Kinetic Effects of Thiourea Addition on Benzylic Solvolyses

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Abstract: Effects of thiourea addition on the solvolysis of benzyl, α-methylbenzyl, and α-*t*-butylbenzyl chlorides were investigated in 50 % aqueous acetone at 45 °C. Logarithmic plots between the second-order rate with thiourea (k_N) and the corresponding solvolysis rate (k_{solv}) provide a scattered pattern of deviations from a straight line defined for the k_c mechanism. Mechanistic change in three solvolyses was discussed based on characteristic deviation behaviors.

McManus and coworkers reported that the rate acceleration due to thiourea addition is a useful probe of nucleophilic assistance in solvolytic reactions[1] since neutral thiourea can eliminate the complexities arising from a kind of salt effect.[1,2] We have attempted to apply their thiourea probe to benzylic solvolyses where continuous mechanistic shift from the limiting k_c[3] to the concerted S_N2 displacement mechanism can be caused by electronic and/or structural perturbation. Solvolysis of primary benzyl chlorides (I) is a typical case of borderline mechanism, which changes widely with ring substituent.[4—6] Solvolysis of α-methylbenzyl chlorides (II) is another borderline case in controversy;[7,8] the S_N1 solvolysis has been established from the Yukawa-Tsuno substituent effect analysis, while nucleophilic involvement has been pointed out for deactivated derivatives in high nucleophilic solvents.[9,10a] Solvolysis of α-*t*-butylbenzyl system (III) is proven to be a k_c mechanism based on the substituent and solvent effect analyses for the whole range of substituents[10] and offers a standard for the behavior of secondary S_N1 systems. The present work investigates the mechanistic shift of primary and secondary benzylic substrates by the comparison with the behavior for system III in the presence of a strong nucleophile, thiourea.

Solvolysis rates of chlorides I—III were followed conductimetrically in the presence or the absence of thiourea in 50 (v/v) % aqueous acetone (50A) at 45 °C where most extensive data can be obtained directly. More than two different concentrations of thiourea were added in the range of 0.05—0.2 mol dm^{-3} at the initial substrate concentration of *ca.* 10^{-4} mol dm^{-3} in 50A. Observed rate constants, k_{obs}, in the presence of thiourea were calculated based on the precise first-order rate plots and are significantly greater than the solvolysis rate constant in the absence of thiourea k_{solv} for all the substrates. Large rate acceleration by the addition of thiourea was observed for I except for more activated derivatives than *p*-SMe. The more the substrate is deactivated, the greater the rate is accelerated. Significant effects were observed for all the substrates, but the rate accelerations in the secondary systems II and III are very small compared with the primary system I. These results reveal that all of these solvolyses should include S_N2 reaction with thiourea along with the ordinary hydrolysis reaction. A precise linearity between k_{obs} and the concentration of thiourea with the intercept of experimental k_{solv} was found for each substrate. These facts suggest that a certain bimolecular reaction of the substrate with thiourea is concurrent with an S_N1 reaction even for the k_c system III, which has a bulky α-*t*-butyl group.

Thus the effect of thiourea on the increasing rate can be described by Eq. (1).[1]

$$k_{obs} = k_{solv} + k_N[N] \qquad (1)$$

where k_N is the second-order rate constant for reaction with thiourea and [N] is the molarity of added thiourea. The k_N for each substrate was calculated from k_{obs} (including k_{solv}) by Eq. (1). The k_N values are summarized in Table 1 together with k_{solv} values. Comparisons of the second-order rates, k_N, with solvolysis rates makes it possible to visualize the extent of nucleophilic assistance. Logarithmic plots between k_N and k_{solv} are shown in Fig. 1. The lines for systems I, II, and III should reflect clearly the difference in solvolysis mechanisms.

The substituent effect on hydrolysis in 50A at 45 °C (abscissa in Fig. 1) was analyzed in terms of the Yukawa-Tsuno equation to reveal the k_c mechanism for systems more reactive than 2-naphthyl for I,[4a] m-halogen derivatives for II,[9a] and whole range of III using 80A at 25 °C for tosylates.[10a] A linear line with a slope of 1.00 (R = 0.9997) was obtained for all the data of III and for those for II with more electron-donating substituents than H. Positive deviations of deactivated derivatives of II are observed though they are not so serious as those observed for I.

It is very important that the k_c substrates in II and III define a linear line with a unit slope. This represents the limiting line of S_N2 reaction with thiourea that is closest to limiting solvolysis. Deviation from this k_c line is a relative measure of enhanced nucleophilic character. In Fig. 1, the points for highly activated substrates of I lie so near the k_c line and these solvolyses may be similar to k_c mechanism for II and III. Because of the small steric hindrance in the primary system, this small deviation may be due to slightly stronger S_N2 character than those of k_c derivatives of II and III. Direct nucleophilic attack on the neutral substrate of the strongly activated p-OMe and 4-OCH₂O-3 derivatives is not enhanced significantly more than found for k_c systems II and III and reaction with thiourea proceeds through a loose S_N2 transition state with positive charge

Table 1. Summary of the k_{solv} and the k_N Values of the Reaction with Thiourea in the Solvolysis of Benzylic Chlorides in 50 % Aqueous Acetone at 45 °C

Substrate	$10^5 k_{solv}$ (s^{-1})	$10^5 k_N$ (s^{-1}M^{-1})	Substrate	$10^5 k_{solv}$ (s^{-1})	$10^5 k_N$ (s^{-1}M^{-1})
Benzyl (I)			**Benzyl (I)**		
p-OMe	9550[a]	16700	m-F	0.0418[a]	116
4-OCH₂O-3	3770[a]	7350	m-NO₂	0.0187[a]	106
p-SMe	543.4	1470			
p-OPh	76.46	929	**α-Me-Benzyl (II)**		
4-OMe-3-Cl	45.36	864	p-Me	6530[a]	8380
2-Fluorenyl	25.14	963	3,5-Me₂	339.5	447
3,4,5-Me₃	5.963	846	H	95.57	139
4-SMe-3-Br	4.050	442	p-Cl	28.46	58.9
3,4-Me₂	2.948	618	m-Cl	0.8748	6.90
p-Me	1.678	530	m-CF₃	0.165[a]	3.69
4-OMe-3-CN	1.227	432			
2-Naphthyl	0.302[a]	328	**α-t-Bu-Benzyl (III)**		
3,5-Me₂	0.279[a]	299	p-SMe	1740[a]	2090
4-SMe-3-CN	0.227[a]	278	4-OMe-3-Cl	245.4	322
H	0.191[a]	227	p-Me	19.34	23.5
p-Cl	0.109[a]	216	3,5-Me₂	1.091	1.31

a) Extrapolated from the data at other temperatures.

as large as that of III. In the flat region between p-OPh and 2-naphthyl derivatives of I, a drastic mechanistic shift occurs from a loose to a tight S_N2 transition state with thiourea while the hydrolysis remains close to a k_c mechanism.[4a] Though both the reactions with water and with thiourea proceed by an S_N2 mechanism, linearity with a slope of 0.36 (R = 0.98) for derivatives less reactive than the 2-naphthyl derivative indicates that a smaller positive charge is developed in the transition state during the reaction with thiourea than during that with water in 50A. These facts lead to the conclusion that the concerted S_N2 reaction of I with thiourea proceeds always through a tighter S_N2 transition state than that in hydrolysis due to the higher nucleophilicity of thiourea than that of water in 50A. Note the points for p-SMe, 4-OCH2O-3, and p-OMe form a smooth line almost parallel to that for the k_c derivatives in the secondary systems, II and III. Since the system I is primary, it is not necessary to fall on the secondary line.

Previous work with II in high nucleophilic solvents like aqueous ethanol shows that a break occurs after the m-Cl derivative.[9,10a] Large deviations from the k_c line occur with the deactivated II while system III does not show any enhanced k_N even when their k_{solv} reactivities are similar. Since the substituent effect on the hydrolysis of II in 50A shows the k_c mechanism for the entire series, the mechanistic break point in Fig. 1 for the last three substituents must be due to the enhanced S_N2 character when thiourea is added.
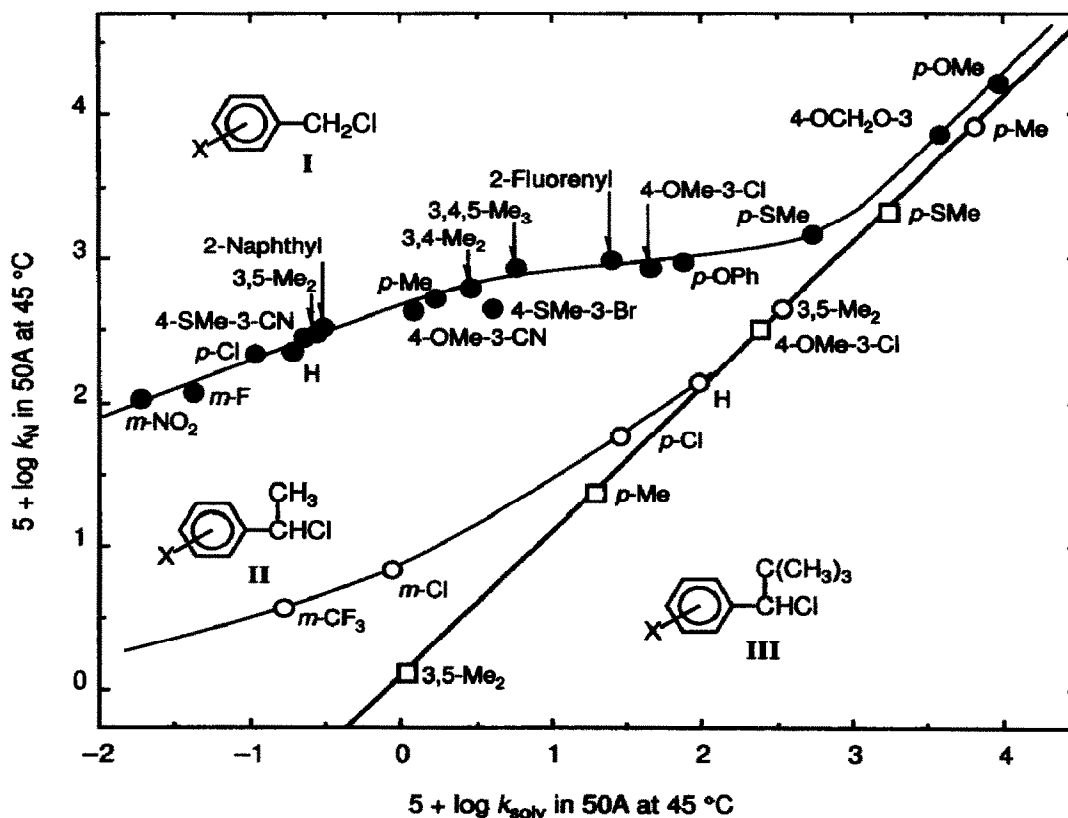

Figure 1. Logarithmic plot between k_N and k_{solv} of I (●), II (O), and III (□) in 50A at 45 °C.

The linear relation with a unit slope for k_c substrates of II and III suggests that the cationic charge developed in a concerted S_N2 transition state with thiourea is essentially as large as that in the carbocationic species from the k_c mechanism. These facts provide very important information about the ultimate position of an S_N2 transition state toward the S_N1 side. The S_N2 reaction never coalesces and exists always concurrently with the k_c reaction regardless of the very close electronic structure for both reactions. These facts provide evidence for the independence of S_N1 and S_N2 reactions. Therefore limiting S_N2 reactions have an extremely loose pentacoordinate transition state. On the other hand, the data demonstrate that the reaction of the deactivated I and II with thiourea proceed through a tighter S_N2 transition state than that with water in 50A. This study shows that the kinetic effect of thiourea is an effective probe for detecting the nucleophilic assistance under usual solvolysis conditions since there is no change in ionic strength. Since there is no way to distinguish between solvent and nucleophile under *pseudo*-first-order solvolysis conditions, it has been impossible to describe the molecularity of solvolysis reactions with concurrent S_N1 and S_N2 mechanisms. Thus the measurement of k_N makes it possible to estimate the sensitivity of a given substrate to the nucleophilicity of an added neutral nucleophile in a solvolysis solvent. Figure 1 shows the spectrum of continuous mechanistic change in benzylic displacement reactions to reveal that this probe is simple but sensitive enough to detect nucleophilic assistance in borderline cases. Further study is in progress.

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