February, 1990] © *1990 The Chemical Society of Japan* NOTES *Bull. Chem. Soc. Jpn., 63, 643—645 (1990)* 643

Analysis of Solvent Effects on the Rate of the Cope Rearrangement: Evidence for Its Hydrogen-Bond-Insusceptible Nature

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(Received October 14, 1989)

Synopsis. The kinetic study was made by ^{1}H NMR for the Cope rearrangement of 4,4-dicyano-5-ethyl-1,5-heptadiene in a variety of solvents at 90 °C, which revealed that the reaction is affected by solvent polarity to some extent but is insusceptible to hydrogen bonding with protic solvents, in agreement with our prediction as to solvation of the dipolar transition state for [3,3]sigmatropic reactions.

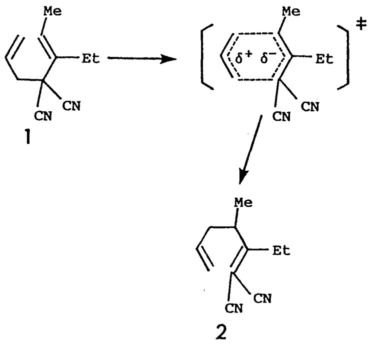
Protic solvents such as methanol and ethanol have generally been accepted as much better ionizing solvents for the substrates undergoing heterolysis than dipolar aprotic solvents such as dimethyl sulfoxide (DMSO) and *N,N*-dimethylformamide (DMF), because common leaving group anions are highly stabilized by hydrogen bonding with protic solvents.[1] We have recently demonstrated that S_N1-E1 reactions can be classified into two types: one is hydrogen-bond-susceptible, and the other hydrogen-bond-insusceptible.[2] In the latter reaction, ionizing power of protic solvents is extremely weakened because of the extensive charge dispersal in the leaving group anion so that the order of the rates is inverted between the above-mentioned protic and aprotic solvents. As another interesting pattern of the reaction that excludes the solvation due to hydrogen bonding, we have also reported an azo Cope rearrangement[3] and a thione-to-thiol conversion reaction.[3,4] These [3,3]-sigmatropic rearrangements proceed via dipolar transition states, in which both termini of the negatively charged fragment are blocked up by those of the positively charged counterpart in the pericyclic interaction. We wish to report here a kinetic study of the well-discussed Cope rearrangement of 4,4-dicyano-5-ethyl-1,5-heptadiene (**1**)[5—9] in various solvents, which presents definitive evidence for the hydrogen-bond-insusceptible behavior of this kind of rearrangement.

Results and Discussion

Table 1. Solvent Effect on the Rate of the Cope Rearrangement of **1** at 90.0 °C[a)]

Solvent	$10^5k/\mathrm{s}^{-1}$	Solvent	$10^5k/\mathrm{s}^{-1}$
(1) DMSO-d_6	4.28	(8) DCB	2.65
(2) DMF-d_7	3.50	(9) $CDCl_3$	2.60
(3) HMPT-d_{18}	3.18	(10) Acetone-d_6	2.43
(4) Pyridine	3.10	(11) Dioxane-d_8	2.29
(5) MeCN-d_3	3.05	(12) Benzene	2.13
(6) Methanol-d_4	2.95	(13) CCl_4	1.43
(7) Ethanol-d_6	2.87	(14) Cyclohexane-d_{12}	1.12
Ethanol[b)]	2.72		

a) Rate constants are reliable to ±2% unless otherwise noted. b) Reliable to ±3.7%.



The first-order rate constants for the rearrangement **1** → **2** at 90.0 °C in fourteen solvents were determined by ^{1}H NMR (Table 1). Among the solvents used, the least efficient is cyclohexane and the most efficient is DMSO, although the rate difference is small (k_{rel}, 1 : 3.8). Cope and his co-workers reported the activation parameters for the rearrangement in the liquid phase in which rates were determined by following the change in refractive index: $\Delta H^{\neq}=25.0\pm0.6$ kcal mol^{-1} (1 cal=4.184 J), $\Delta S^{\neq}=-11.0\pm1.5$ eu.[6] The rate at 90 °C (2.63×10^{-5} s^{-1}) calculated from their parameters falls within the range of our data. However, the rate data reported by Wigfield and Feiner (UV method)[8] are considerably different from ours: both of their rates in 1,4-dioxane (4.7×10^{-5} s^{-1}) and in ethanol (4.9×10^{-5} s^{-1}) at 79 °C are about twice as much as those measured by us at 90 °C. Although the origin of this discrepancy is uncertain, we will discuss here the effect of solvation on the basis of our own data.

It has empirically been established that the ionizing power of the following four aprotic solvents increases in the order of acetone<pyridine<DMF<DMSO in polar unimolecular reactions of any type.[2,3] The rearrangement **1** → **2** obeys this order of solvent ionizing power as well. Figure 1 shows a plot of $RT\ln k_{\mathrm{rel}}$ against W_{ion} together with other relevant plots. W_{ion} ($\equiv RT\ln k_{\mathrm{ion,rel}}$ where k_{ion} is the rate constant for the S_N1-E1 decomposition of *p*-methoxyneophyl tosylate reported by Winstein and his co-workers[10]) is the most reliable scale of solvent ionizing power for hydrogen-bond-susceptible reactions throughout a large number of protic and aprotic solvents, since the decomposition does not involve internal return. The above four data points define a good straight line with a rather gentle slope compared with other polar [3,3]-sigmatropic rearrangements such as the azo Cope rearrangement of **3**[3] and the thione-to-thiol conversion of **4**,[3,4] suggesting that the activated complex is distinctly polarized but to a limited extent. It is evident that both the methanol and ethanol points exhibit downward shifts. If the transition state for the rearrangement is stabilized through hydrogen bonding, these points should have values large enough to be placed

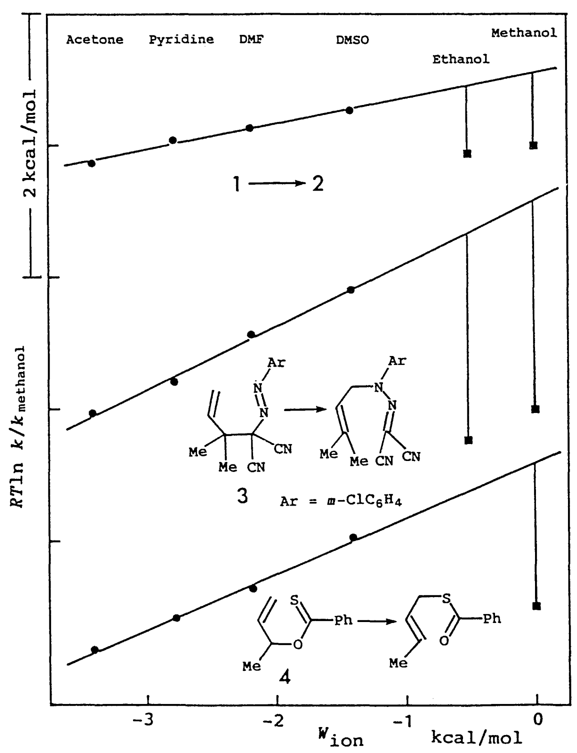


Fig. 1. Plot of $-\Delta\Delta G^{\neq}$ vs. W_{ion}.
The rate data including W_{ion} are those obtained from the reactions in deuteriated solvents except for pyridine. The W_{ion} values were calculated based on the data from Ref. 2 and this work (the rate in ethanol-d_6 only).

on the line,[2,3] namely, 6.4×10^{-5} s^{-1} for methanol and 5.5×10^{-5} s^{-1} for ethanol. These values are about twice as much as those observed, indicating that the differences between the calculated and observed rate constants are much greater than limits of experimental error (±2%). We therefore conclude that the Cope rearrangement of **1** behaves as a hydrogen-bond-insusceptible reaction analogously to the above-mentioned sigmatropic reactions. These three examples in Fig. 1 provide sufficient evidence that such behavior quite commonly arises irrespective of the nature of the bonds cleaved and formed.

The observed lower sensitivity to solvent ionizing power in the rearrangement of **1** suggests a tighter pericyclic interaction. It should be noted that even though the extent of charge separation is small, mixing of such an intramolecular charge-transfer-type interaction is responsible for high stabilization of the transition state as can be inferred from the fact that the rate increases with increasing electron-withdrawing power of substituents attached to a saturated carbon.[5,6]

The effects of a variety of solvents are compared with those in the azo Cope rearrangement of **3** in Fig. 2. A good linear free energy relationship holds when four data points [methanol-d_4, ethanol-d_6, o-dichlorobenzene (DCB), and $CDCl_3$] are omitted. Upward shifts of the protic solvent points suggest that the effect of hydrogen bonding still survives slightly in the rearrangement of **1** as compared with that of **3**. To date we cannot explain large deviations of the DCB and $CDCl_3$ points; these two solvents may have substrate-dependent specific interactions.

Experimental

Compounds **1** and **2** were prepared according to the literature procedure.[5] The ^{1}H NMR spectra were obtained on a Varian EM-390 spectrometer operating at 90 MHz in the CW mode at about 34 °C. The rates were determined by monitoring the decrease in the intensity of the doublet signal due to the olefinic methyl protons of **1** relative to that of the methyl signal of anisole added as an internal reference. Initial concentrations were about 0.1 M (1 M=1 mol dm^{-3}). For reactions in solvents other than ethanol, a sample solution in a sealed NMR tube was heated in a thermostated water bath (±0.01 °C) and was subjected to NMR measurement at appropriate intervals.

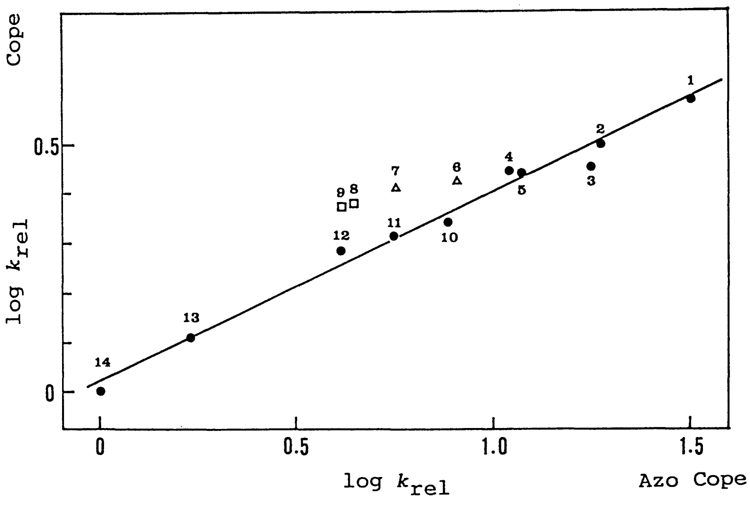


Fig. 2. Plot of log k_{rel} of the Cope rearrangment of **1** at 90 °C against log k_{rel} of the azo Cope rearrangement of **3** at 60 °C [Numbers correspond to those in Table 1; the slope is 0.375 (R=0.993) when the four data points, methanol (6), ethanol (7), DCB (8), and $CDCl_3$ (9), are omitted].

The rate in ethanol was measured for the purpose of comparison with that in ethanol-d_6. Thirteen ampoules each containing 2 ml of an ethanol solution of **1** (0.05 M, including anisole) were simultaneously heated at 90 °C. At 1.5 h intervals one of them was withdrawn and immediately ice-cooled. The content was poured onto 10 ml of CCl_4, and the solution was washed with water three times, dried, quickly concentrated to 1 ml below 40 °C, and subjected to NMR measurement.

Rates for the rearrangement of **3** at 60 °C in the solvents other than those reported[3)] were measured: $k\times10^5$ (s^{-1}) hexamethyl-d_{18}-phosphoric triamide (HMPT-d_{18}), 139; ethanol-d_6, 44.4; 1,4-dioxane-d_8, 43.8; cyclohexane-d_{12}, 7.80. Further, the rate for the decomposition of *p*-methoxyneophyl tosylate in ethanol-d_6 at 75 °C was measured [$k\times10^5$ (s^{-1}) 54.5 (cf. 62.5 in ethanol[10)])].

This work was partially supported by a grant from the Ministry of Education, Science and Culture. We are grateful to Dr. Takayuki Kawashima for useful suggestions.

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