceed by the $(E1cB)_R$ mechanism. It appears that the concerted E2 mechanism is disfavored by the poor leaving group and the unfavorable dihedral angle, and the $(E1cB)_R$ mechanism becomes the favored alternative probably because the nitrogen anion can be stabilized by solvation in MeOH.

Experimental Section

Materials. (1-Anilino-1-cyanoethyl)benzenes **3a,b** were synthesized by reacting aniline, acetophenone, and NaCN by the literature method.[8] *N*-Arylacetophenonimines **4a**,**b** were obtained by the pyrolysis of **3a,b** at 210 °C as reported in the literature.[8] The melting points and the spectroscopic data of the compounds were consistent with the structures.

X-ray Crystallography. The compound was crystallized from ethanol solution. Crystal data were obtained with using an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Cu Kα radiation ($\lambda = 1.5416$ A). The crystal ($C_{15}H_{14}N_2$, $M_r = 222.28$) is monoclinic, $P2_1$, with $a = 5.929(1)$ Å, $b = 8.427(1)$ Å, $c = 12.500(1)$ Å, $\beta = 99.91(1)°$, $Z = 2$, $F(000) = 236$, $T = 293$ K, $D_c = 1.20$ g/cm^3.

The 1087 independent reflections were measured with the range of $2° \leq 2\theta \leq 130°$, of which there were 1074 reflections with $|F_o| > 4\sigma|F_o|$. The structure was solved by direct methods and refined by the full-matrix least-squares using the program SHELXS-93.[16] The final R and weighted Rw values were 0.086 and 0.161 for 1074 observed reflections, respectively. The final atomic coordinates and thermal parameters for the non-hydrogen atoms, bond lengths, bond angles, and torsion angles are available from one of the authors (Y.J.P.) and have been deposited with the Cambridge Crystallographic Data Centre.[17]

Kinetic Studies. All of the reactions were followed using a UV–vis spectrophotometer with thermostated cuvette holders. Reactions were monitored by the increase in the absorption of the product at 243 and 244 nm for **3a** and **3b**, respectively, under pseudo-first-order conditions employing at least a 10^4-fold excess

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[11] A reviewer raised a question whether the solid-state structure for **3a** is the same as that in MeOH. An ab initio calculation with the Gaussian 94 program with the STO-3G basis set[12] reveals that the gas phase structure is very similar to that in the solid state except that the dihedral angle between the N–H and C–CN bonds is 81.605°. Therefore, it seems reasonable to assume that the solution-state structure for **3a** should also be similar to that in the solid-state.

[12] *Gaussian 94*, Gaussian Inc., Pittsburgh, PA, 1995.

[13] (a) Gold, V; Morris, K. P.; Wilcox, C. F. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1615–1620. (b) More O'Ferall, R. A. *J. Chem. Soc., Chem. Commun.* **1969**, 114–115.

[14] (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper and Row: New York, 1987; pp 591–560. (b) Gandler, J. R. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; Wiley: Chichester, 1989; Vol. *2*, Part 1, pp 734–797.

[15] Cary, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990; Part A, pp 196–209.

[16] Sheldrick, G. M. *SHELXS-86 and SHELXL-93, Program for Crystal Structure Determination*; Cambridge University Press: Cambridge, 1986, 1993.

[17] The author has deposited atomic coordinates for (1-anilino-1-cyanoethyl)benzene with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

of base as described before.[3,10] In almost every case, plots of $-\ln (A_\infty - A_t/A_\infty - A_o)$ vs time were linear over at least 2 half-lives. The slope was the pseudo-first-order rate constant. However, when the methoxide ion concentration was lower than 0.51 M, the reactions were too slow to follow to completion conveniently. Therefore, a Guggenheim method was employed.

H−D Exchange Experiment. The H−D exchange experiment was conducted by dissolving a small amount of **3a** in CD_3OD. The NMR spectrum immediately after preparing the sample showed that the N−H signal that appeared at δ 4.2 in $CDCl_3$ was completely absent, indicating that the exchange rate is reasonably fast.

Product Studies. The yields of *N*-arylacetophenonimine, determined by comparing the UV absorbances of the infinity samples of the kinetic runs with those of authentic samples of **4**, were in the range 75−100%. To isolate the elimination product, (1-anilino-1-cyanoethyl)benzene (**3a**) (1.0 g, 4.5 mmol) and MeONa (65 mmol) were reacted in 35 mL of MeOH for 20 h at room temperature. The product was isolated by extracting the aqueous layer with petroleum ether. Evaporation of the solvent produced 0.50 g (57%) of *N*-phenylacetophenonimine as a yellow solid: mp 38−41 °C (lit.[8] mp 37−41 °C).

Control Experiments. The stability of **3** and **4** and their solutions was determined by measuring the melting point and periodical scanning of the solutions with the UV spectrophotometer. No change in melting point or UV spectrum was detected for **3** and its solution during 4 months in the refrigerator. However, the dilute solution of **4** in MeOH (10^{-5} M) started to hydrolyze to acetophenone and aniline by the small amount of water present as an impurity after 12 h at room temperature.

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