Reactions of *N*-Halogenobenzylmethylamines with Triethylamine in Acetonitrile. Effect of Leaving Group upon the Imine-forming Transition State

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Reactions of *N*-halogenobenzylmethylamines (**1**) and (**2**) with Et_3N–MeCN have been investigated kinetically. Eliminations from (**1**) and (**2**) were quantitative and regiospecific, producing only benzylidenemethylamines. For the elimination reaction of (**1**) with Et_3N, k_H/k_D 5.7, ρ 0.88, $\Delta H^‡$ 9.1 kcal mol^{-1}, and $\Delta S^‡$ −42.4 cal mol^{-1} K^{-1} were determined. The transition-state structure is assessed as being highly symmetric with similar extents of C_β–H and N_α–Cl bond cleavage, little carbanionic character, and significant π-bond formation. The structure of the transition state changes only slightly with the change in the leaving group from Cl to Br.

Recently we have reported kinetic studies of base-promoted, imine-forming eliminations from *N*-halogenobenzylmethylamines.[1–4] When the leaving group was chlorine and the base–solvent combination MeONa–MeOH, Bu^{t}OK–Bu^{t}OH, or R_2NH–MeCN, the reactions proceeded by a normal *E*2 mechanism *via* an *E*2-central type of transition state with appreciable C_β–H and N_α–Cl bond cleavage and significant double-bond character.[1–4] On the other hand, when bromide was the leaving group the reactions were complicated by competing bimolecular elimination and nucleophilic substitution at halogen.[3] However, the structure of the imine-forming transition state was relatively insensitive to variation of the leaving group from Cl to Br.[3] The result is somewhat surprising in view of the fact that the reactions of $ArCH_2NHOSO_2Ar$ with benzylamine proceed *via* an *E*1-like transition state[5–7] even though OTs is known as a poorer leaving group than Br in elimination reactions.[8] At this stage it is not possible to deduce whether the small difference in the transition-state structure for *N*-halogenoamine eliminations results from the intrinsic properties of the *N*-halogenoamines or because the substitution reaction predominates before the N_α–Br bond can be fully stretched in the imine-forming transition state.

To assess the influence of the change to a better leaving group in *N*-halogenoamine eliminations it seems necessary to conduct the reactions under conditions where they proceed by a clean *E*2 mechanism. Accordingly we have investigated the reactions of *N*-chlorobenzylmethylamines (**1a**—**f**) and *N*-bromobenzylmethylamines (**2a**—**f**) with Et_3N–MeCN under the same experimental conditions. It was expected that the combination of tertiary amine base and aprotic solvent would completely suppress the substitution reaction and increase the extent of N_α–X bond cleavage in the transition state.[3,4]

$$YC_6H_4CL_2N(X)CH_3 + Et_3N \xrightarrow{MeCN} YC_6H_4CL{=}NCH_3 \quad (1)$$

(**1**) X = Cl (**3**)
(**2**) X = Br

a; Y = L = H
b; Y = H, L = D
c; Y = *p*-CH_3O, L = H
d; Y = *m*-Br, L = H
e; Y = *m*-NO_2, L = H
f; Y = *p*-NO_2, L = H

Results

Reactions of (**1**) and (**2**) with Et_3N–MeCN produced only *N*-benzylidenemethylamines (**3**). Eliminations were followed by monitoring the appearance of absorption at the wavelength of maximum absorption for the *N*-benzylidenemethylamines (**3**) in the region 240—280 nm.[2] Excellent pseudo-first-order kinetic plots which covered at least two half-lives were obtained. Pseudo-first-order rate constants were divided by the base concentration to provide second-order rate constants which remained constant for 10-fold variations in base concentration (Tables 1 and 2).

Both (**1**) and (**2**) were found to be stable in MeCN for periods of time similar to those used for the base-promoted elimination reactions.

Rates of elimination from (**1a**) and (**2a**) promoted by Et_3N–MeCN were measured at four temperatures spanning 40 °C. Arrhenius plots were linear with excellent correlation coefficients. Calculated enthalpies and entropies of activation are presented in Tables 3 and 4.

The influence of aryl substituents upon elimination rates

Table 1. Rate constants for elimination from $ArCH_2N(Cl)CH_3$ promoted by Et_3N–MeCN[a]

Compound[b]	t/°C	$10^3\,k_2$/l mol^{-1} s^{-1} [c]
(**1a**)	25.0	0.648
(**1a**)	35.0	1.10
(**1a**)	45.0	1.90
(**1a**)	55.0	2.86
(**1b**)	25.0	0.113
(**1c**)	25.0	0.418
(**1d**)	25.0	1.46
(**1e**)	25.0	2.75
(**1f**)	25.0	7.78

[a] $[Et_3N]$ 5.00 × 10^{-3}—2.00 × 10^{-2}M. [b] [Substrate] 5.0—7.0 × 10^{-5}M. [c] Estimated uncertainty, ±3%.

Table 2. Rate constants for elimination from $ArCH_2N(Br)CH_3$ promoted by Et_3N–MeCN[a]

Compound[b]	t/°C	$10^3\,k_2$/l mol^{-1} s^{-1} [c]
(**1a**)	25.0	2.18
(**1a**)	35.0	3.19
(**1a**)	45.0	5.02
(**1a**)	55.0	8.09
(**1b**)	25.0	0.343
(**1c**)	25.0	1.51
(**1d**)	25.0	5.22
(**1e**)	25.0	8.65
(**1f**)	25.0	19.9

[a] $[Et_3N]$ 5.00 × 10^{-3}—2.00 × 10^{-2}M. [b] [Substrate] 5.0—7.0 × 10^{-5}M. [c] Estimated uncertainty, ±3%.

Table 3. Transition-state parameters for eliminations from $ArCH_2N(Cl)CH_3$ promoted by Bu_2NH and Et_3N in MeCN at 25.0 °C

Base-solvent	Bu_2NH-MeCN[a]	Et_3N-MeCN
pK_a	18.3	18.4
Rel. rate	1	0.3
ρ	0.98	0.88
k_H/k_D	8.8 (β 0.41)	5.7
k_{Br}/k_{Cl}	24.1 (β_{lg} −0.41)	33.6 (β_{lg} −0.45)
$\Delta H^{\ddagger}$/kcal mol^{-1}	7.6	9.1
$\Delta S^{\ddagger}$/cal mol^{-1}	−45.1	−42.4
$\Delta G^{\ddagger}$/kcal mol^{-1}	21.0	21.7

[a] Ref. 4.

Table 4. Effect of leaving group upon transition-states for elimination from $ArCH_2N(X)CH_3$ promoted by Et_3N-MeCN at 25.0 °C

Compound	**(1a)**	**(2a)**
ρ	0.88[a] (r[b] 0.997)	0.79[c] (r[b] 0.997)
k_H/k_D	5.7	6.4
$\Delta H^{\ddagger}$/kcal mol^{-1}	9.1	7.9
$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}	−42.4	−39.6

[a] For (**1a**—**f**). [b] Correlation coefficient. [c] For (**2a**—**f**).

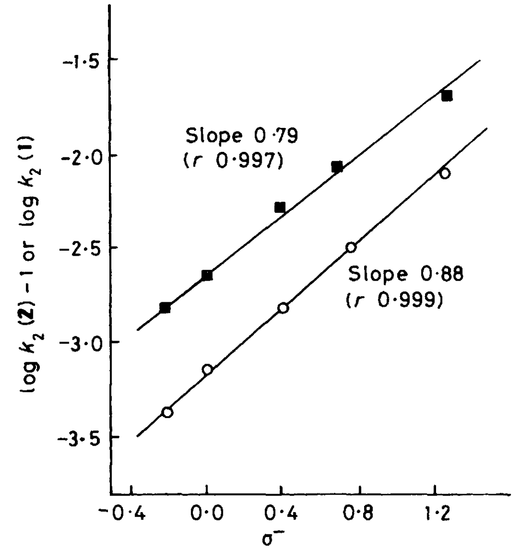

Figure 1. Hammett plots for eliminations from $ArCH_2N(Cl)CH_3$ (○) and $ArCH_2N(Br)CH_3$ (■) promoted by Et_3N-MeCN

correlated satisfactorily with the Hammett equation using σ^- values (Figure 1). Hammett ρ values are given in Tables 3 and 4.

From the rate coefficients for eliminations from (**1a**) and (**2a**) and their deuteriated analogues (**1b**) and (**2b**) at 25.0 °C, primary deuterium isotope effect values were calculated. The values are listed in Tables 3 and 4.

Discussion

Mechanism of Reactions between N-*Halogenoamines and* Et_3N-MeCN.—Earlier we reported that reactions of (**1**) with MeONa-MeOH, Bu^{t}OK-Bu^{t}OH, and R_2NH-MeCN produced (**3**) quantitatively, but those of (**2**) with the same base-solvent systems afforded (**3**) and benzylmethylamines.[3,4] The formation of the amine product was attributed to the nucleophilic substitution reaction at halogen, which is assisted by the hydrogen bond to the departing nitrogen.[3] In contrast, when the same substrates were treated with Et_3N in MeCN, only (**3**) was formed. Since hydrogen bonding is not possible under the present reaction conditions, the results provide additional support for the proposed mechanism for the substitution reaction.

The kinetic investigation and control experiments establish that the reactions of (**1**) and (**2**) with Et_3N-MeCN proceed *via* an *E*2 mechanism. Since (**1**) and (**2**) were stable in MeCN and the reactions exhibited second-order kinetics, all except bimolecular pathways can be ruled out. In addition an *E*1cb mechanism is negated by the substantial values of the primary deuterium isotope effect and the element effect of the leaving group (Table 3).[9]

Transition State for Elimination from (**1**) *promoted by* Et_3N-MeCN.—Comparison of transition-state parameters for base-promoted eliminations from (**1**) (Table 3) reveal that the structure of the transition state changes appreciably when the base is changed from Bu_2NH to Et_3N even though the pK_a values of the bases are nearly the same. The Hammett ρ value for Et_3N-promoted elimination from (**1**) is 0.88, which is slightly smaller than that for Bu_2NH-promoted elimination from the same substrate. Thus the carbanionic character of the transition state decreases slightly with this variation of the base.

The primary deuterium isotope effect indicates the extent of proton transfer in the transition state. Previously it has been shown that the k_H/k_D value increases to the maximum of 8.8 with Bu_2NH, and then decreases as the base strength increases in eliminations from (**1**) promoted by R_2NH-MeCN. Together with β 0.41, the maximum isotope effect value observed with Bu_2NH has been interpreted as indicating *ca.* 0.4 proton transfer in the transition state.[4] If a similar trend of isotope effect with the base strength variation is assumed for tertiary amines[10] the less than maximum isotope effect observed in the present study may be interpreted as either a greater or a smaller extent of proton transfer than 0.4. However, since Et_3N would be more hindered than Bu_2NH from attack on the C_β-H bond for steric reasons, the former interpretation is favoured.

The leaving group element effect for elimination from *N*-halogenobenzylmethylamines promoted by Et_3N-MeCN is 33.6. Utilizing this k_{Br}/k_{Cl} ratio, pK_a^{HCl} 8.9, and pK_a^{HBr} 5.5 in MeCN,[11] β_{lg} −0.45 is calculated. This is somewhat greater than that for Bu_2NH-promoted elimination from (**1**) and indicates a significant degree of N_α-Cl bond cleavage in the transition state.

The combined results reveal that the transition state for Et_3N-promoted elimination from (**1**) is more product-like than that for Bu_2NH-promoted elimination. Thus it appears that the structure of transition state for reaction of (**1**) with Et_3N-MeCN is highly symmetrical with approximately half-broken C_β-H and N_α-Cl bonds, little carbanionic character, and well developed double-bond character.

The change in the transition state structure with variations in the base can be attributed to the base-steric effect. Since Et_3N is bulkier than Bu_2NH it would be more hindered from attack on the C_β-H bond, and thus the extent of C_β-H bond breaking would be increased in the transition state. Moreover, it has been suggested that the symmetric transition state would be more stable than the *E*1-like or *E*1cb-like transition state in aprotic solvents, because the latter cannot be stabilized by solvation.[4] Therefore, the transition state for Et_3N-promoted elimination from (**1**) should become more product-like with a greater extent of C_β-H and N_α-Cl bond cleavage and extensive double-bond character in order to maintain a symmetric structure.

Effect of Leaving Group upon the Imine-forming Transition State.—For eliminations from *N*-halogenobenzylmethylamines promoted by Et_3N in MeCN, the Hammett ρ value decreases

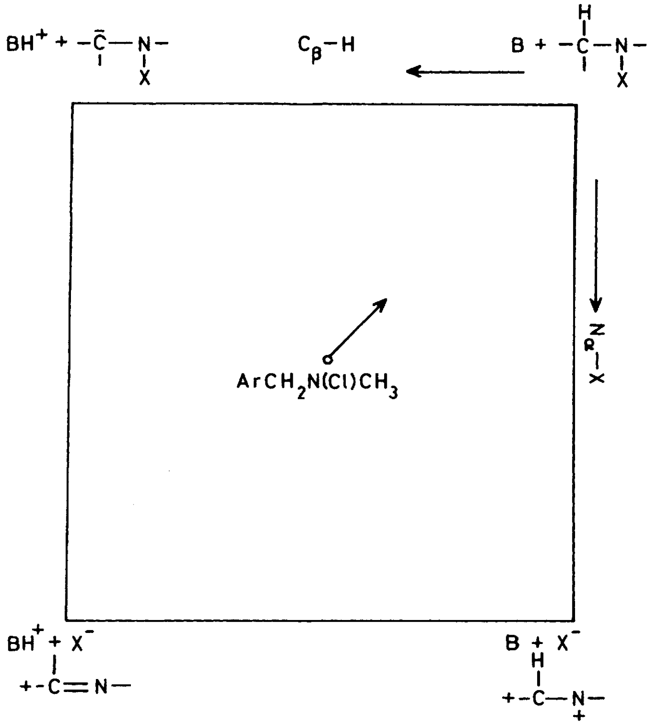

Figure 2. Reaction co-ordinate energy diagram from reactions of $ArCH_2N(X)CH_3$ with Et_3N-MeCN. Energy contours are omitted. Effects of change to a better leaving group upon the transition-state position is shown by solid line

slightly but the k_H/k_D value increases as the leaving group is changed from Cl to Br (Table 3). The results can readily be rationalized by assuming predominant parallel motion in the reaction co-ordinate diagram.[12,13]

As previously mentioned, the transition state for elimination from (**1**) promoted by Et_3N-MeCN is highly symmetrical with approximately half-broken C_β-H and N_α-Cl bonds and thus can be located near the centre of the reaction profile. A change to a better leaving group would increase the energy of the reactant and the *E*1cb intermediate. If parallel motion is assumed to be predominant,* the transition state would then move along the reaction co-ordinate toward the reactant (Figure 2). Thus the extent of C_β-H bond breaking would be decreased but the transition-state carbanionic character would remain nearly the same. This would predict that the ρ value should change only slightly and the k_H/k_D value should increase with variations in the leaving group if the change in the structure of the corresponding transition state is small,† as observed. The changes in $\Delta H^\ddagger$ and $\Delta S^\ddagger$ with variations in the leaving group are also in agreement with this interpretation. Since the transition state becomes more reactant-like with Br as the leaving group, the enthalpy of activation should decrease. In addition, the entropy of activation is also expected to increase because the reactant-like transition state would have less charge separation and thus would require less solvent reorganization to solvate the transition state.

These results are similar to those for MeONa-promoted eliminations from *N*-halogenobenzylmethylamines in MeOH.[3] Thus the ρ value decreased only slightly and k_H/k_D remained the same with a change of the leaving group from Cl to Br. It should be noted that the effect of the leaving group upon the structure of the imine-forming transition states does not differ significantly with a change in the base–solvent system from MeONa–MeOH to Et_3N–MeCN, even though the competing substitution reaction is completely suppressed and the N_α–X bond is more extended in the transition state with Et_3N–MeCN as the base–solvent system. Thus it appears that the small difference in the transition-state structure with a change in the leaving group in these reactions does not result from the complication of a competing substitution reaction but from the intrinsic nature of the *N*-halogenoamine elimination.

A possible explanation for this result may be related to the energies of the bonds involved in these reactions.‡ Since the C=N bond is *ca.* 75 kcal mol^{-1} stronger than the corresponding single bond and the bond dissociation energy of N–Cl is *ca.* 50 kcal mol^{-1},[14] the formation of a C=N bond would have more influence than N–Cl bond cleavage on the energy of the transition states. Moreover, the difference in bond energy between N–Cl and N–Br is anticipated to be rather small.§ Therefore, the structure of the transition state for *N*-halogenoamine elimination should be relatively insensitive to the leaving-group variation as long as the transition state has significant π-bond character.

Experimental

Reagents.—*N*-Benzylidenemethylamines (**3**) and *N*-benzylmethylamines were available from previous investigations.[1–4] *N*-Chlorobenzylmethylamines (**1**) were prepared by the reaction of *N*-benzylmethylamine with *N*-chlorosuccinimide in pentane. The mixture was stirred for 20 min and filtered through a sintered glass funnel. MeCN (5ml) was added to the pentane solution and pentane was removed *in vacuo*. The resulting acetonitrile solution of (**1**) was diluted to 10.0 ml with MeCN.

N-Bromobenzylmethylamines (**2**) were prepared in similar fashion using *N*-bromosuccinimide. Owing to the lower stability of (**2**) than (**1**), acetonitrile solutions were freshly prepared before kinetic runs.

Reagent grade acetonitrile and triethylamine were fractionally distilled from CaH_2.

Kinetic Studies of Elimination from (**1**) *and* (**2**).—Base-promoted eliminations from (**1**) and (**2**) were followed by monitoring the increase of absorption at the wavelength of maximum absorption for (**2**) with time, using a Cary 17D

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* For reactions of (**1**) with R_2NH–MeCN, the parallel effect was assumed to be predominant because the curvature of the potential energy surface in the perpendicular direction was estimated to be much greater than that in the parallel direction, due to the increased energy of the *E*1 and *E*1cb intermediates and the product resulting from poor solvation in MeCN.[4] Since Et_3N–MeCN is very similar to Bu_2NH–MeCN in every respect, the parallel effect can also be assumed to the predominant for the present system.

† For reactions of (**1**) with R_2NH-MeCN, the k_H/k_D value increased to a maximum of 8.8 with *ca.* 0.4 proton transfer, and then decreased as the extent of C_β–H bond cleavage decreased in the transition state.[4] Assuming a similar trend for Et_3N-promoted elimination from (**1**), the k_H/k_D value of 5.7 observed for *ca.* 0.5 proton transfer should increase until it reaches a maximum with 0.4 proton transfer. However, a further decrease in the extent of C_β–H bond rupture should decrease the k_H/k_D value.

‡ As a referee pointed out, the prediction of transition-state structure based on the bond energy changes is very difficult. However, if there is no way to observe the transition state directly, at least a qualitative interpretation of the observed trend should be possible based on ground-state energies.

§ Although bond energies for H_2N–Cl and H_2N–Br or related nitrogen–halogen bonds are not known, the bond energies for CH_3–Cl, CH_3–Br, HO–Cl, and HO–Br or 84, 70, 60, and 56 kcal mol^{-1}, respectively.[15] The lower difference for the latter pair indicates that the corresponding difference for nitrogen–halogen bonds should be smaller than 14 kcal mol^{-1} noted for carbon–halogen bonds.

spectrophotometer with a thermostatted cuvette holder as described previously.[1] Reactions were followed under pseudo-first-order conditions employing at least a ten-fold excess of base. Plots of $-\ln(A_\infty - A_t/A_\infty - A_0)$ *versus* time were linear over at least two half-lives of the reaction. The slope was the pseudo-first-order rate constant. The pseudo-first-order rate constants were divided by the base concentration to afford the second-order rate constants, k_2. The k_2 values were found to be constant for a ten-fold variation in base concentration.

Product Studies of Elimination from (**1**) *and* (**2**).—Product studies of the reactions of *N*-chloro- and *N*-bromo-benzylmethylamines with Et_3N were carried out by stirring the solution of the *N*-halogenoamine (2.0 mmol), Et_3N (10.0 mmol), and benzene (internal standard, 2.0 mmol) in MeCN (20 ml) for 2 days. The solution was analysed by gas chromatography on a 2 ft × $\frac{1}{8}$ in column of 20% PEG 400 on Chromosorb P at 130 °C. The product was *N*-benzylidenemethylamine from (**1a**) (95%) and (**2a**) (90%). Yields of (**3**) from reactions of other *N*-halogenoamines (**1c**—**f**) and (**2c**—**f**) were determined by comparing the u.v. absorbance of the infinity samples from the kinetic reactions with those for authentic samples. On the basis of the starting amine concentrations, the yields of (**3**) were 90—96%.

Control Experiments.—When solutions of (**1a**) or (**2a**) in MeCN were heated at 55 °C for times comparable with those required to obtain infinity samples from the base-promoted eliminations, no increase in the u.v. absorption at the wavelength of maximum absorbance was noted.

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