

190. The Isotopic Exchange between *o*-Iodoanisole and Inorganic Iodine.

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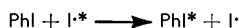
The isotopic exchange between *o*-iodoanisole and inorganic iodine has been investigated in different solvents and at temperatures in the range 79–136°. The reaction follows a rate law, $R = k[\text{PhI}]$ ($k = 20 \times e^{-15,700/RT} \text{sec.}^{-1}$, in solvents of moderate polarity), which implies that only the iodo-aromatic compound is involved in the rate-determining step. The rates of spontaneous deiodination, as well as deiodination in the presence of nucleophiles and electrophiles, are much slower than the rate of isotopic exchange. Chloride, butoxide, and stannous ions inhibit the exchange process. It is suggested that the reactive species in the exchange process are elementary iodine and an excited form of the iodo-aromatic compound which is produced in the rate-determining step.

THE carbon-iodine bond in iodo-aromatic compounds can undergo cleavage by a variety of mechanisms, which include thermal homolysis, photolysis, electrophilic substitution, bimolecular nucleophilic displacement, and free-radical bimolecular substitution. The isotopic exchange between inorganic iodine and iodo-aromatic compounds is a special case of these displacement reactions, and it may proceed by almost any of the given mechanisms. Iodine exchange may occur as a result of a back reaction of a thermal or photochemical homolysis:

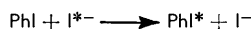


This pathway could not, however, be experimentally verified.¹

An electrophilic substitution by H_2OI^+ has been experimentally excluded² owing to a much faster electrophilic displacement by H_3O^+ . Alternative pathways for the exchange reaction are the homolytic substitution by iodine atoms,



which was experimentally verified,¹ and the nucleophilic substitution by iodide ions,



which was reported in certain systems.^{3,4}

Many experimental results have been reported on the isotopic exchange between iodide or elementary iodine and various iodo-aromatic compounds, showing a zero-order dependence on the inorganic species.⁵ The purpose of the present work was to elucidate the mechanism of the zero-order reactions, namely exchange reactions whose rate is independent of inorganic iodine.

The isotopic exchange between *o*-iodoanisole and iodide ions has been investigated in butan-1-ol solutions in the concentration ranges 0.077–1.5M-*o*-iodoanisole and 5×10^{-5} – 1.2×10^{-2} M-iodide. From Table I it can be seen that the rate of exchange (R) depends solely on the concentration of the iodo-aromatic compound: $R = k[\text{PhI}]$. Constant k values, $3.3 \pm 0.3 \times 10^{-9}$ and $1.1 \pm 0.2 \times 10^{-8}$, were found throughout the given range of concentrations at 80° and 100°, respectively. The rate was not affected by diffuse light or by the presence of oxygen.

The exchange was studied in different solvent systems, including ethanol, ethanol-water, anisole, decane-butanol, acetic acid, and acetic acid-sulphuric acid. The same

¹ Anbar and Rein, *Chem. and Ind.*, 1963, 1524.

² Rein, Thesis, Jerusalem, 1960.

³ Kristjanson and Winkler, *Canad. J. Chem.*, 1951, **29**, 154.

⁴ May, Gerandel, and Regnault, *Compt. rend.*, 1953, **237**, 613.

⁵ May and Dawdel, *I. Chim. Phys.*, 1956, **53**, 274, and references therein.

TABLE 1.

Isotopic exchange between *o*-iodoanisole and iodide ions in butan-1-ol.

[IA] (moles l. ⁻¹)	10 ⁴ [I ⁻] (moles l. ⁻¹)	Temp. (°c)	<i>t</i> _½ (hr.)	10 ⁸ <i>R</i> (moles l. ⁻¹ sec. ⁻¹)	10 ⁸ <i>k</i> (sec. ⁻¹) { <i>k</i> = <i>R</i> /[IA]}	Remarks
1.5	0.5	100	0.7	1.36	0.9	Air and diffuse light
1.5	10	"	10.0	1.9	1.27	" "
1.5	120	"	143.5	1.6	1.06	" "
0.77	1	"	1.8	1.06	1.42	" "
0.77	10	"	29.9	0.64	0.85	" "
0.77	100	"	208	0.92	1.23	" "
1.57	11	"	14	1.5	0.99	Deaerated and dark
0.77	10	"	32	0.6	1.0	" "
0.77	17	"	59	0.54	0.77	" "
0.385	5	"	32	0.3	0.81	" "
0.385	32	"	125	0.49	1.3	" "
0.077	0.5	"	9	0.108	1.4	" "
0.77	1.6	80	11	0.27	0.35	Air and diffuse light
0.77	8	"	57	0.28	0.36	" "
0.385	3.2	"	55	0.11	0.3	" "
0.19	8	"	236	0.065	0.34	" "
0.077	0.8	"	60	0.026	0.31	" "

TABLE 2.

Isotopic exchange between *o*-iodoanisole and iodide ions in different solvents.

Solvent	Temp. (°c)	[IA] (moles l. ⁻¹)	10 ⁴ [I ⁻] (moles l. ⁻¹)	<i>t</i> _½ (hr.)	10 ⁸ <i>R</i> (moles l. ⁻¹ sec. ⁻¹)	10 ⁸ <i>k</i> (sec. ⁻¹)
Ethanol	79	0.77	2	6	0.24	0.31
"	"	0.77	4	40	0.19	0.25
"	"	0.77	6	60	0.19	0.25
"	"	0.77	8	90	0.17	0.22
"	"	0.58	0.5	5.3	0.18	0.31
"	"	0.385	0.5	6.4	0.15	0.39
"	"	0.28	0.1	2	0.1	0.36
"	"	0.27	0.5	14	0.068	0.24
"	"	0.16	0.2	15.4	0.025	0.22
"	"	0.155	0.5	29	0.033	0.21
"	"	0.155	1	32.3	0.059	0.38
"	"	0.077	0.1	19.3	0.01	0.2
Ethanol-water (9:1)	"	0.385	0.5	9.6	0.1	0.28
Anisole	100	1.55	8	10.9	1.4	0.91
"	"	0.77	9	21.6	0.8	1.04
"	80	1.55	8	33	0.46	0.3
"	"	0.77	9	75	0.23	0.29
Butan-1-ol-decane* (6.7)	100	0.77	7	13.4	0.99	1.3
"	"	(3.3)	9	15.0	1.15	1.5
"	"	(1.1)	0.77	8.4	14.8	1.09
"	"	(0.89)	0.77	0.5	1.1	0.85
"	"	(0.66)	0.77	0.5	1.45	0.69
"	"	(0.55)	0.77	4	8.5	0.91
"	"	(0.44)	0.77	0.5	1.7	0.56
"	"	(0.32)	80	10	88	0.23
"	"	(0.27)	0.77	0.5	3.2	0.3
"	"	(0.11)	0.77	2	14.7	0.26
Acetic acid	100	0.77	9	4.4	3.9	5.1
"	"	0.77	3.5	1.9	3.45	4.5
"	"	0.77	2.5	2.1	2.3	3.0
"	"	0.77	1	0.6	3.4	4.4
Acetic acid-H ₂ SO ₄ (39:1)	"	0.77	1	0.66	2.9	3.8
"	"	0.77	1	0.66	2.9	3.8
Acetic acid (9:1)	80	1.55	0.5	0.8	1.24	0.85
"	"	0.77	0.5	2.2	0.48	0.65

* Concentration of butan-1-ol in moles per litre.

specific rate of exchange is obtained (Table 2) in all the systems studied, with the exception of acetic acid, in which a substantial increase in *k* was observed. It should be noted that the addition of water or sulphuric acid did not affect the rate of exchange, nor did the

addition of butanol to decane. The activation energies and the Arrhenius pre-exponential factors are given in Table 3.

For *o*-[¹³¹I]iodoanisole, spontaneous deiodination at 100° in butan-1-ol, acetic acid, and ethanol did not exceed one part in 10⁶ within 100 hours. This gives a lower limit to the half-life (*t*_½) of spontaneous deiodination of 5 × 10⁷ hours.

TABLE 3.
Energies of activation and pre-exponential factors (according to $k = Ae^{-\Delta E/RT}$) in different solvents.

Exchange	Solvent	ΔE (kcal. mole ⁻¹)	$\log A$	Exchange	Solvent	ΔE (kcal. mole ⁻¹)	$\log A$
IA—I ⁻	Butan-1-ol	15.7	1.3	IA—I ⁻	Acetic acid	22.2	5.5
,,	Anisole	15.5	1.1	IA—I ₂	Butan-1-ol	18.5	2.0

TABLE 4.
Isotopic exchange between *o*-iodoanisole and molecular iodine.

[IA] (moles l. ⁻¹)	10 ⁴ [I ⁻] (moles l. ⁻¹)	<i>t</i> _½ (hr.)	10 ⁸ <i>R</i> (moles l. ⁻¹ sec. ⁻¹)	10 ⁸ <i>k</i> (sec. ⁻¹)	[IA] (moles l. ⁻¹)	10 ⁴ [I ⁻] (moles l. ⁻¹)	<i>t</i> _½ (hr.)	10 ⁸ <i>R</i> (moles l. ⁻¹ sec. ⁻¹)	10 ⁸ <i>k</i> (sec. ⁻¹)
<i>In butan-1-ol at 80°.</i>					<i>In butan-1-ol at 100°.</i>				
0.385	1.6	54	0.12	0.3	0.385	1.6	10.6	0.58	1.5
0.77	0.8	14.6	0.22	0.29	0.77	4.0	12	1.3	1.7
					0.077	0.4	14	0.11	1.4
<i>In decane at 136°.</i>									
0.77	0.5	0.8	2.3		0.77	20.0	14.4	5.3	
0.77	1.5	2.3	2.5		0.77	30.0	16	7.2	
0.38	2.5	5.6	1.7		0.77	40.0	23	6.6	
0.77	2.5	3.5	2.7		0.77	50.0	30	6.4	
1.55	2.5	2.5	3.9		1.55	50.0	11.3	17.5	
3.1	2.5	1.5	6.4		0.77	100.0	57	6.7	
0.77	3.0	3.7	3.1		0.77	150.0	68	8.5	
0.77	4.5	7.2	2.4		0.77	200.0	97	7.9	
0.77	10.0	6.1	6.3						

The isotopic exchange between *o*-iodoanisole and molecular iodine in butan-1-ol at 100° (Table 4) shows a behaviour similar to that of iodide ions, with specific rate constants comparable with those obtained for iodide.

A more extensive study on the iodine-*o*-iodoanisole exchange, carried out in decane at 136°, reveals (Table 4) a complex dependence on iodine concentration. At 136° the exchange proceeds by two independent simultaneous pathways, one zero-order and the other square-root-order in iodine:

$$R = k_1[\text{PhI}] + k_2[\text{PhI}][\text{I}_2]^{\frac{1}{2}}$$

A least-mean-square analysis of the data yields: $k_1 = 3.2 \pm 0.8 \times 10^8 \text{ sec.}^{-1}$ and $k_2 = 5.3 \times 10^7 \text{ l.}^{\frac{1}{2}} \text{ mole}^{-\frac{1}{2}} \text{ sec.}^{-1}$.

The rate of isotopic exchange was inhibited by the addition of chloride ions (Table 5).

TABLE 5.
Effect of additives on the rate of isotopic exchange in butan-1-ol at 100°.

[IA] (moles l. ⁻¹)	10 ³ [I ⁻] (moles l. ⁻¹)	Additive	10 ³ [Additive] (moles l. ⁻¹)	<i>t</i> _½ (hr.)	10 ⁸ <i>R</i> (moles l. ⁻¹ sec. ⁻¹)	10 ⁸ <i>k</i> (sec. ⁻¹)
0.77	1.0	None	—	31	0.64	0.83
0.77	1.0	NaCl	1.0	36	0.55	0.74
0.77	1.0	NaCl	10	160	0.12	0.16
0.77	1.0	NaCl	100	530	0.038	0.049
0.77	1.0	BuONa	0.1	—	nil	nil
0.77	1.0	SnCl ₂	0.01	—	nil	nil
0.5	0.1	Zn	Powder	—	nil	nil

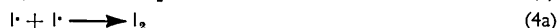
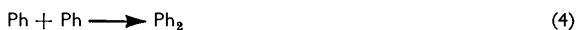
The addition of a ten-fold amount of chloride as compared with iodide, decreased k by a factor of 6, and a hundred-fold excess by a factor of 20. Butoxide, as well as stannous ions, inhibited the exchange completely, and metallic zinc had a similar effect.

With similar concentrations to those given above, no deiodination of o -[^{131}I]iodoanisole was detected in the presence of chloride, butoxide, or stannous ions ($t_{\frac{1}{2}} > 5 \times 10^6$ hr.). Metallic zinc induced deiodination with a half-life of over 250 hours. Also, deiodination of o -[^{131}I]iodoanisole (0.1M), in the presence of 0.15M-iodine and 0.15M-bromine, did not exceed 0.05% in 100 hours ($t_{\frac{1}{2}} > 10^5$ hours).

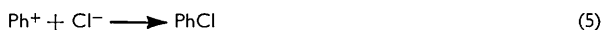
The rate law for the isotopic exchange between inorganic iodine and o -iodoanisole, $R = k[\text{PhI}]$, was characteristic of many isotopic exchange processes among iodo-aromatic compounds. This rate law implies that the rate-determining step depends only on the iodo-aromatic component and does not involve the inorganic species, suggesting, at first sight, a dissociative mechanism, homolytic or heterolytic:



If $\text{I}\cdot$, I^- , and I^+ are in a fast isotopic equilibrium with I^- or I_2 in solution, each of these dissociative reactions may account for the first-order rate law. Each of these mechanisms is, however, inconsistent with the experimental findings: (i) The homolysis by reaction (1) should be followed by recombination reactions



which should lead to net deiodination. As the upper limit of the rate of spontaneous deiodination is three orders of magnitude slower than the rate of isotopic exchange, this would require the back reaction of (1) to proceed at a much faster rate than reactions (4) and (4a), which is unlikely for simple free-radical interactions; (ii) A heterolytic dissociation according to reaction (2) should be accompanied by a net deiodination induced by any nucleophilic reagent like chloride or butoxide ion, according to a conventional $\text{S}_{\text{N}}1$ mechanism:



It was found, however, that no deiodination takes place in the presence of these nucleophiles, at a rate comparable to the isotopic exchange; (iii) A mechanism involving reaction (3) should require net deiodination in the presence of electrophiles, *e.g.*, H^+ .



It was shown that the addition of sulphuric acid to acetic acid did not affect the rate of isotopic exchange. An exchange according to reaction (3) is expected to be completely suppressed by reaction (6), under these conditions. The rate of deiodination in the presence of mineral acids in acetic acid² was found to fall below the rate of isotopic exchange at acidities as high as 10^{-3}M -sulphuric acid. The acid-catalysed deiodination proceeds by a different mechanism, namely, it is due to the formation of PhIH^+ which undergoes subsequent dissociation to $\text{PhH} + \text{I}^+$.²

It could still be argued that, even if PhH is formed through reaction (6), the exchange may proceed by reaction (7). This pathway, however, was excluded by the transiodination



experiment, which showed that anisole is not iodinated under the conditions of the iodine exchange.

Once the dissociative pathways have been refuted by experiment, one has to suggest

an alternative interpretation for the $R = k[\text{PhI}]$ rate law. Consistent with the experimental findings, is the non-dissociative conversion of the iodo-aromatic compound into a species PhI' which may undergo isotopic exchange with inorganic iodine:



It is hard to envisage the chemical nature of PhI' , which may eventually be a biradical or a very low-level electronically excited molecule of considerable stability. Some idea may be obtained from the activation energy and pre-exponential factor of the Arrhenius equation derived from the rate data. The activation energy of formation of PhI' is only 15–18 kcal./mole, which is rather low for an electronically excited state. On the other hand, an extremely low pre-exponential factor is involved, which means that the formation of PhI' is highly improbable. The interaction of PhI with the solvent has an effect on the formation of PhI' . In a solvent with stronger solvent-solute interaction, PhI is stabilised in relation to PhI' , followed by an increase in its activation energy of formation. This has been observed in acetic acid. The stronger interaction with the solvent has another effect on the rate of formation of PhI' , namely an increase in the probability of energy-transfer from the solvent to the solute, which is manifested by a substantial increase in the pre-exponential factor. If PhI is even more strongly solvated, the activation energy of formation of PhI' may increase further, and the rate of exchange by this mechanism will diminish. At the same time, the carbon-iodine bond may undergo polarisation by the solvent, which will facilitate a nucleophilic displacement by an $\text{S}_{\text{N}}2$ mechanism. This behaviour has been observed in the case of *o*- and *p*-iodonitrobenzene and *p*-iodophenol which underwent isotopic exchange with iodide ions in octanol as solvent by a first-order rate law, whereas in acetonitrile they follow a second-order dependence, according to an $\text{S}_{\text{N}}2$ mechanism.⁵ The mechanism involving PhI' explains the unusual behaviour of these reactions in the two solvent systems; if it were a transition from an $\text{S}_{\text{N}}2$ to an $\text{S}_{\text{N}}1$ mechanism, one would expect $\text{S}_{\text{N}}1$ to predominate in the more polar solvent.

A serious limitation of the proposed mechanism is the fact that PhI' could not be demonstrated by an independent chemical or physical method, *e.g.*, spectroscopy; nevertheless, this is, to the best of our understanding, the only plausible interpretation of the experimental findings of this work, as well as of other workers in the field.

The effect of butoxide and stannous ions and of metallic zinc on the rate of exchange can be explained if it is assumed that elementary iodine is the main reactant in the second, fast step [reaction (9)]. In the presence of butoxide, iodine will undergo alcoholysis, whereas stannous ions and zinc act as reductants. Iodide ions are also expected to act as inhibitors by the formation of I_3^- , but since this ion was absent in the molecular iodine experiments, where a zero-order dependence was followed at the same rate, it has to be concluded that I_3^- is capable of isotopic exchange with PhI' at a relatively fast rate (which may still be slower than that of I_2). It should be noted that the concentrations of inorganic iodine in the calculation of R includes $\text{I}^- + \text{I}_2$, as long as these species are in fast isotopic equilibrium. The extremely low specific rate of reaction (8) allows even small amounts of iodine impurities to act as intermediates. If one assumes an impurity of 1% of iodine in sodium iodide, then, in the most dilute iodide solution examined, I_2 should be $5 \times 10^{-8}\text{M}$. In view of the extremely low probability factors involved, a life-time of 0.1 sec. is assumed for PhI' , and from it a steady-state concentration of 10^{-9}M can be derived; using this, the specific rate constant of reaction (9) should exceed $10^9 \text{ l. mole}^{-1} \text{ sec.}^{-1}$, in order to obtain a zero-order dependence in inorganic iodine. This rate constant is plausible for a reaction with a highly reactive species like PhI' .

The effect of chloride ions is rather difficult to interpret. The very gradual retarding effect with increasing concentration of chloride ions cannot be due to its interaction with

iodine, by the formation of I_2Cl^- , as this would be inconsistent with the zero-order dependence on iodine concentration; a possible explanation is the deactivation of PhI' to PhI by chloride ions without any chemical change, which may also account for the effects of butoxide and stannous ions. Consequently, it is still possible that the fast step in reaction (9) involves an iodide ion; this interpretation releases us from ascribing an extra long life-time to PhI' .

At higher temperature another independent mechanism of isotopic exchange is encountered, namely, the bimolecular homolytic substitution by iodine atoms:



This mechanism will follow a rate law $R = k[PhI][I_2^{\ddagger}]$. This mechanism has been independently demonstrated under photochemical conditions.¹

EXPERIMENTAL

Reagents.—*o*-Iodoanisole, an Eastman white label product, was purified by distillation, the fraction of b. p. 240—241° being used.

[¹⁴C]Anisole was prepared from phenol and [¹⁴C]methyl iodide. Commercial samples of reagent-grade sodium iodide (Baker analysed) were used without further purification. Iodine (analytical grade) was resublimed before use.

Carrier-free iodine-131 was obtained (the Radiochemical Centre, Amersham) in dilute thiosulphate solutions of ~10 mc/ml. The desired specific activity was attained by adding sodium iodide. Approximately 10⁻² μc/ml. were used in the exchange experiments.

Commercial samples of butan-1-ol were purified by successive extractions with sulphuric acid, sodium hydrogen sulphate, and distilled water, followed by distillation, the fraction of b. p. 116—117° being used. 99·9% *n*-Decane (Philips) was used without further purification. Ethanol was purified as described in the literature.⁶

Analytical-grade zinc granules (50 mesh) were washed with dilute acetic acid under nitrogen and dried under a vacuum; the metal was not exposed to air after purification.

All the other reagents were of analytical grade and were used without further purification.

Procedures.—The radioassay of iodine-131 was carried out with a well-type scintillation counter using a single-channel analyser. The carbon-14 was assayed in a liquid scintillator solution of toluene-terphenyl-POPOP [1,4-bis(2-5'-phenyloxazolyl)benzene].

The iodide concentration was assayed by a microanalytical method⁷ adapted to the experimental conditions. Aliquot parts of the reaction mixture were diluted with acetone, sodium bromide was added, and the halides were precipitated by silver ions. The precipitate was oxidised with bromine to iodate, the excess of bromine was boiled off, and the iodate was assayed iodometrically.

The exchange experiments were carried out on 10—20 ml. samples. The reaction vessels were kept in a thermostat ($\pm 0\cdot03^\circ$) and aliquots (1 ml.) were withdrawn at intervals. In experiments carried out in the absence of air, the samples were deaerated by the freeze-thaw technique and kept in sealed vials.

The iodide was precipitated from alcoholic solutions by silver ions, after addition of chlorine ions as carriers. Acetone was added to avoid any substantial coprecipitation of the organic iodo-compound. The precipitate was separated by centrifugation, washed with acetone, dissolved by addition of ammonia, and reprecipitated from an aqueous acetone solution by acidification. The efficiency of separation was checked radiometrically and it was found that 99% of the iodide present was recovered, whereas not more than 0·5% of the organic component was carried over and counted with the inorganic iodide. In the deiodination experiments, the reprecipitation was repeated four times and the overall decontamination factor was smaller than 1×10^{-8} .

The separation of inorganic iodine from the organic component, in the case of water-immiscible solvents, was carried out by aqueous extractions, after addition of carrier iodide; the completeness of separation was established radiometrically. In exchange reactions with

⁶ Vogel, "Practical Organic Chemistry," Longmans, London, 1961, p. 168.

⁷ Belcher and Wilson, "Inorganic Microanalysis," Longmans, London, 1957, p. 195.

elementary iodine, dilute thiosulphate was added titrimetrically to determine any change in iodine concentration, as well as to reduce iodine to iodide, prior to extraction.

The absence of eventual iodination of the solvent was re-checked by carrier fractionation of the solvent after adding its iodo-derivative as carrier. No radioactive organic fraction, except the iodoanisole, could be detected.

The check on transiodination was carried out by adding [^{14}C]anisole to iodoanisole under the conditions of exchange, separating iodoanisole by fractional distillation, and assaying its carbon-14 content. No [^{14}C]iodoanisole was produced under these conditions.

Treatment of the Data.—The rate of isotopic exchange (R) was calculated from the expression:

$$R = [XY/(X + Y)](1/t) \ln F$$

where $F = (A_t - A_0)/(A_\infty - A_0)$. X and Y are the concentrations of *o*-iodoanisole and of inorganic iodine, respectively, and A_0 , A_t , and A_∞ are the activity of the iodo-organic compound at times zero, t , and infinity. When the iodide activity was followed, the same formula was used but this time $F = (A_0 - A_t)/(A_0 - A_\infty)$. In all cases where $X > 100Y$, R was calculated from the approximate formula $R = (X/t) \ln F$.

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