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ABNORMAL DISPLACEMENT REACTION OF 2-(CHLOROMETHYL)FURAN WITH CYANIDE ION

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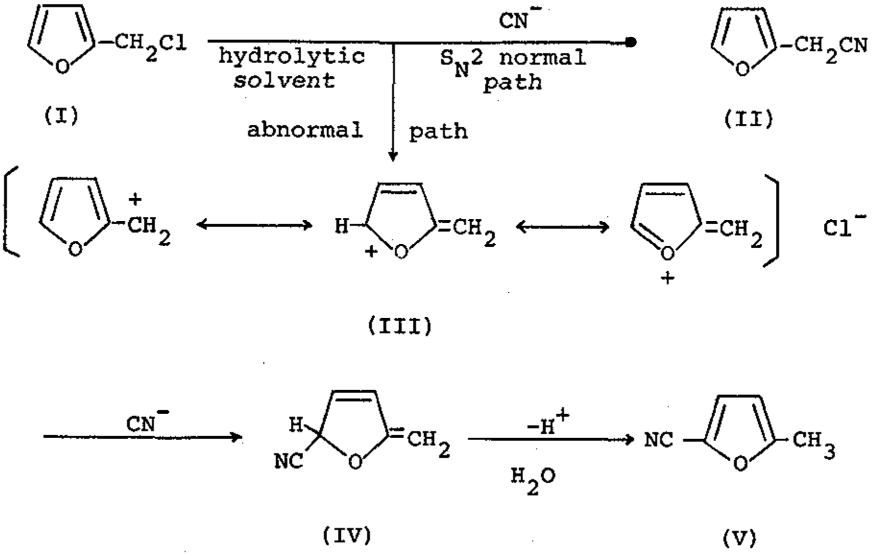
Among similar chloromethyl aromatics, only 2-(chloromethyl)furan (I) gives abnormal displacement product, i.e., 5-methyl-2-cyanofuran(V) in the reaction with cyanide ion in aqueous media.

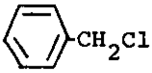
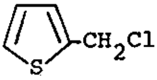
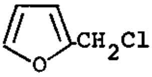
The remarkably high rate of solvolysis of (I), the negligible or small kinetic isotope effect due both to α- or 5-deuterium substitution and other pertinent data suggest the mechanism involving the rate-determining proton transfer in the intermediate, i.e., 5-methylene-2,5-dihydro-2-furonitrile(IV).

Scott and his co-workers reported some three decades ago that the reaction of 2-(chloromethyl)furan(I) with aqueous sodium cyanide gives an abnormal substitution product, i.e., 5-methyl-2-cyanofuran(V) as the major product and 2-(cyanomethyl)furan(II) as the minor product.[1] Later, Komori and his co-workers found that the formation of the abnormal product(V) can be avoided when the reaction was carried out in various aprotic solvents.[2] The formation of the abnormal substitution product(V) has intrigued many workers[3] and the intervention of a relatively stable intermediate(IV) has been suggested[4] and partially substantiated. The mechanism of the over-all reaction may be formulated as shown below. However, the scope and the mechanistic details of the reaction have not been fully investigated yet.



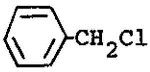
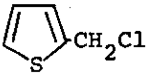
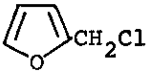
At first we have extended the reaction on similar 2-chloromethyl aromatics, i.e., 2-(chloromethyl)thiophene and benzyl chloride. None of the two chloromethyl aromatics gave any abnormal substitution product and only cyanomethyl derivatives were obtained in the reaction with either potassium or sodium cyanide in 30% (v/v) aqueous acetonitrile, in which the predominant formation of abnormal product was observed with 2-(chloromethyl)-furan. In this case the oxygen atom would make the dissociated ion pair(III) highly stable by resonance stabilization. (vide infra) Since water is considered to assist the A-1 type dissociation of the C-Cl bond and the facile dissociation would lead to the abnormal substitution via the addition of CN^- ion to the dissociated ion pair(III), we have measured, on one hand, the rate of formolyses of three chloromethyl derivatives, for typical S_N1 process and those of their Menshutkin reaction as a model for S_N2 process, on the other.

TABLE I. Rate of Formolyses in 20% Dioxane at 20°C.
($k_1 \times 10^4$ sec^{-1})

		
0.846*	1.51	695.0

* in 100% formic acid at 80°C.

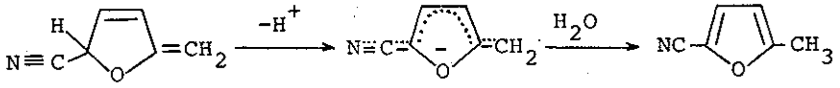
TABLE II. Rate of the Reaction with Various Amines in DMF.
($k_2 \times 10^3$ $M^{-1}sec^{-1}$, at 80°C)

Amines			
Cyclohexylamine	4.81	8.57	12.7
Anisidine	0.498	0.662	2.15
Aniline	0.142	0.270	0.384
Piperidine	55.5	16.6	275.0
Morpholine	20.6	36.8	576.0
Pyridine	0.300	0.706	0.899

As shown in TABLE I and II, although the rates of these chloromethyl compounds in the S_N2 process do not differ so widely, those of formolysis vary in the following order: 2-(chloromethyl)furan > 2-(chloromethyl)thiophene ≫ benzyl chloride, and the furan derivative reacts markedly faster than the other two. Thus, it appears as though the facile S_N1 type C-Cl dissociation is related to the formation of abnormal ring substitution product.

The hydrogen-deuterium kinetic isotope effect(k_H/k_D) was determined with α-dideuterated-2-(chloromethyl)furan in the reaction with sodium cyanide in 30% (v/v) aqueous acetonitrile and found to be 0.98. This suggests clearly that the C-Cl bond cleavage is not involved at the rate-determining step of the reaction, but rather a fast step.

Then , the rate-determining step could either be the addition of the nucleophile to the dissociated ion pair(III), or the proton removal from the addition intermediate(IV). In oder to examine the possibility of the addition of the nucleophiles as the rate-determining step, the kinetic isotope effect was measured with 5-deuterated-2-(chloromethyl)furan under the same condition and found to be 1.24. This value rules out the mechanism involving the rate-determining addition of cyanide ion at the position-5 of the dissociated ion pair(III), since it would require the reverse isotope effect of around 0.8 - 0.9 in the other examples.[5] The other alternative is that the reaction proceeds through the rate-determining proton removal from the addition intermediate(IV). Although the value, k_H/k_D = 1.24, appears to be small, it is not that for the elemental process of proton-removal from the intermediate(IV), but that for the over-all process involving mainly these two steps, i.e., the step of the addition of cyanide ion at the position-5 of (III) and the one of the proton-removal from the addition intermediate(IV). Furethermore, the small isotope effect has been observed in many of the well known base-catalyzed H-D exchange reactions bearing electron-withdrawing substituent.[6]



(IV) (VI) (V)

Undoubtedly the proton-removal is facilitated by the vicinal cyano group in view of the facile H-D exchange of α-methylene hydrogen atoms of the normal product, 2-(cyanomethyl)furan(II). (We observed during the same reaction, both hydrogen atoms are replaced by deuterium when the reaction was carried out in D_2O containing media.) The facile proton-removal could take place by substitution of other nucleophiles. Thus, the possibility of abnormal substitution has been examined with various other nucleophiles, such as PhS^-, SCN^-, $S_2O_3^{2-}$, N_3^-, HCO_2^-, $TlSO_2^-$, piperidine, aniline and cyclohexylamine. However, in no case any abnormal substituion was observed but only the normal substitution products were obtained quantitatively in all cases.

Thus, the abnormal substitution is limited only to the reaction with cyanide ion in aqueous media. This may be rationalized on the basis of the following few reasons: (1) the use of aqueous media would facilitate the A-1 type cleavage of the C-Cl bond, (2) the addition intermediate(IV) would be markedly stabilized by the substituion of an electron-withdrqwing cyano group, moreover, (3) the proton-removal from 5-position will give an intermediate carbanion(VI) which could be stabilized substantially by the through conjugation shown by the formula(VI) and , (4) cyanide ion, inview of its large σ^* value, is basic enough to remove the activated proton, unlike other electronegative nucleophiles.

The small value of activation enthalpy(ΔH^{*}= 11.2, 11.8 kcal/mol) and the large negative value of activation entropy (ΔS^{*}= -33.5, -29.5 eu.) for both abnormal and normal substitution reactions are also in keeping with the suggested mechanism; namely, S_N1 type cleavage of the C-Cl bond, subsequent addition of cyanide ion to form the addition intermediate(IV) and final rate-determining proton-removal for the abnormal substitution reaction to give 2-(cyanomethyl)furan(II).

REFERENCES

1. M. M. Runde, E. W. Scott, and J. R. Johnson, J. Amer. Chem. Soc., 1930, 52, 1284.
2. Y. Ohoshiro, H. Tanisake, and S. Komori, J. Synthetic Org. Chem. Japan, 1966, 24, 950.
3. K. Yu. Noviydkii, Yu. K. Yure'v, and V. N. Zhingrava, Zh. Obsch. Kim., 1962, 32, 3303; Yu. K. Yure'v, and M. A. Galbershtam, Izv. Vyssh. Ucheb. Zaved. Khim. Teknol., 1964, 7, 598; B. Ostman, J. Amer. Chem. Soc., 1965, 87, 3136; S. Noyce, C. A. Lipinski, and R. W. Nichols, J. Org. Chem., 1972, 37, 2615.
4. S. Divald, M. C. Chun, and M. M. Joullìe, Tetrahedron Letters, 1970, 777.
5. S. Oae, and S. Kozuka, ibid., 1965, 1971; S. Seltzer, J. Amer. Chem. Soc., 1961, 83, 1861; M. Feld, A. P. Stefani, and M. Szwarc, ibid., 1962, 84, 4451.
6. D. J. Cram, D. A. Scott, and W. D. Nielsen, ibid., 1961, 83, 3696.

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