MECHANISM OF α-SUBSTITUTION REACTIONS OF ACRYLIC DERIVATIVES

JON S. HILL AND NEIL S. ISAACS*

Department of Chemistry, University of Reading, Whiteknights, PO Box 224, Reading, Berkshire RG6 2AD, UK

Reactions between acrylic esters, nitriles and similar compounds on the one hand and aldehydes and ketones on the other, catalysed by tertiary amines, lead to α-(hydroxyalkyl)acrylic compounds. Evidence on the basis of kinetics, volumes of activation and of reaction, and kinetic isotope effects is presented to deduce a mechanism in which amine first undergoes Michael addition, the resulting enolate ion adds to the carbonyl compound in a rate-determining step and finally base is eliminated. An analysis of the solvent effect on rates is also presented.

INTRODUCTION

α-Substitutions of acrylic compounds (sometimes referred to as the Bayliss–Hillman reaction[1]) are a fairly widespread family of reactions whose scope has been recently reviewed by Drewes and Roos[2] and which is of considerable synthetic utility in giving easy access to some highly functionalized products, 1. We present here evidence for the mechanism of a representative case from a detailed study particularly of one example, the reaction between acrylonitrile and acetaldehyde catalysed by 1,4-diazabicyclo[2.2.2]octane (DABCO):

$$CH_2 = CHCN$$
$$+ RCHO \xrightarrow{\text{base}} CH_2 = C(CN)CH(OH)R$$

1
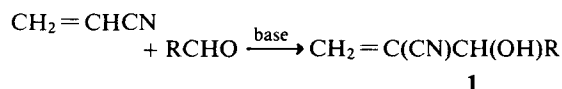
This is one of the most facile reactions of the type; when acrylonitrile and acetaldehyde are allowed to stand in the presence of a tertiary amine catalyst for several days, a good yield of 2-cyanobut-1-en-3-ol (1, R = Me) is obtained.[3,4] The reaction has now been subjected to a kinetic investigation, the volume profile delineated and a kinetic isotope effect measured. The unusual pattern of solvent activity has also been studied.

EXPERIMENTAL

Acrylonitrile was purified by drying over molecular sieve (3Å) and distillation, collecting at 77–78 °C. Acetaldehyde was distilled, collecting at 21 °C. DABCO was recrystallized from pentane, m.p. 160 °C. [2-²H]-

Acrylonitrile was prepared according to the method of Stephenson *et al.*[5] by the reduction of 2-chloroacrylonitrile using the zinc–copper couple in D_2O.

Kinetic measurements were made by dissolving appropriate amounts of acrylonitrile, acetaldehyde and DABCO in the appropriate solvent (each at a final concentration of 0·1–0·5 M) and a small amount of a reference compound (chlorobenzene) maintaining the temperature constant at 25·0 ± 0·1 °C and then withdrawing samples periodically. These were then analysed by gas–liquid chromatography using a Carbowax 20M column at 120 °C and the amount of product estimated relative to the chlorobenzene peak. The initial concentrations of the reagents were systematically varied to obtain the order of the reaction with respect to each. High-pressure reactions were carried out in the sampling apparatus described previously[6] and performed in duplicate. Except where reactions were carried out under pseudo-first-order conditions, progress of reaction curves were fitted by computer to the equation

$$d/dt \, [\text{product}] = A + B \exp(Ct) \qquad (1)$$

and relative rates obtained by comparison of initial slopes, BC. This proved a satisfactory and reproducible procedure, since reactions times were typically several hours to several days. Plots of $\ln k_{rel}$ against pressure were slightly curved but fitted a simple quadratic expression:

$$\ln k = A + BP + CP^2 \qquad (2)$$

from which the volume of activation was calculated from the equation

$$d(\ln k)/dp_{p \to 0} = B = -\Delta V^{\ddagger}/RT \qquad (3)$$

---

*Author for correspondence.

Table 1. Rate of reaction as a function of pressure for α-addition between acrylonitrile and acetaldehyde

Pressure/bar	Initial slope/10^3 min^{-1}	Relative rate (k_{rel})
1	1.28	1.0
360	3.74	2.9
600	6.95	5.4
740	10.22	8.0
Projected rates:		
1000		15
5000		1.1×10^6

The results are summarized in Table 1. The volume of reaction was obtained by algebraic summation of the separate partial molar volumes of reagents and product. The latter were obtained from densities of solutions of each measured by means of a high-precision densitometer (Anton Paar).

RESULTS AND DISCUSSION

The reaction between acetaldehyde and acrylonitrile was followed as described above and relative rate constants were obtained while varying separately the concentrations of acetaldehyde, acrylonitrile and DABCO. In each case the rates depended linearly on the first power of each concentration, confirming the empirical rate expression

$$\text{rate} = k_3 [\text{MeCHO}] [\text{ACN}] [\text{DABCO}] \qquad (4)$$

The three molecular species must therefore be present in the activated complex of the slow step of the reaction. It may be assumed that the base initially coordinates with the β-carbon of acrylonitrile and then the resulting enolate ion in turn to the carbonyl compound (Scheme 1). The final product would then be obtained by a β-elimination of the ammonium ion from the intermediate 2. The kinetic results point to step 2 being rate determining because, if step 1 were slow, the reaction would be zero order in aldehyde, whereas if the elimination, step 3, was rate-limiting, presumably the reaction would need to be second-order in base.

Further evidence corroborates this inference. α-[^{2}H] Acrylonitrile was prepared and its rate of reaction compared with that of the ^{1}H analogue. The kinetic isotope effect was found to be $k_H/k_D = 1 \cdot 03 \pm 0 \cdot 1$, confirming that fission of the α-proton, which must occur at some stage, does not occur in a rate-determining step. The volume profile is also confirmatory. Rates of reaction were measured by a sampling technique at pressures up to 740 bar. An extraordinarily large pressure effect on the rates was observed, possibly as large as any reaction hitherto examined. The volume of activation was calculated as -79 ± 5 cm^{3}mol^{-1}, corresponding to a 15-fold increase at only 1000 bar. It is this property that makes synthesis using α-substitutions so amenable to high pressure.[3,4]
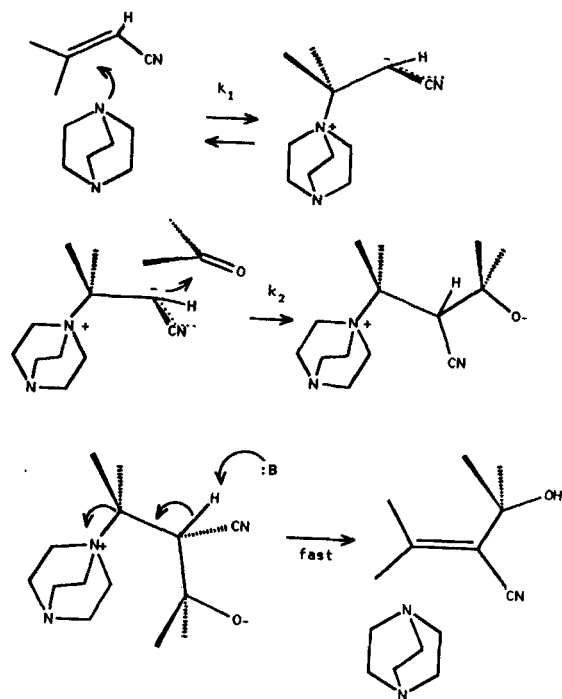
Scheme 1

The magnitude of this value is far too large to be accounted for by bond formation alone. The volume of activation for a Diels—Alder reaction, for example, is only of the order -35 cm^3 mol^{-1}.[7] Solvation must also play a prominent role in creating such a volume reduction by electrostriction. A typical dipole-creating process such as a Menshutkin reaction is associated with ca -30 to -50 cm^{3}mol^{-1}, depending on the nature of the solvent and also on steric hindrance.[7] However, a value of the observed magnitude for the reaction under investigation could credibly be associated with a process in which two successive bond formations occurred in conjunction with the creation of full charges, as proposed in Scheme 1.

It must be assumed that step 1 is reversible in order for step 2 to be rate determining and, in step 1, the

necessary full ionic charges are formed. Step 2 therefore consists in bond formation and an increase in dipole moment by further separating the charge centres, both features of which are associated with a reduction in volume:

$$\Delta V_{obs} = \Delta V_1(b) + \Delta V_1(e) + \Delta V_2^{\ddagger} \qquad (5)$$

the components terms being, respectively, the volume of reaction, bond formation only, of reaction 1, the volume of electrostriction of reaction 1 and the volume of activation for reaction 2, each of these being negative. Plausible values of the individual contributions could be around -15, -35 and $-30\ \text{cm}^3\,\text{mol}^{-1}$, respectively.[8] The overall volume of reaction, on the other hand was found to be only $-20\ \text{cm}^3\,\text{mol}^{-1}$, which is in agreement with the neutralization of charges in the final product and in the fission of the DABCO molecule.

The role of the solvent is seen to be important in accounting by electrostriction for the volume of activation. We surveyed the effects of 18 solvents on the reaction rate (Table 2) and conclude that the interplay of several facets of solvent behaviour must be taken into account. Through the range of solvents used there is a rough increase in rate with solvent polarity, a factor of some 400-fold between the extremes, alcohols being prominent in promoting rapid reaction. Surprisingly, 1,2-diols are more effective than simple alcohols and the slowest solvents were ethers and esters rather than hydrocarbons or chlorocarbons. The results were subjected to multi-correlation analysis according to Kamlet and Taft's procedure using the three solvent property descriptors π^* (polarity and polarizability), α (hydrogen bond donor acidity) and β (hydrogen bond acceptor basicity).[9] The resulting correlation [equation (6)], significant although with some scatter (Fig. 1), gave the coefficient values as follows;

$$\log k = -0\cdot512 + 0\cdot834\pi^* + 0\cdot775\alpha + 0\cdot474\beta \quad (6)$$

All three terms appear to be of importance, suggesting a solvation pattern along the lines of 2a. Two-parameter correlation using the Swain et al.[10] solvation constants A (anion-solvating) and B (cation solvating) led to the regression

$$\log k = -0\cdot29 + 1\cdot631A + 0\cdot319B \qquad (7)$$

from which it appears that anion solvation is more important, as would be predicted for a transition state such as 2.

The special activation of the reaction by vicinal diols as solvents deserves further comment. The addition of ethanediol to the neat reaction mixture was found to accelerate the rate of reaction by a factor of about four at an equimolar concentration ratio, despite the concomitant dilution effect which would cause a reduction of $(1\cdot5)^2$. The catalytic effect of the diol therefore is to cause an increase of an order of magnitude. We speculate that this may be indicative of a specific solvation effect, a result of hydrogen bonding by both hydroxyl groups. If only the developing oxide ion was stabilized in this way, one would expect all carbonyl additions to be catalysed by diols, which does not seem to be the case. Perhaps, therefore, the nitrile group also is
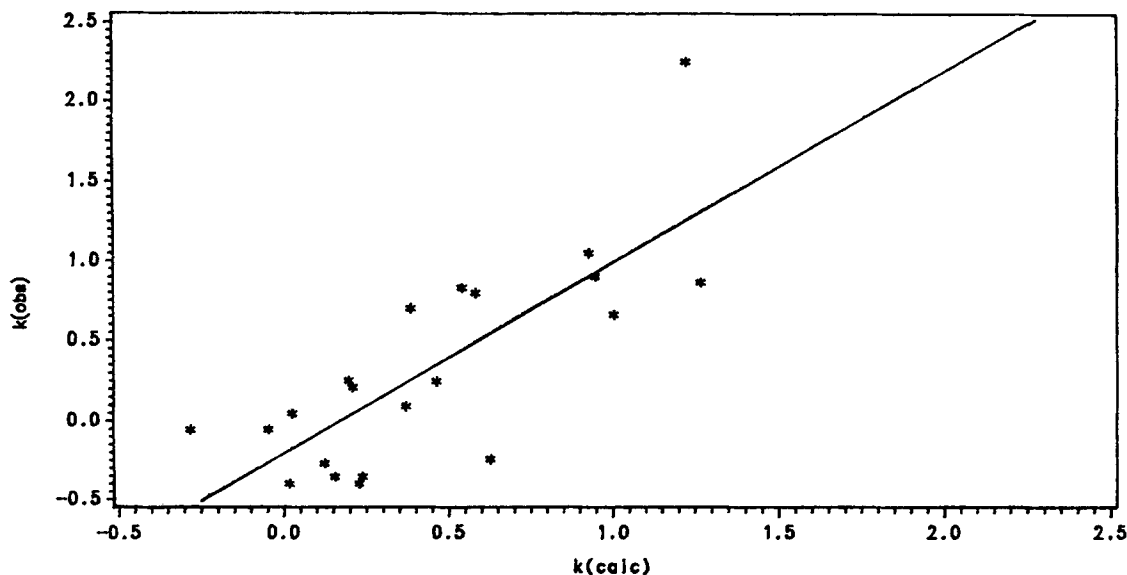

Figure 1. Correlations of the solvent effect on the rate of reaction between acetaldehyde and acrylonitrile catalysed by DABCO (see Table 2). The line is the least-squares fit between experimental values of rate coefficient and values calculated from equation (6)

Table 2. Effect of solvents on the rate of formation of 3-hydroxy-2-methylenebutanenitrile

Solvent	$\log k_{rel}$	Solvent	$\log k_{rel}$
Ethane-1,2-diol	2.25	Bromobenzene	0.25
Propan-2-ol	1.05	Chloroform	0.24
Ethanol	0.90	o-Dichlorobenzene	0.21
Trifluoroethanol	0.86	Acetone	0.089
Dimethylformamide	0.83	Benzene	0.043
Dimethylacetamide	0.80	Hexane	0.0
Acetonitrile	0.70	Dichloroethene	−0.056
Methanol	0.66	1,4-Dioxane	−0.27
		Ethyl acetate	−0.36
		Tetrahydrofuran	−0.40

⊖—H - H-bonding solvent

⊕—► dipolar solvent
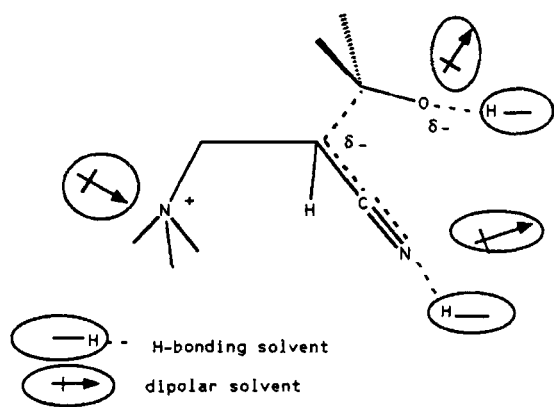
2

simultaneously involved in hydrogen bonding to the diol.

The final elimination to form the product occurs presumably by an E2 mechanism, although the present experiments do not permit its stereochemistry to be ascertained. We assume, as did Hoffmann and Rabe,[11] that this will be *anti*, although *syn* elimination of ammonium ions in particular has been shown often to make an important contribution.[12]

REFERENCES

1. A. B. Baylis and M. E. D. Hillman, *Ger. Pat.* 2 155 113 (1972); *Chem. Abstr.* 77, 34174q (1972).
2. S. E. Drewes and G. H. P. Roos, *Tetrahedron* 44, 4653 (1988).
3. J. S. Hill and N. S. Isaacs, *J. Chem. Res.* (S) 330, (M) 2641 (1988).
4. J. S. Hill and N. S. Isaacs, *Tetrahedron Lett.* 27, 5007, 1986.
5. L. M. Stephenson, R. V. Gemmer and S. P. Current, *J. Org. Chem.* 42, 212 (1977).
6. N. S. Isaacs, K. Javaid and B. Capon, *J. Chem. Soc., Perkin Trans.* 2 101 (1982).
7. T. Asano and W. J. le Noble, *Chem. Rev.* 78, 407, (1978).
8. N. S. Isaacs, *Liquid Phase High Pressure Chemistry.* Wiley, Chichester (1981).
9. J. L. M. Abboud, M. J. Kamlet and R. W. Taft, *Prog. Phys. Org. Chem.* 13, 485 (1981).
10. C. G. Swain, M. S. Swain, A. L. Powell and S. Alunni, *J. Am. Chem. Soc.* 105, 502 (1983).
11. H. M. R. Hoffman and J. Rabe, *Angew. Chem., Int. Ed. Engl.* 22, 795 (1983).
12. R. A. Bartsch and J. Zavada, *Chem. Rev.* 80, 453 (1980).