The Use of Radioisotopes in Studies of Reaction Mechanism. Part I. Reaction Order and Activation Parameters of Iodide Exchange in 1-Iodo-2,4-dinitrobenzene

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The exchange reaction between iodide ion and 1-iodo-2,4-dinitrobenzene in methanol has been reinvestigated in a series of kinetic studies using a modified experimental technique. It has been shown that, contrary to earlier published work but in accordance with theoretical expectations, the reaction is overall second-order, being first-order with respect to each reagent. The Arrhenius activation energy of 22·8 kcal. is significantly higher than previously published values and in reasonable agreement with the value of ΔE^* calculated by Miller's method for a bimolecular mechanism. It supports further the existence of a heavy-atom interaction mildly reducing the value of ΔE^* below that calculated but with compensating reduction in ΔS^*.

APART from the S_N1-like special mechanism applicable to nucleophilic substitution of aromatic diazonium salts,[1] almost all available evidence suggests that aromatic nucleophilic substitutions are bimolecular, first-order in reagent and substrate.[2-4] A number of the more highly activated substrates react through isolable cyclohexadienide intermediates, and it is widely accepted,[2,3,5,6] as a general rule, that activated aromatic S_N reactions, which form the great majority, occur by a two-stage addition–elimination mechanism through a relatively stable cyclohexadienide intermediate complex. This has two flanking transition states, one involving bond-making without concurrent bond-breaking and *vice versa*, and formation of either may be rate-limiting. For an exchange reaction such as we are considering here, the energy–reaction co-ordinate profile is symmetrical about the intermediate complex, with the levels of the two transition states equal. Less reactive substrates are known to be able to react with strongly basic reagents through an elimination–addition (benzyne) mechanism,[7-10] also S_N2, but these are much less common.

On the basis of the two-stage addition–elimination mechanism, Miller[11a] calculated potential-energy–reaction co-ordinate profiles for a wide range of reactions of anionic nucleophiles with mono- and poly-nitro activated aromatic substrates, which include halide exchange reactions and reactions in which insolable intermediates occur. They are in satisfactory agreement with experiment in all cases. The calculations have been extended to reactions with neutral nucleophiles,[11b] and further extended to consideration of heats and entropies of reactions,[11c] all in satisfactory agreement with experiment.

There have nevertheless been a few conflicting reports[12-16] as to the kinetic order of some iodide isotopic exchange reactions of activated substrates such as *o*- and *p*-iodonitrobenzenes, 1-iodo-2,4-dinitrobenzene, and 1-iodo-2,4-dinitronaphthalene, as well as of a few substrates of very low reactivity at temperatures above 200° or at low temperatures at which only a very minute fraction of reaction occurs. Whilst the latter reactions are suspect because of the conditions of reaction and insufficiency of kinetic data, the results for the activated substrates are much more detailed and should be straightforward. In particular, Marcopoulos,[16] working with 1-iodo-2,4-dinitro-benzene and -naphthalene, reported kinetic data over a range of temperatures, and determined values for Arrhenius parameters for iodide exchange in methanol. He concluded that, at the low concentrations of iodide ions used in the studies, the reactions are first-order in aromatic substrate and zero-order in iodide ion. He reported that reaction occurs readily at temperatures between 25 and 55°, the activation energies varying with iodide ion concentration. For 1-iodo-2,4-dinitrobenzene, values were in the range 7·24—20·69 kcal. mole^{-1} at iodide concentrations between 10^{-10} and 10^{-1}M,[16a] and for the iodo-naphthalene 12·93—17·22 kcal. mole^{-1} over iodide concentration ranges from 10^{-5} to 10^{-2}M.[16b] Corresponding values of $\log_{10}B$ are 0·6—7·4 and 3·2—6·6.

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[6] J. Miller, " Aromatic Nucleophilic Substitution," Elsevier, Amsterdam, 1966, in preparation.

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[16] C. A. Marcopoulos, (*a*) *Chemika Chronika*, 1962, *A*, **27**, 151; (*b*) *J. Chem. Soc.*, 1965, 4613.

Miller's calculations[11a] based on a bimolecular addition–elimination mechanism are in satisfactory agreement with experiment for, *inter alia*, the reaction of iodide ion with 1-fluoro- and 1-bromo-2,4-dinitrobenzene, and of chloride ion with picryl chloride, and can readily be made for the isotopic exchange reaction of iodide ion with 1-iodo-2,4-dinitrobenzene (see Table 4). The result indicates that reaction should be much slower, and have a higher activation energy than any of the values reported by Marcopoulos.[16a] His results are also unexpected because the values of log B quoted are lower than any previously reported for reactions of anionic nucleophiles with neutral aromatic substrates in methanol.

We have therefore reinvestigated the iodide exchange of 1-iodo-2,4-dinitrobenzene in methanol, and find that the results are in satisfactory agreement with those predicted by Miller's calculations and that the reaction is cleanly second-order, first-order in aromatic substrate and iodide ion. Only in extremely low concentrations of iodide ion, when spurious effects are likely to arise, does the reaction order become indeterminate.

EXPERIMENTAL

Materials.—1-Iodo-2,4-dinitrobenzene was prepared from commercial 1-chloro-2,4-dinitrobenzene by exchange with sodium iodide in dimethylformamide;[17] it had m. p. 88° (lit.,[17] 88·5—90°). Commercial methanol was purified by refluxing with an equal mass of freshly dried quicklime, and then distilled through a fractionating column, the middle 80% of the distillate being collected. Traces of water were removed by refluxing with magnesium turnings (10 g./l. of methanol) and resublimed iodine (1·5 g./l. of methanol).[18]

Analytical Procedure.—Iodine-131 is a β,γ-emitter of principal energies $E_{\beta_{\max.}} = 0{\cdot}33$, 0·61 Mev and $E_\gamma = 0{\cdot}36$, 0·64 Mev; its half-life is 8 days. It can be measured either by counting the β-particles or, more conveniently, the γ-radiation. In this investigation, the concentration of radioactive iodine incorporated into 1-iodo-2,4-dinitrobenzene by exchange was determined by measurement of the 0·36 and 0·64 Mev γ-emission using a scintillation counter (Panax Equipment Ltd., type USC/B). In this instrument a well-type, thallium activated, sodium iodide crystal (2 × 1·75 in. with 0·75 × 1·25 in. well) is optically coupled to a photomultiplier tube (E.M.I. type 6097F), the whole detector being shielded by 1½ in. of lead in all directions. The output of the photomultiplier tube was taken through an emitter follower to a linear amplifier, pulse height analyser, and automatic 1-μsec. scaler-timer assemblage (Panax PX type P7703). Optimum working conditions for measurement of the radiation from ^{131}I were determined from E.H.T. and discriminator bias curves for reference samples and background. Visual inspection of these characteristic curves and confirmation by a statistical method[19] led to the choice of E.H.T. = 900 v and discriminator bias of 5 v at an amplifier gain of 30 dB. Under these conditions the count rate/E.H.T. plateau slope was less than 1% per 100 v with a background of about 10 counts/sec. which is considered to be very satisfactory.

Preliminary investigation of methods for separation of the active 1-iodo-2,4-dinitrobenzene from the reaction mixture suggested that solvent extraction as used by other workers[15,16] was unreliable. Apart from difficulties due to poor phase separation and losses in the washing procedure, at high specific activities appreciable count rates above background could be obtained from the solvent blank runs, even in the absence of the iododinitrobenzene substrate. Such difficulties are to be expected with high specific activity materials owing to traces of radiochemical impurities in the active solution and, more probably, chemical impurity of the solvents.

A much cleaner and more rapid separation was achieved by precipitation of the 1-iodo-2,4-dinitrobenzene by pouring the methanolic reaction mixture into a little water. After coagulation, the precipitate could be readily filtered and could be easily purified from excess of iodide by washing with water. To simplify the kinetic technique and to reduce transfer errors to a minimum, a one-piece filter-counting tube was designed (Figure 1). Using this apparatus, filtration, weighing, and counting could be carried out without handling or transferring the precipitate. Referring to Figure 1, a grade 2 sintered glass filter disc, A, is sealed 5 mm. from the end of a glass tube, B, which is of a diameter such that it just fits into the well of the sodium iodide scintillation crystal. The lower end of the tube B is ground to make a vacuum-tight joint into the filter vessel, C.

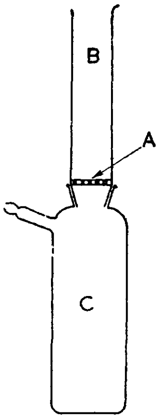

FIGURE 1

In use, the precipitate is filtered off into the weighed tube B, and, after washing, it is dried in an air-oven, cooled, and reweighed to constant weight. The count-rate of the precipitate is obtained by insertion of the tube directly into the well counter. This procedure has the further advantage over liquid extraction that the active material is packed down into a small volume at the bottom of the well so that maximum and constant counting efficiency is obtained. This simple technique is of general application wherever it is required to collect solid radioactive samples from suspension and to count by the scintillation well technique.

The separation method was shown to be entirely satisfactory in a series of proving experiments which established the linearity of the counting procedure using accurately weighed samples of 1-[^{131}I]iodo-2,4-dinitrobenzene. The purity and stability of the active iododinitrobenzene was

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[17] *Org. Synth.*, 1960, **40**, 34.

[18] A. I. Vogel, " Textbook of Practical Organic Chemistry," Longmans, 1956, p. 169.

[19] K. D. Outteridge, " The Statistics and Comparison of Counters," A.E.R.E. Memorandum 1/M 32, Harwell, 1954.

confirmed by measurement of specific activity after repeated washing with distilled water in the filter tube.

Kinetic Rate Determination.—The rate of exchange between iodide ion and the organic substrate was determined from the equation: [20]

$$R = -\frac{[A][B]}{\beta[A] + \alpha[B]} \times \frac{\ln(1 - F)}{t} \qquad (1)$$

where [A] = concentration of I^- in the reaction medium (active + inactive), [B] = concentration of 1-iodo-2,4-dinitrobenzene, α and β represent the kinetic isotope effects in the two opposing transfer reactions constituting the exchange equilibrium, and F = fraction of exchange occurring in time *t*.

In these studies using radioactive iodine, the isotope effect between ^{131}I and ^{127}I is quite negligible, so the isotope effect terms α and β are each equal to unity. The fraction of exchange, F, at any time *t* is then given by

$$F = (S_t - S_0)/(S_\infty - S_0) \qquad (2)$$

where S = specific activity in suitable units, in this case counts $sec.^{-1}$ $mg.^{-1}$, and subscripts refer to zero and infinite time.

Values of [A] and [B] were obtained directly from the quantities weighed out for the reaction mixtures. The ^{131}I used to label the potassium iodide was obtained by serial dilution in pure methanol of high specific activity (100 mc./ml.) sodium [^{131}I] iodide solution. Since each reaction mixture in the kinetic studies contained only about 0·1 μc of ^{131}I, this corresponded to a dilution of about 10^{-6}, so the mass of ^{131}I was negligible compared with the mass of inactive iodide; also, any chemical impurities carried over from the labelled material were at quite negligible concentrations. After preliminary experiments the general procedure adopted for determination of exchange rates was as follows.

The required quantities (2—5 ml.) of 1-iodo-2,4-dinitrobenzene in methanol and potassium iodide (analytical grade) containing about 0·1 μc of ^{131}I in methanol were transferred by piston-pipette into 7-ml. glass ampoules which were then sealed, preheated to 10° below the chosen reaction temperature, and transferred to a vapour-bath maintained at the required temperature. Ampoules were removed from the bath at timed intervals and immediately cooled in tap water. Equilibrium values of exchange were obtained by leaving ampoules in the vapour-bath until no change in specific activity could be detected between consecutive samples. After opening, the contents of each ampoule were discharged into a 25-ml. beaker and the ampoule was rinsed with 1—2 ml. of distilled water. Water was added dropwise to the beaker until no further precipitation of 1-iodo-2,4-dinitrobenzene occurred.

The precipitate was allowed to stand for 10 min. with occasional stirring and scratching, then filtered through the weighed filter tube described above. Each sample was washed with five 2-ml. portions of distilled water; the last portion contained a trace of wetting agent to ensure that the precipitate was washed down off the sides of the tube to form a neat mat on the filter disc. The filter tube was dried in an air-oven at 70° and weighed to constant weight.

All samples from any one run were collected and counted together so that corrections for radioactive decay were unnecessary. For each sample, measurements of at least 10,000 counts were made (fractional standard deviation 1%), and if there was satisfactory statistical agreement the mean was taken for calculations of specific activity after correction for background. Counter paralysis–time losses were negligible.

The fraction of exchange, F, was calculated using equation (2). A typical set of experimental results are shown in Table 1, and some plots of $\log_{10}(1 - F)$ against time illustrated in Figure 2.

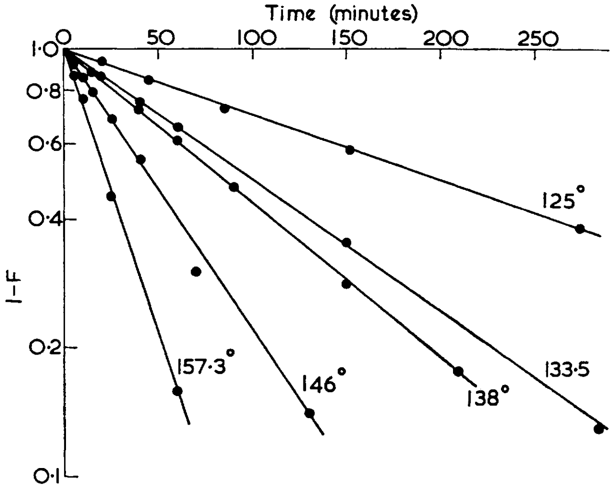

FIGURE 2

TABLE 1

Typical count rate from a kinetic run

[I^-] = 0·0905M; [$C_6H_3(NO_2)_2I$] = 0·2002M; temp. 133·5°

Reaction period (min.)	Wt. of $C_6H_3(NO_2)_2I$ (mg.)	Sp. activity (counts/sec./mg.)	(1 − F)
0	54·4	0·711	—
10	54·3	0·905	0·915
30	54·9	1·258	0·759
50	56·9	1·572	0·620
130	54·4	2·321	0·289
281	54·4	2·825	0·067
680 (infinity)	57·8	2·976	—

Reaction Order.—Reaction order was established by substituting the kinetic data, from a series of runs at constant temperature, in the various simple integrated rate equations. The experimental results (Table 2) fit satisfactorily to a second-order equation. The last column gives values of the second-order rate constant *k''* calculated from

$$k'' = -\frac{1}{[A] + [B]} \ln \frac{(1 - F)}{t} \qquad (3)$$

Order with respect to each reactant was determined from the same data by application of the general rate equation

$$R = k[A]^a[B]^b \qquad (4)$$

in which reaction orders *a* and *b* were evaluated by plotting log *R* against log [A] and against log [B] to give :

$$a = \frac{\delta(\log R)}{\delta(\log[A])_{B,T}} = 0{\cdot}96 \qquad b = \frac{\delta(\log R)}{\delta(\log[B])_{A,T}} = 0{\cdot}99$$

These data establish that, over the concentration range investigated, the reaction is overall second-order, and first-order with respect to each reactant.

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[20] L. Melander, *Arkiv Kemi*, 1955, **7**, 287.

TABLE 2

Exchange rates and specific rate constant at 133·5°

[A]	[B]	10^5R (l. mole^{-1} sec.$^{-1}$)	$10^3k''$ (l. mole^{-1} sec.$^{-1}$)
0·0905	0·2002	0·986	0·545
0·0503	0·2002	0·562	0·559
0·2591	0·2002	2·72	0·523
0·0905	0·0200	0·099	0·547
0·2410	0·1087	1·31	0·500
0·0739	0·1087	0·519	0·645

TABLE 3

Activation parameters

$[I^-] = 0·0739$M; $[C_6H_3(NO_2)_2I] = 0·1087$M

T (°K)	$10^3/T$	$t_{\frac{1}{2}}$ (min.) *	$10^3k''$ (l. mole^{-1} sec.$^{-1}$)	log k''	$\log_{10} B$
398	2·514	198	0·319	−3·496	9·06
406·5	2·460	98	0·645	−3·191	9·08
411	2·435	83·5	0·758	−3·121	9·04
419	2·387	46	1·37	−2·862	9·08
430·3	2·324	22·5	2·81	−2·552	9·07

$E_A = 22·8 \pm 0·5$ kcal. Mean $\log_{10} B = 9·07$.

* Reaction half-time.

Activation Energy.—In another series of measurements at five different temperatures, data were obtained for calculation of the Arrhenius activation parameters. Values (Table 3) were calculated from large-scale plots of specific rate constant against $1/T$ (Figure 3).

TABLE 4

Energy levels calculated according to Miller's procedure,[11] and experimental data for some aromatic S_N2 reactions in methanol or ethanol

Reagent and solvent	Benzene subst.	Calculated energy levels (*a*)						Experimental data			Ref.
		I.St.	T.St.1	I.C.	T.St.2	F.St.	ΔE^* (*b*)	ΔE^* (*b*)	$\log_{10} B$ (*c*)	k_2 (*d*)	
Li^+ Cl^- (EtOH)	1-Cl-2,4,6-$(NO_2)_3$	−10	+13·5	0	+13·5	−10	23·5	22·8	11·5	$1·4 \times 10^{-2}$	21
K^+ I^- (MeOH)	1-F-2,4-$(NO_2)_2$	−17·5	+4·5	0	+15·5	−21·5	33·0	Reaction very slow; methanolysis occurs instead			11*a*, 22
K^+ I^- (MeOH)	1-Br-2,4-$(NO_2)_2$	−17·5	+8·5	0	+10	−19·5	27·5	$24·9_5$	9·8	$1·5 \times 10^{-5}$ (*e*) (*f*)	22
K^+ I^- (MeOH)	1-I-2,4-$(NO_2)_2$	−17·5	+8·5	0	+8·5	−17·5	26·0	22·8 (*g*)	9·1 (*g*)	$4·7 \times 10^{-5}$ (*h*)	This Paper
Na^+ OMe^- (MeOH)	1-I-2,4-$(NO_2)_2$	−2	+17	0	+4·5	−22·5	19	$18·9_5$	11·7	$3·61 \times 10^0$	23

(*a*) Kcals. relative to I.C. = 0; initial and final states; transition states 1 and 2; intermediate complex. (*b*) Kcal. mole^{-1}. (*c*) For anion–neutral substrate reactions in methanol $\log_{10} B$ usually ranges from 11·0 to 11·5. (*d*) L. mole^{-1} sec.$^{-1}$ at 100°. (*e*) With Li^+I^- in MeOH, $k_2(100°) = 1·6 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$. (*f*) Based on $\Delta E^* = 27·5$ and $\log_{10} B = 11·0$, k_2 (100°) is estimated as about 10^{-5}. [g] Marcopoulos [16a] for a reported unimolecular reaction gives values of ΔE^* between 7·24 and 20·69, and of $\log_{10} B$ between 0·6 and 7·4. (*h*) Prior to carrying out experimental work we had estimated k_2 (100°) as about 5×10^{-5} l. mole^{-1} sec.$^{-1}$ based either on $\Delta E^* = 26·0$ and $\log_{10} B = 11·0$, or, if similar pattern to reaction with 1-bromo-2,4-dinitrobenzene, 23·5 and approximately 9·0, respectively.

RESULTS AND DISCUSSION

The calculations of potential-energy–reaction coordinate profiles for a wide range of activated aromatic S_N reactions made by Miller,[11] which give, *inter alia*, values of ΔE^*, have been shown to give satisfactory, often very good, agreement with experiment. They are least precise in the reactions with anionic nucleophiles when both entering and replaced groups are themselves heavy atoms or are attached to the reaction centre by a heavy atom; [11a,c] calculated values are then high. Even in those cases, the values of $\log_{10}B$ (and ΔS^*) are lower (ΔS^* more negative) than is normal for reactions with anionic nucleophiles, so measured reactivity in all cases so far investigated is close to that predicted.

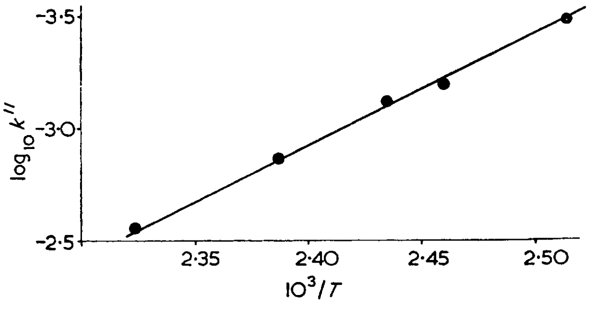

FIGURE 3

Table 4 compares calculated and experimental results [16,21-24] for some halide exchanges, *viz.*, chloride ion with picryl chloride, iodide ion with 1-fluoro-, 1-bromo-, and 1-iodo-2,4-dinitrobenzene, and for comparison, methanolysis of the iodo-compound, in a typical protic solvent such as methanol or ethanol. In each case there is satisfactory agreement between theory and experiment.

Our measured ΔE^* value, which differs markedly from those of Marcopoulos,[16a] is in accord with the very large body of data from activated aromatic S_N reactions with anionic reagents in protic solvents, as well as with the theoretical predictions. The $\log_{10}B$ value of 9·1, although higher than those previously reported,[16a] is still below typical values for most anion–neutral substrate reactions in methanol, but low values of $\log_{10}B$ seem to be characteristic of heavy-atom exchange in this

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[21] C. W. L. Bevan and J. Hirst, *J. Chem. Soc.*, 1956, 254.

[22] J. Miller and A. J. Parker, *J. Amer. Chem. Soc.*, 1961, **83**, 117.

[23] A. L. Beckwith, G. D. Leahy, and J. Miller, *J. Chem. Soc.*, 1952, 3552.

[24] A J. Parker, *Quart. Rev.*, 1962, **16**, 163.

type of reaction. Marcopoulos suggests that the reaction is unimolecular, being first-order in aromatic substrate and zero-order in iodide ion, whereas we find it to be cleanly second-order, first-order in each reactant, except at extremely low iodide concentrations, where spurious effects are to be expected and where the order is indeterminate.

We have not yet obtained kinetic data for the corresponding reactions in aprotic solvents, but it is well known[22] (cf. ref. 24) that, whilst anionic nucleophiles are much more reactive in dipolar aprotic than in protic solvents, the kinetic order is unaffected in any of the aromatic S_N reactions for which reliable results are available. It is, in any case, relevant that Broadbank *et al.*[15] indicate that the reaction of iodide ion with 1-iodo-2,4-dinitrobenzene in acetone is second-order.

The addition–elimination S_N2 mechanism for activated substrates is thus further substantiated, and there is still no reliable evidence for any activated aromatic S_N reaction being other than bimolecular. The results for 1-iodo-2,4-dinitronaphthalene,[16b] which suggest that this reaction too is zero-order in iodide ion, were obtained by techniques similar to those used with 1-iodo-2,4-dinitrobenzene, and must, we believe, also be regarded as applying only to very low concentrations of iodide ion and therefore as not being of general application.

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