Kinetics of Hydrogen Isotope Exchange Reactions. Part XXIII.[1] Isomer Distributions in the Radiation-induced Tritiation of Benzene Derivatives in Aqueous Solution

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The isomer distribution of aromatic tritiation induced by γ-irradiation of solutions of aromatic compounds (anisole, toluene, chlorobenzene, and fluorobenzene) in tritiated water was examined by nitration of the reaction product, separation, and tritium assay of the isomeric mononitration products. In toluene and anisole, *ca.* 70% of tritium atom attack occurs at *ortho*-positions; in the two halogenobenzenes the attack appears to be approximately statistical.

In the preceding paper[1] it was shown that aqueous hydrogen (tritium) atoms, produced by the self-radiolysis of tritiated water discriminate in their reactions with aromatic compounds, the alkylbenzenes and anisole appearing as more reactive substrates than benzene. These are overall intermolecular reactivity comparisons and refer to attack at all positions. By themselves, they do not indicate whether the slightly enhanced reactivity is also an attribute of the individual nuclear positions of the aromatic compounds or whether a greater or lesser degree of discrimination might apply to the intramolecular competition. *A priori*, it is possible that primary attack on the aromatic molecules, resulting in ' capture ' of the hydrogen atom, might be less selective than the consequent bonding of that atom to a particular site, *i.e.* it is conceivable that rate-controlling and product-controlling steps of the mechanism are different. Whether this type of mechanistic model is valid for electrophilic aromatic substitution, for example, is still debatable.[2] For the reaction of tritium atoms this possibility can be probed by determination of isomer proportions of the tritiated aromatic compounds produced in the reaction. Such measurements are now reported.

Although the required determination of the labelling pattern of aromatic compounds is well understood and has been performed before,[3-5] special problems are set in the present work by the low level of tritium labelling achieved during the radiation-induced exchange. The reactivity of only certain positions in each compound could therefore be established with reasonable accuracy.

The compounds studied were toluene, anisole, chlorobenzene, and fluorobenzene. Of these, the first two are more reactive than benzene (2·2 and 2·7 times, respectively), whereas the two halogenobenzenes have an overall reactivity close to that of benzene (implying a slightly enhanced reaction rate per available nuclear position). For all these compounds the isomer distribution was investigated by mononitration, followed by gas-chromatographic separation of isomers and determination of the amount of tritium lost as a result of substituting a particular hydrogen-bearing position (labelled with tritium) by a nitro-group. The fraction of the total activity in a particular position of the parent compound is then given by a ratio (ω, μ, π, according to whether an *ortho*-, a *meta*-, or a *para*-position is being considered) as defined in equation (1) for the case of *ortho*-substitution in toluene. The quantity thus calculated refers to *one ortho*-position, *i.e.* the fraction of the

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[1] Part XXII, C. L. Brett and V. Gold, preceding paper.

[2] G. A. Olah, *Accounts Chem. Res.*, 1971, **4**, 240; J. H. Ridd, *ibid.*, p. 248.

[3] F. Cacace and S. Caronna, *J. Amer. Chem. Soc.*, 1967, **89**, 6848.

[4] F. Cacace and G. Perez, *J. Chem. Soc.* (*B*), 1971, 2086.

[5] F. Cacace, R. Cipollini, and G. Ciranna, *J. Chem. Soc.* (*B*), 1971, 2089.

activity in both *ortho*-positions will be 2ω. The

$$\omega = \frac{\text{activity of toluene} - \text{activity of } o\text{-nitrotoluene}}{\text{activity of toluene}} \quad (1)$$

' activity ' used in equation (1) is the number of disintegrations per minute (d.p.m.) per mole of a given irradiated sample.

The application of this method relies on two main assumptions, (*a*) that attack by the nitrating species on protium- and tritium-bearing positions occurs with the same velocity, *i.e.* without an isotope effect, and (*b*) that the nitrating medium does not cause loss of tritium from the aromatic compound by hydrogen exchange prior to or subsequent to nitration. Both assumptions seem justified in the light of Melander's thorough investigations of the nitration of tritiated aromatic compounds.[6] In the present experiments it was occasionally found that the un-nitrated residue of the aromatic compound was less active than the starting material and (by use of specifically labelled toluenes) that the loss was more noticeable when the temperature was allowed to rise. However, it would appear that this incompleteness of some reactions was due to exhaustion of the nitrating mixture, allowing unchanged aromatic compound to remain in contact with sulphuric acid, instead of with a nitrating medium, and hence to undergo a small amount of exchange. This tritium loss has accordingly been disregarded in the evaluation of our results.

Because the main limitation of the procedure is set by the low activities of the samples subjected to nitration, the irradiations were carried out with the cobalt-60 source, so as to introduce maximum activity into the substances studied. The optimum dose was found to be obtained by placing the specimen at the position of maximum intensity of the source and irradiating for 40—60 min. Longer irradiation times did not improve the yield of labelled compound, owing to the increased importance of radiation damage. The tritium concentration in these experiments was either 8 or 16 Ci dm^{-3}. Present indications are that there is no fundamental difference between β- and γ-radiation-induced aromatic exchange reactions.

The following conclusions from the experiments are considered reliable. In the case of the two activated compounds (toluene and anisole) there is a pronounced preference for tritium atom attack to occur in an *ortho*-position. The share of each of the *ortho*-positions of such attack is *ca.* 35% for both compounds. These figures imply that the slight intermolecular reactivity differences between these compounds and benzene find a counterpart in a corresponding slight activation of *ortho*-positions over other nuclear positions. Because in aggregate the *ortho*-positions account for *ca.* 70% of the total reaction it follows that, even if the reaction at the *para*-position is totally disregarded, each *meta*-position can account at the very most for 15% of the total reaction. Hence the *ortho*-positions in toluene and anisole are considerably activated. An *ortho*-position of toluene is *ca.* 4 times more reactive than a position in benzene and an *ortho*-position in anisole is *ca.* six times more reactive. Taken together the other three positions of each compound are very slightly activated but it is probable, on the available approximate evidence, that activation is confined to the *para*-position and that the *meta*-positions are not very different from a benzene site in reactivity.

For chlorobenzene and fluorobenzene the results indicate that the amount of reaction at the *para*-position (21—22%) is approximately statistical (20%). The overall reactivity of these compounds towards tritium

Experimental results

Compound	Sample no.*	Specific activity/d.p.m. mol^{-1} Parent compound	*o*-Nitro-derivative	*p*-Nitro-derivative	100ω †	100π †
Toluene	1	4·17	3·01	3·88	28 ± 2	(7 ± 3)
	2	5·29	3·33	4·71	38 ± 2	(11 ± 3)
	4	7·05	4·43	6·5	37 ± 2	(8 ± 3)
	5	8·13	5·07	6·08	38 ± 2	(25 ± 2)
	6	6·90	4·51	5·55	35 ± 2	(20 ± 3)
Anisole	1	24·9	18·6	21·4	25 ± 3	(14 ± 3)
	2	25·5	16·4	19·1	36 ± 2	(25 ± 3)
	4*a*	38·9	26·7	30·2	32 ± 2	(22 ± 2)
	4*b*	38·9	25·5	33·4	35 ± 2	(14 ± 3)
	5*a*	41·9	28·0	27·6	34 ± 1	(34 ± 2)
	5*b*	41·9		31·5		(25 ± 3)
Chlorobenzene	1*a*	4·10		3·21		22 ± 3
	1*b*	4·10		3·23		21 ± 3
	2	3·62	2·93	2·85	(19 ± 3)	21 ± 3
	3	3·75	2·32	2·9	(38 ± 3)	23 ± 3
Fluorobenzene	1	6·01	4·98	4·68	(17 ± 8)	22 ± 4
	2	5·98	4·30	4·56	(28 ± 4)	24 ± 4
	3	6·4	5·1		(20 ± 5)	
	4*a*	15·0		11·8		21 ± 5
	4*b*	15·0		11·7		22 ± 8

* The letters *a*, *b* refer to independent determinations for the product of the same irradiation and nitration. Different sample numbers indicate separate irradiations. † Values in parentheses in this column refer to the nitro-compound eluted second (less reliable result).

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[6] L. Melander, *Arkiv. Kem.*, 1950, **2**, 211.

atoms is very close to that of benzene, and it thus follows that the reactivity of the *para*-position in each halogenobenzene is very similar to that of a benzene site.

Altogether, these findings give no grounds for supposing that the overall reactivity of an aromatic compound is other than the sum of the reactivities of individual sites.

A comparison of these results with more extensive determinations of partial rate factors for aromatic phenylation [7] reveals a striking similarity. In toluene, 65% of the nuclear phenylation occurs at an *ortho*-position and in anisole the corresponding figure is 70%. In these cases the partial rate factors for *ortho*-positions (relative to a single position in benzene) are 2·4 for toluene and 4·2 for anisole, implying a slightly lower selectivity in phenylation.

Chlorobenzene and fluorobenzene give only 15 and 17·5% of the phenylation reaction at the *para*-position but, like the present results, these figures lead to the conclusion that the *para*-position is, in each case, of approximately equal reactivity to a benzene position.

EXPERIMENTAL

Materials and general procedures of sample preparation, separation, and counting were as in the preceding paper, except that solutions were de-gassed by only two pump–freeze–thaw cycles. The solutions also contained a small concentration of sulphuric acid (*ca.* 4×10^{-5}M), not sufficient to produce a significant amount of acid-catalysed exchange, with the object of increasing the yield of the hydrogen-atom reaction by conversion of solvated electrons into hydrogen atoms. γ-Irradiations of samples were performed on the Imperial College cobalt-60 source, as in the preceding paper. Irradiation times varied from 40 to 60 min, corresponding to total irradiation doses of *ca.* 10^6 rad (10^4 J kg^{-1}).

Irradiations were carried out at ambient temperature of the source chamber (*ca.* 22 °C), except for the experiments with *p*-iodoanisole which were done at 85—100 °C in order to achieve a higher substrate solubility and concentration (*ca.* 0·01M).

Specifically tritium-labelled toluenes ([*o*-^{3}H], [*m*-^{3}H], and [*p*-^{3}H]) were prepared from the corresponding bromotoluenes *via* the Grignard compounds.[8]

Determination of Positions of Exchange.—(a) *Toluene.* A portion (0·5 g) of purified toluene was oxidised by boiling for 24 h with neutral potassium permanganate solution (5 g in 30 cm^3). The solution was acidified with a few drops of sulphuric acid and the benzoic acid formed was recrystallised from water to constant specific activity. Practically all (99%) of the original activity of toluene was found to be retained in the benzoic acid, indicating that, as for mesitylene,[9] exchange occurs exclusively or almost exclusively in the aromatic ring. To determine the position(s) of nuclear substitution, a sample of the tritiated toluene (0·5 cm^3) was slowly added (20 min—1 h) to an equal volume of a cooled (0°) mixture of equal volumes of conc. sulphuric acid and fuming nitric acid (*d* 1·5).[6] At the end of this period ice (5 g) was added and the reaction product was extracted with ether. The extract was washed 3—4 times with a dilute solution of sodium hydrogen carbonate and twice with water, and then dried (Na_2SO_4). The nitrotoluenes were separated by g.l.c. on temperature-programmed Apiezon L or M columns, and collected in weighed vials. After dilution by weight with toluene, aliquot portions of the solution were transferred to scintillator vials for counting.

(b) *Halogenobenzenes.* The nitration procedure was similar to that used for toluene, except that the reaction temperature was 50—60 °C and that a Bentone 34 column, operated at 200°, was used for the separation of reaction products.[4]

(c) *Anisole.* For this nitration,[10] fuming nitric acid (15 parts) was dissolved in acetic anhydride (85 parts) and an equal volume of a solution of anisole (0·5 g) in acetic anhydride (16 cm^3) was slowly (1 h) added to the mixture at 0°. After partial neutralisation with sodium carbonate, extraction with ether, and washing of the ether solution with aqueous sodium hydrogen carbonate and water, the products were separated by g.l.c. as for the nitrotoluenes. The same method was used to examine the tritium distribution in anisole produced by radiolysis of *p*-iodoanisole in aqueous solution.[11] It was found that 74·8 ± 0·2% of the tritium activity was at the *para*-position of anisole, *i.e.* at the position from which iodine had been displaced. The remaining 24% of activity were distributed between *ortho*- and *meta*-positions (9·6 ± 2·2% at each *ortho*-position, 3·5 ± 4·6% at each *meta*-position).

The compounds studied are known [12] not to give significant amounts of *meta*-nitration and no *meta*-isomers were detected in the preparative gas-chromatographic separations. The separations of *ortho*- and *para*-nitro-compounds on Apiezon columns were not perfectly sharp and 1 or 2% of the wrong isomer may in every case have been included with the main fraction. However, since the specific activities of the isomers were of the same order of magnitude, this cross-contamination will not lead to any serious error. A more serious source of error is the possible elution of higher-boiling, highly tritiated impurities along with the second nitro-compound to emerge from the column during the temperature-programmed phase of operation. It was found that the activities of compounds eluted at this stage were more variable and, if this lack of reproducibility is due to additional impurities, the lowest activities measured for these compounds (*i.e.* corresponding to the highest isomer proportions) should be the most reliable ones. Although the full raw measurements for the second eluates are included in the Table, the corresponding isomer distributions given in the final columns of the Table are placed in parentheses (being less reliable than other values).

The assay of tritium in nitro-compounds by the scintillation method is less efficient than that of the parent compounds owing to the quenching characteristics of the former. In order to obtain exactly comparable activity values for parent compounds and the respective nitro-derivatives, the parent compounds were always assayed in the presence of the same concentration of (inactive) nitro-compound as used in the tritium count of the nitro-

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[7] G. H. Williams in 'Essays on Free-Radical Chemistry,' Chem. Soc. Special Publ. No. 24, 1970, p. 25.

[8] A. Murray and D. L. Williams, 'Organic Syntheses with Isotopes,' Interscience, New York, 1958, vol. II, pp. 1448, 1684.

[9] J. R. Adsetts and V. Gold, *J. Chem. Soc.* (*B*), 1969, 1108.

[10] K. Halvarson and L. Melander, *Arkiv. Kem.*, 1957, **11**, 77.

[11] C. L. Brett and V. Gold, following paper.

[12] R. O. C. Norman and R. Taylor, 'Electrophilic Substitution in Benzenoid Compounds,' Elsevier, Amsterdam–London–New York, 1965.

derivative. As an additional check, *ca.* 0·1 g of a toluene sample of known specific activity was weighed into each vial after the completion of the sample count. The increase in the observed count rate thus leads to the comparative counting efficiency for each sample. In some cases this evaluation of the relative counting efficiency of chemically identical samples was achieved by the external standards ratio. However, the use of this method by itself on samples of widely different quenching characteristics is not reliable and was avoided throughout. The optimum amount of nitro-compound for tritium assay was 10 mg. Normally, larger amounts of the compounds were weighed out and dissolved and then diluted by weight.

The cumulative random error of the final result, due to statistical errors of sample and background counts, including those involved in the determination of counting efficiency (±0·5%) and to errors in weighing (±0·5 mg) and volatility losses, was calculated for each determination and is given in the Table.

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