

Kinetic Medium Isotope Effect in Nucleophilic Substitution

By P. Beltrame, M. G. Cattania, G. Massolo, and M. Simonetta,* Istituto di Chimica fisica, Università di Milano, 20133 Milano, Italy

Kinetics of various kinds of nucleophilic substitution were studied in ethanol and in [*hydroxy*-²H]₁ethanol in order to evaluate the rate ratios due to pure medium effects. The values of $k_{\text{EtOD}}/k_{\text{EtOH}}$ were 1.84 and 1.83 for substitution of 1-chloro-2,4-dinitrobenzene and of 1-chloro-2,2-di-(*p*-nitrophenyl)ethylene, respectively, by ethoxide ion at 25°; 1.30 for substitution of 1-chloro-2,4-dinitrobenzene by pyridine at 90°; 1.3—1.4 for substitution, and 1.7—1.8 for elimination, in the concurrent reactions of *n*-butyl chloride with ethoxide ion at 60—80°.

SECONDARY solvent kinetic isotope effects¹ usually include secondary effects due to isotopic change of reactant(s), as a consequence of the change of solvent, and pure medium effects directly due to change of solvent. Both are present when OH[−] in H₂O is compared with OD[−] in D₂O. The pure medium effects, largely recognised but differently named,² will be here referred to as 'kinetic medium isotope effects.'

Direct observation of a kinetic medium isotope effect is possible when reactants are free from atoms exchangeable with the isotopic solvent at a rate greater than, or comparable with, that of the reaction under examination. In solvolyses, the absence of nucleophilic interaction between reactant and solvent would be required. The field of solvolysis in protium and deuterium oxides has been recently reviewed.^{2p}

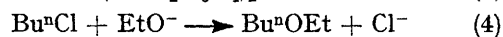
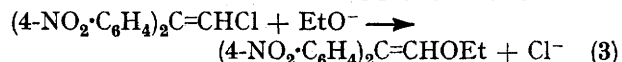
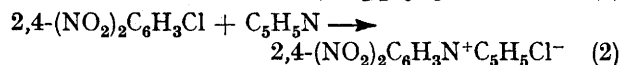
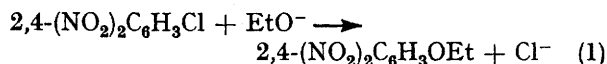
For a few base-catalysed reactions in aqueous solution, with rate-determining bimolecular attack of the base on the substrate, the kinetic medium isotope effect on the catalytic coefficients was directly measured. Reitz *et al.*^{2a,b} reported ratios $k_{\text{OCoR}}(\text{H}_2\text{O}) : k_{\text{OCoR}}(\text{D}_2\text{O})$ between 1.14 and 1.30 for the bromination of nitromethane, catalysed by acetate and chloroacetate ions, and for that of acetone, catalysed by acetate ion, reagents being not in equilibrium with the solvent. Analogous measurements on enolisation of 2-acetylcyclohexanone and bromination of 3-methylpentane-2,4-dione were reported by Long *et al.*; ^{2d,f} their values of $k_{\text{OAc}}(\text{H}_2\text{O}) : k_{\text{OAc}}(\text{D}_2\text{O})$ are around 1.2 in both cases. In the formate ion-catalysed hydrolysis of acetic anhydride it was found $k_{\text{OCoH}}(\text{H}_2\text{O}) : k_{\text{OCoH}}(\text{D}_2\text{O}) = 1.1$.³ In the acetate-catalysed hydrolysis of two nitro-substituted arylacetates

(nucleophilic catalysis) $k_{\text{OAc}}(\text{H}_2\text{O}) : k_{\text{OAc}}(\text{D}_2\text{O}) = 1.4—1.8$.⁴

Where pure medium effects are superimposed on secondary isotope effects due to reactants they are usually neglected, out of necessity. This approximation, which is included in theoretical treatments of solvent isotope effects,⁵ may be justified in some cases,⁶ but has been criticised.^{7,2s} Free energies of solvation, particularly of ionic species in hydroxylic solvents, should be expected to show isotope effects, and in some cases their amount has been evaluated for water solutions.^{6,8}

Little is known about kinetic medium isotope effects in non-aqueous solvents. For the hydrogen exchange of 1-*H*-perfluoroheptane, catalysed by methoxide ion in methanol, it has been indirectly evaluated: $k_{\text{OMe}}(\text{MeOD}) : k_{\text{OMe}}(\text{MeOH}) = 1.5$.⁹ Analogous medium effects for the alkoxide ion-catalysed isomerisation of 3-phenylbutene in *t*-butyl alcohol and 1,1-diethylpropanol were estimated as 0.9 and 1.5, respectively.²ⁱ In basic methanolysis of aryl esters, where nucleophilic attack of methoxide ion on carbonyl carbon is considered to be the rate-determining step, ratios $k_{\text{OMe}}(\text{MeOD}) : k_{\text{OMe}}(\text{MeOH})$ between 1.6 and 2.6 were measured.^{2a,7}

We measured kinetic medium isotope effects in various kinds of nucleophilic substitution at carbon, employing the couple ethanol-[*hydroxy*-²H]₁ethanol as solvents. The typical cases of aliphatic, activated aromatic and activated ethylenic substitution shown in equations (1)–(4) were chosen. As an unavoidable side-reaction,



¹ (a) C. A. Bunton and V. J. Shiner, jun., *J. Amer. Chem. Soc.*, 1961, **83**, 3207; (b) W. J. Albery, *Progr. Reaction Kinetics*, 1967, **4**, 353.

² (a) O. Reitz, *Z. phys. Chem.*, 1936, **A**, **176**, 363; (b) O. Reitz and J. Kopp, *ibid.*, 1939, **A**, **184**, 429; (c) J. G. Pritchard and F. Long, *J. Amer. Chem. Soc.*, 1956, **78**, 6008; (d) F. A. Long and D. Watson, *J. Chem. Soc.*, 1958, 2019; (e) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1959, **81**, 2347; (f) T. Riley and F. A. Long, *ibid.*, 1962, **84**, 522; (g) P. A. Salomaa, L. L. Schaleger, and F. A. Long, *ibid.*, 1964, **86**, 1; (h) C. G. Swain, A. D. Ketley, and R. F. W. Bader, *ibid.*, 1959, **81**, 2353; (i) C. G. Swain and E. R. Thornton, *ibid.*, 1961, **83**, 3884, 3980; (j) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *ibid.*, 1965, **87**, 1553; (k) L. J. Steffa and E. R. Thornton, *ibid.*, 1963, **85**, 2680; (l) D. J. Cram and R. T. Uyeda, *ibid.*, 1964, **86**, 5466; (m) J. F. Bunnett and C. Bernasconi, *ibid.*, 1965, **87**, 5209; (n) J. R. Jones, *Trans. Faraday Soc.*, 1965, **61**, 95; (o) E. R. Thornton, *Ann. Rev. Phys. Chem.*, 1966, **17**, 365; (p) R. E. Robertson, *Progr. Phys. Org. Chem.*, 1967, **4**, 213; (q) F. M. Menger, *J. Amer. Chem. Soc.*, 1966, **88**, 5356; (r) C. G. Mitton, M. Gresser, and R. L. Schowen, *J. Amer. Chem. Soc.*, 1969, **91**, 2045; (s) V. Gold, *Adv. Phys. Org. Chem.*, 1969, **7**, 259.

³ A. R. Butler and V. Gold, *Proc. Chem. Soc.*, 1960, 15.

⁴ D. G. Oakenfull, T. Riley, and V. Gold, *Chem. Comm.*, 1966, 385.

⁵ See, e.g., W. E. Nelson and J. A. V. Butler, *J. Chem. Soc.*, 1938, 957; V. Gold, *Trans. Faraday Soc.*, 1960, **56**, 255; also ref. 2g.

⁶ C. G. Swain and R. F. W. Bader, *Tetrahedron*, 1960, **10**, 182; C. G. Swain, R. F. W. Bader, and E. R. Thornton, *ibid.*, p. 200.

⁷ E. A. Halevi, F. A. Long, and M. A. Paul, *J. Amer. Chem. Soc.*, 1961, **83**, 305.

⁸ R. W. Kingerley and V. K. La Mer, *J. Amer. Chem. Soc.*, 1941, **63**, 3256; P. Salomaa and V. Aalto, *Acta Chem. Scand.*, 1966, **20**, 2035; J. Greyson, *J. Phys. Chem.*, 1967, **71**, 2210.

⁹ S. Andreades, *J. Amer. Chem. Soc.*, 1964, **86**, 2003.

the elimination to butene concurrent with reaction (4), was studied. Some results have been given.¹⁰

EXPERIMENTAL

Spectra were scanned on Perkin-Elmer 21 (i.r.), Beckman DK-2A (u.v.), and Varian A-60 (n.m.r.) equipment.

Ethanol and [hydroxy-³H]₂Ethanol.—Commercial 'anhydrous' ethanol was dried by a standard method. EtOD was obtained either from aluminium ethoxide prepared *in situ*¹¹ or from commercial triethyl orthoformate by deuteriolysis with 99.8% deuterium oxide.^{12,13} Final drying was effected as for ethanol. Water content was less than 0.1% (Karl Fischer). Isotopic purity of EtOD, as determined by i.r. analysis of OH at 3 μ , was 90–95% (from aluminium ethoxide) and 96–99% (from orthoformate).

Reactants.—1-Chloro-2,4-dinitrobenzene, n-butyl chloride, and pyridine were purified by standard methods, and their purity checked by g.l.c. 1-Chloro-2,2-di-(*p*-nitrophenyl)ethylene was obtained from 1,1-di-(*p*-nitrophenyl)ethylene by chlorination and dehydrochlorination;¹⁴ it had m.p. 147–148° and the correct elemental analysis.

Sodium ethoxide was prepared from sodium purified by melting in dry xylene under nitrogen.¹⁵

Reaction Products.—Products of reaction (1) carried to completion in ethanol and in EtOD at 25° had identical m.p.s and u.v. spectra; n.m.r. spectra revealed, in the region of aromatic protons, an ABX system for the product in ethanol, and an AB system for the product in EtOD, proving the fast exchange of the hydrogen atom in position 3 on the ring.

Reaction (2) was carried out at reflux temperature in both solvents: the isolated products were crystallized and showed identical u.v. spectra, and almost identical i.r. spectra (Found: C, 46.8; H, 2.8; N, 14.9. Calc. for C₁₁H₈ClN₂O₄: C, 46.91; H, 2.86; N, 14.92%), λ_{max} (in ethanol) 228 nm. (ϵ 22,930). U.v. absorption at 293 nm. of crude product from kinetic runs revealed the presence of ca. 10% of 2,4-dinitrophenetole.

Reaction (2) was also carried out with [²H₅]pyridine in both solvents: the products showed the same ABX pattern in their n.m.r. spectra.

From reaction (3) carried in [²H₁]ethanol at 25°, a product was isolated that was shown to be identical to that obtained in ethanol by n.m.r. spectroscopy;¹⁶ in particular, the ethylenic proton gave a signal at least 90% as intense as the signal from the product obtained in ethanol, alkylic protons being taken as reference.

1-Chloro-2,2-di-(*p*-nitrophenyl)ethylene was also treated with pyridine in ethanol at 130–140°, but the only isolated product was the ethoxy-derivative, as for reaction (3).

Kinetics.—Reaction (1) was carried out within a 10 mm. quartz cell in the thermostatted cell compartment of a Beckman DU spectrophotometer at 25.0° \pm 0.1°. Readings at known times were taken at either 320 or 300 nm. for analysis of product, or at 260 nm. for analysis of reactant. Mostly the wavelength 300 nm. was used (ϵ of

reactant = 1980; ϵ of product = 12,630). Initial concentrations were 10⁻⁴–10⁻⁵M-chloro-derivative and 10⁻²–10⁻³M-ethoxide ion.

Runs (2) were done in sealed Hysil glass tubes in a thermostat at 90.0° \pm 0.2°. Initial concentrations were ca. 5 \times 10⁻²M for the chloro-derivative and ca. 10⁻¹M for pyridine; each tube contained 3 ml. of solution. Reaction was quenched by cooling and acidifying (HNO₃) the contents of each tube; after addition of methanol (ca. 10 ml.) chloride ion was electrometrically titrated with 0.02M-AgNO₃.

Stoppered glass tubes were used for runs (3), carried out in a thermostat at 25.00° \pm 0.03°. Initial concentrations were ca. 5 \times 10⁻³M for the chloroethylene and 10⁻²–10⁻¹M for sodium ethoxide; each tube contained a volume of solution corresponding in some runs (i) to ca. 0.02 mmole, in other runs (ii) to ca. 0.07 mmole of chloro-derivative. Quenching and titration were as in the previous case. Statistical analysis of the results showed that runs (ii) had a much larger weight.

Runs (4) were carried out in sealed Hysil tubes, in thermostats at 60.0° \pm 0.1°, 70.0° \pm 0.2°, and 80.0° \pm 0.3°. n-Butyl chloride was initially ca. 10⁻¹M and sodium ethoxide ca. 2 \times 10⁻¹M. The procedure for determination of chloride ion was as in (2), apart from the use of 0.1M-AgNO₃. At times in the range 2–6 τ (τ = half-life), olefins were analysed by withdrawal of larger tubes (10 ml. of content), extraction by carbon tetrachloride,¹⁷ and titration with 0.05N-bromate-bromide.¹⁸ Average values of the elimination fraction (f_E) were calculated for each solvent and temperature. They were: 0.034, 0.039, and 0.047 (in EtOH) and 0.042, 0.049, and 0.057 (in EtOD) at 60, 70, and 80°, respectively.

All kinetics were followed up to 1–2 half-lives, often in parallel runs in ethanol and EtOD.

Rate coefficients (k) were computed by standard methods; a correction for solvent expansion was applied to results at temperatures different from 25°. In case (4), separate rate coefficients for substitution (k_S) and elimination (k_E) were obtained from overall rate coefficients (k) by the formulae $k_S = k(1 - f_E)$ and $k_E = kf_E$.

TABLE 1

Example of kinetic run in [³H]₂ethanol; rate coefficients in l. mole⁻¹ sec.⁻¹; reaction of 2,4-(NO₂)₂C₆H₃Cl with pyridine at 90.0° (10⁴ k_{EtOH} = 1.178)¹⁰

| Solvent isotopic purity (x) | 10 ⁴ k_x | 10 ⁴ k_{EtOD} |
|---------------------------------|-----------------------|-----------------------------------|
| 0.92 | 1.5557 | 1.5886 |
| 0.92 | 1.5088 | 1.5376 |
| 0.92 | 1.5828 | 1.6180 |
| 0.90 | 1.4762 | 1.5093 |
| 0.90 | 1.4118 | 1.4377 |
| 0.90 | 1.4571 | 1.4882 |

Average 10⁴ k_{EtOD} = 1.530 \pm 0.065.

Rate coefficients in pure EtOD (k_{EtOD}) were calculated by assuming a linear relation between solvent composition and reactivity, that is: $k_{\text{EtOD}} = [k_x - k_{\text{EtOH}}(1 - x)]/x$

¹⁰ C. H. De Puy, G. F. Morris, J. S. Smith, and R. J. Smat, *J. Amer. Chem. Soc.*, 1965, **87**, 2421.

¹¹ P. Beltrame, P. L. Beltrame, O. Sighinolfi, and M. Simonetta, *J. Chem. Soc. (B)*, 1967, 1103.

¹² C. A. Vernon, *J. Chem. Soc.*, 1954, 4462.

¹³ S. Siggia, 'Quantitative Organic Analysis via Functional Groups,' Wiley, New York, 1954, p. 69.

¹⁰ I. R. Bellobono, P. Beltrame, M. G. Cattania, and M. Simonetta, *Tetrahedron Letters*, 1968, 2673.

¹¹ *Org. Synth.*, Coll. Vol. II, Wiley, New York, 1943, p. 599.

¹² D. Pitca and P. Beltrame, *Chimica e Industria*, 1967, **49**, 56.

¹³ V. J. Shiner, jun., and M. L. Smith, *J. Amer. Chem. Soc.*, 1961, **83**, 593.

¹⁴ P. Beltrame, P. L. Beltrame, G. Carboni, and M. L. Cereda, *J. Chem. Soc. (B)*, in the press.

where k_x is a rate coefficient obtained from runs in EtOD of isotopic purity x , and k_{EtOH} refers to pure ethanol. An example of this kind of correction is given in Table 1; in every other set of kinetic runs the isotopic purity of the deuteriated solvent was better than in the example.

Arrhenius activation energies (ΔE^\ddagger), frequency factors (A), and activation entropies (ΔS^\ddagger) of the reactions of *n*-butyl chloride, as well as their standard deviations, were obtained by a standard computer programme.

RESULTS AND DISCUSSION

Several measurements of rate coefficients in ethanol and in [*hydroxy*- $^2\text{H}_1$]ethanol were made for each reaction, at a single temperature for reactions (1)–(3) and

TABLE 2

Average values of rate coefficients (l. mole $^{-1}$ sec. $^{-1}$) of aromatic and ethylenic substitutions

| Solvent | No. of runs | $10^4 k$ | $k_{\text{EtOD}} : k_{\text{EtOH}}$ |
|---|-------------|----------------------------|-------------------------------------|
| (1) 2,4-(NO ₂) ₂ C ₆ H ₃ Cl + EtO ⁻ , 25.0° (ref. 10) | | | |
| EtOH | 13 | 842 ± 32 ^a | 1.84 |
| EtOD | 7 | 1545 ± 44 | |
| (2) 2,4-(NO ₂) ₂ C ₆ H ₃ Cl + C ₅ H ₅ N, 90.0° (ref. 10) | | | |
| EtOH | 10 | 1.178 ± 0.038 ^b | 1.30 |
| EtOD | 6 | 1.530 ± 0.065 | |
| (3) (4-NO ₂ ·C ₆ H ₄) ₂ C=CHCl + EtO ⁻ , 25.0° | | | |
| EtOH | 12 | 3.15 ± 0.09 ^c | 1.83 |
| EtOD | 10 | 5.75 ± 0.04 | |

^a Lit.,¹⁹ 825. ^b Lit.,²⁰ 1.3 (from Arrhenius equation).
Lit.,¹⁶ 2.91 (from Arrhenius equation).

at three different temperatures for reaction (4). Second-order rate coefficients were calculated in every case, the reaction orders being accepted as given by the

to pyridine as the nucleophile. The low nucleophilicity of pyridine, compared with that of ethoxide ion, prevents a study of the reaction of this base with the substrates of cases (3) and (4) in dilute ethanolic solutions. A comparison of kinetic medium isotope effect between different substrates was therefore possible only for reactions with ethoxide ion.

The S $_N$ 2 reaction of *n*-butyl chloride presents ratios ($k_{\text{EtOD}} : k_{\text{EtOH}}$) of 1.3–1.4 at 60–80°, with a dependence on temperature apparently lesser than the experimental uncertainty. In fact, differences in activation energies measured in the two solvents are within the standard deviations (Table 3).

Nucleophilic substitutions at aromatic and at ethylenic carbon atoms show remarkably similar ratios ($k_{\text{EtOD}} : k_{\text{EtOH}}$) of 1.84 and 1.83 for reactions (1) and (3), respectively, at 25° (Table 2). Either exactly, or to a good approximation, the measured ratios are values of the kinetic medium isotope effect as defined. Spectroscopy of products has shown that other possible effects are negligible. Side effects are the fast hydrogen–deuterium exchange in position 3 on the ring in reaction (1) and a small amount of substitution by ethoxide ion, due to acid–base equilibrium of pyridine in the solvent, in reaction (2). The former brings about a γ -secondary isotope effect, which should be very close to unity;²¹ the latter too was neglected, as only 10% of the kinetic product derived from the side-reaction. No hydrogen–deuterium exchange on the ring or on the double bond of the diarylhalogenoethylene was detected during reaction (3), although a nitro-group was present on each of the phenyl rings. It has been assumed that isotopic

TABLE 3

Average values of rate coefficients (l. mole $^{-1}$ sec. $^{-1}$) and activation parameters of reactions of Bu n Cl with ethoxide ion (S = substitution; E = elimination)

| Temperature | Solvent | No. of runs | $10^5 k_s$ | $\left(\frac{k_{\text{EtOD}}}{k_{\text{EtOH}}}\right)_S$ | $10^5 k_E$ | $\left(\frac{k_{\text{EtOD}}}{k_{\text{EtOH}}}\right)_E$ |
|-------------|---------|-------------|-----------------------------|--|------------------------------|--|
| 60.0° | EtOH | 4 | 1.83 \pm 0.21 | 1.36 | 0.063 \pm 0.007 | 1.72 |
| | EtOD | 4 | 2.48 \pm 0.39 | | 0.109 \pm 0.017 | |
| 70.0 | EtOH | 7 | 4.54 \pm 0.41 | 1.34 | 0.185 \pm 0.017 | 1.71 |
| | EtOD | 4 | 6.10 \pm 0.24 | | 0.316 \pm 0.012 | |
| 80.0 | EtOH | 4 | 11.6 \pm 1.1 ^a | 1.44 | 0.58 \pm 0.05 ^b | 1.77 |
| | EtOD | 4 | 16.8 \pm 1.5 | | 1.02 \pm 0.09 | |

Substitution in EtOH: ^c log A = 9.4 \pm 0.5; ΔE^\ddagger = 21.6 \pm 0.8 kcal./mole; ΔS^\ddagger = –17.6 \pm 2.4 e.u.

Substitution in EtOD: log A = 10.1 \pm 0.6; ΔE^\ddagger = 22.4 \pm 0.9 kcal./mole; ΔS^\ddagger = –14.7 \pm 2.6 e.u.

Elimination in EtOH: ^d log A = 10.7 \pm 0.8; ΔE^\ddagger = 25.8 \pm 1.2 kcal./mole; ΔS^\ddagger = –11.8 \pm 3.4 e.u.

Elimination in EtOD: log A = 11.2 \pm 0.6; ΔE^\ddagger = 26.1 \pm 0.9 kcal./mole; ΔS^\ddagger = –9.8 \pm 2.6 e.u.

^a Lit.,¹⁷ 13.6 (from Arrhenius equation). ^b Lit.,¹⁷ 0.71 (from Arrhenius equation). ^c Lit.,¹⁷ log A = 9.3; ΔE^\ddagger = 21.2.
^d Lit.,¹⁷ log A = 10.2; ΔE^\ddagger = 24.7.

literature.^{16,17,19,20} Results for each set of reaction conditions were averaged; these averages are in Tables 2 and 3, together with standard deviations. The amount of kinetic medium isotope effect ($k_{\text{EtOD}} : k_{\text{EtOH}}$) was evaluated for nucleophilic substitutions (1)–(4) and for the elimination accompanying reaction (4). Numerical results of runs in ethanol are in substantial agreement with published data.^{16,17,19,20}

Among the substitutions (1)–(4) only one (2) refers

exchange on the alkyl group of *n*-butyl chloride is much slower than reactions with ethoxide ion, in the conditions of experiments.

In conclusion, the kinetic medium isotope effect clearly discriminates between the S $_N$ 2 reaction on one

¹⁹ J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 357.

²⁰ R. Bishop, E. A. S. Cowell, and N. B. Chapman, *J. Chem. Soc.*, 1952, 437.

²¹ E. A. Halevi, *Progr. Phys. Org. Chem.*, 1963, **1**, 109.

hand, and activated aromatic-ethylenic nucleophilic substitutions on the other, providing further evidence for a fundamental difference in mechanism between S_N2 and S_NAr reactions, and for a strict analogy of mechanism of aromatic and ethylenic substitutions.

A difference in bulk dielectric constant of the solvent may have an influence on the measured values of $k_{EtOD} : k_{EtOH}$. However, this does not seem to be the main contribution to the observed medium effect, as in such a case the reactions of chlorodinitrobenzene with an anion [case (1)] and with a dipolar molecule [case (2)]

should be affected in opposite directions. A large contribution is likely owing to specific solvation of reactants and transition states, subject to deuterium isotope effects. An approximate calculation of the effects attributable to hydrogen-bonding solvation by ethanol in nucleophilic substitutions by ethoxide ion and pyridine has been reported.¹⁰

We thank the Italian Consiglio Nazionale delle Ricerche for support.

[9/1186 Received, July 14th, 1969]
