759. *The Kinetics of Hydrogen Isotope Exchange Reactions. Part VI.* The Reactivity of Anisole in Aqueous and Non-aqueous Acidic Media.*

By D. P. N. SATCHELL.

Hydrogen isotope exchange between both aqueous sulphuric and aqueous perchloric acids and the nuclear positions in anisole shows a kinetic dependence on acidity similar to that found previously for other aromatic compounds in contact with aqueous mineral acids. The partial rate factors for the reactions of [*o*-$^2H_1$]anisole and [*p*-$^2H_1$]anisole with 8·53M-aqueous sulphuric acid at 25° are 2·3 × 10^4 and 5·5 × 10^4 respectively. The *ortho/para* rate ratio † in aqueous sulphuric acid media, *viz.*, 0·42, is shown to be independent of medium composition over a wide range. [*m*-$^2H_1$]Anisole is deactivated towards hydrogen isotope exchange compared with [$^2H_1$]benzene in both aqueous sulphuric and aqueous perchloric acid. This behaviour is discussed. The partial rate factor for the *meta*-position in 10·43M-aqueous perchloric acid is 0·25. Measurements of the rate of hydrogen isotope exchange between [$^2H_1$]benzene and aqueous perchloric acid media are reported.

In acetic acid–sulphuric acid media the exchange reaction shows a similar kinetic behaviour to that characteristic in aqueous media, and it is concluded that the mechanisms are similar. At the same value of H_0, [*o*-$^2H_1$]anisole and [*p*-$^2H_1$]anisole react somewhat less rapidly in acetic acid–sulphuric acid than in sulphuric acid–water: the *ortho/para* rate ratio is 0·55 in the former as compared with 0·42 in the latter medium.

IN Part V* the behaviour of toluene in hydrogen isotope exchange with aqueous mineral acid was described and shown to be in accord with a mechanism for aromatic hydrogen

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* Part V, *J.*, 1956, 2743.

† This term implies simply the ratio of the partial rate factors for the *ortho*- and the *para*-position.

isotope exchange previously proposed.[1] The importance of time-variable electrical effects in the exchange process was revealed. We now report work with anisole. A start has also been made in the study of exchange kinetics in non-aqueous acidic media, about which little is known. Acetic acid–sulphuric acid mixtures were the non-aqueous acidic media chosen.

There appears to have been only one previous study of the behaviour of anisole towards hydrogen isotope exchange with aqueous mineral acids. Ingold, Raisin, and Wilson [2] included it in their survey of the behaviour of various aromatic compounds with different aqueous acids, when they established the electrophilic nature of the exchange process in such systems. They found that, at room temperature, in contact with deuterosulphuric acid of greater concentration than the monohydrate, three nuclear positions of anisole exchange rapidly and the remaining two (the *meta*-positions) much more slowly. They studied benzene under similar, heterogeneous conditions and also recorded approximate sulphonation losses for both compounds. Their experiments were only semiquantitative but the tentative deduction may be made that, in 54·5 mole % aqueous sulphuric acid, the exchange at a *meta*-position in anisole is less rapid than at a position in benzene and also less rapid than the total rate of sulphonation of anisole.

In the present investigation the rate of reaction of the three nuclear, monodeuterated anisoles with sulphuric acid–water mixtures has been studied at 25°. Each compound was allowed to react with a series of media in order to discover the dependence of its exchange rate upon acidity. The *meta*-isomer was also studied with a series of perchloric acid–water mixtures.

Two previous investigations of the behaviour of anisole towards hydrogen isotope exchange with acetic acid–sulphuric acid media have been recorded. (1) Brown, Wilzbach, and Urry [3] dissolved anisole in deuteroacetic acid containing a trace of sulphuric acid, and their semiquantitative experiments, conducted at 90°, revealed exchange at three positions only, demonstrating the expected strong *ortho–para*-direction and electrophilic nature of the exchange process. (2) Lauer and Day [4] measured the rate of loss of deuterium from the *ortho*- and *para*-positions to a light sulphuric acid–acetic acid medium. Their reaction mixtures had the approximate molar composition anisole : sulphuric acid : acetic acid, 0·01 : 0·001 : 0·05. The *ortho*/*para* rate ratios at 100° and 80° were found to be 0·52 and 0·33 respectively. Discussion of these results is deferred.

In the present study the *ortho*- and *para*-deutero-isomers were each allowed to react with a series of acid mixtures at 25°. The reaction mixtures were homogeneous, the acid solvent being initially completely light and present in large excess. The same was true of the aqueous reaction mixtures.

EXPERIMENTAL

Preparation of Deutero-compounds.—(a) *Monodeuteroanisoles.* The standard Grignard procedure was used. The ethereal solutions of the Grignard reagents prepared from *o*- and *p*-bromoanisole and from *m*-iodoanisole were decomposed with 99·7% deuterium oxide. The solid products were decomposed in each case with ammonium chloride, and the ether layers separated and dried. Fractional distillation led to anisole in yields of about 70%, the products containing probably about 90 mole % of heavy isomer. All three deutero-isomers have been previously prepared, and the essentials of their infrared spectra recorded.[5] The samples prepared in the present work had spectra similar to those recorded, except that the peaks occurring at 8·90 μ for the *ortho*- and at 12·65 μ for the *meta*-isomer were doublets.

(b) $[^2H_1]$*Benzene.* This was prepared as previously described.[6]

Other Materials.—(*a*) The ordinary anisole used was a redistilled specimen, of b. p. 154°.

(*b*) The acetic acid–sulphuric acid mixtures were made up by weight from 100% sulphuric acid and anhydrous acetic acid, the former prepared by addition of oleum to the 95% acid until

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[1] Gold and Satchell, *J.*, 1955, 3609.

[2] Ingold, Raisin, and Wilson, *J.*, 1936, 1637.

[3] Brown, Wilzbach, and Urry, *Canad. J. Res.*, 1949, **27**, *B*, 398.

[4] Lauer and Day, *J. Amer. Chem. Soc.*, 1955, **77**, 1904.

[5] Hall, Piccolini, and Roberts, *ibid.*, p. 4540.

[6] Bryce-Smith, Gold, and Satchell, *J.*, 1954, 2743.

the f. p. reached 10·4°. The anhydrous acetic acid was prepared by azeotropic distillation of " AnalaR " acetic acid with benzene. It had m. p. >16·6°. (*c*) The concentrations of the aqueous acid mixtures were determined by titration.

Procedure for Exchange Experiments.—The reactions of the deutero-compounds were studied under homogeneous conditions at 25°.

(a) *Sulphuric acid–water media.* [p-$^2H_1$]Anisole was allowed to react with five different sulphuric acid–water mixtures having H_0 (Hammett's acidity function [7]) values varying from $-1·50$ to $-3·44$. For [o-$^2H_1$]anisole, also studied with five mixtures, the H_0 values varied from $-2·25$ to $-3·59$. [m-$^2H_1$]Anisole was allowed to react with three mixtures, the H_0 values varying from $-4·78$ to $-6·32$.

The experimental procedure was similar to that previously used with benzene and toluene.[8] Small measured samples of deutero-compound were dissolved in a large excess of a given acid mixture contained in flasks fitted with ground-glass stoppers and having an additional sealing of Apiezon Q compound. Four or five samples were used with each acid–water mixture. After an appropriate period in a thermostat bath at 25° a flask was opened and a measured amount of light anisole added to its contents which, after resealing of the flask, were agitated for 15 min., thus equilibrating the dissolved and the added anisole. The resulting anisole sample was separated and analysed for the deutero-isomer by infrared spectroscopy.[8] In this way the exchange reaction could be followed.

For the *ortho*- and *para*-isomers ~0·15 ml. samples were dissolved each in 400-ml. of acid and equilibrations were carried out with ~1·1 ml. of light anisole. Since the solubility of anisole in sulphuric acid–water increases markedly when $-H_0$ becomes greater than ~4·5, the *meta*-isomer can be used with smaller acid samples. Usually ~0·15 ml. of deutero-compound was dissolved in 100 ml. of acid, and equilibration performed with ~0·5 ml. of light anisole.

For the fastest rates studied a small correction was made for the time occupied by shaking when this interval was no longer negligible compared with the reaction time.

By reversing the procedure described it is also possible to measure the rate of destruction of anisole by the media used. It is important that this rate should be small compared with the rate of exchange, since otherwise measurement of the latter becomes either inaccurate or impossible.

To measure the rate of destruction of anisole, samples of light compound were dissolved and finally that remaining in solution was equilibrated with a suitable light–heavy mixture. (When necessary the acid was diluted to prevent exchange during this equilibration.) As previously mentioned,[8] the reversed procedure is analytically less sensitive than the normal procedure when the solubility is low. However, for anisole in the media with $-H_0$ values >4·5 it can be made of comparable accuracy, giving figures reproducible within ±8%.

The results obtained with the three anisoles are collected in Tables 1, 2, and 5. Their discussion is deferred.

(b) *Sulphuric acid–acetic acid media.* Similar analytical methods can be used with these media by working at somewhat higher concentrations. In practice, ~1 ml. of deuteroanisole was dissolved in 100 ml. of acid mixture. At appropriate intervals 20 ml. samples were removed and run into ~200 ml. of water, thus effectively stopping the exchange reaction and providing a solution which could be equilibrated with light compound as described above.

The rates of destruction of anisole in some of these media were also studied. [p-$^2H_1$]Anisole was studied with six acid mixtures, and [o-$^2H_1$]anisole with three. The results are collected in Table 3 and 4.

(c) *Perchloric acid–water media.* [m-$^2H_1$]Anisole was studied with four, and [$^2H_1$]benzene with three acid mixtures in the H_0 range $-5·45$ to $-7·35$. Both exchange rates and rates of destruction were studied. The procedure was similar to that described for aqueous sulphuric acid except that 30-ml. samples of acid could be used. The results are given in Tables 6 and 7.

DISCUSSION

Behaviour of the ortho- *and* para-*Isomers.*—(a) *Sulphuric acid–water media.* The rate of destruction of anisole in the mixtures used for these isomers was found to be negligible compared with the exchange rates. The solutions remained clear and colourless. Under the experimental conditions used the exchange reaction is a first-order process.[9] In Fig. 1

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[7] Hammett, " Physical Organic Chemistry," McGraw-Hill Book Co. Inc., New York, 1940.

[8] Gold and Satchell, (*a*) *J.*, 1955, 3619; (*b*) *J.*, 1956, 2743; (*c*) *ibid.*, p. 1635.

[9] *Idem, Quart. Rev.*, 1955, **9**, 51.

the logarithms of the first-order rate constants (λ) are plotted against $-H_0$. Both the *ortho*- and the *para*-isomer give straight-line plots. The two slopes are the same, within experimental error, and have the value 1·18. Because the range of media studied for the two isomers was roughly the same, parallel straight-line plots were predictable on the basis of the previously suggested mechanism for the reaction. The value of the slope is also acceptable in the light of previous discussion.[10]

Data referring to [$^2H_1$]benzene are also included in Fig. 1. The benzene plot was, of course, obtained from the results of experiments in more concentrated acid mixtures.[8] If it is permissible to extrapolate either, or both, of the benzene and anisole graphs, then the partial rate factors for the *ortho*-and *para*-positions of anisole may be calculated at any desired medium composition.

Although it is certain from the general kinetic behaviour [1, 8] that, except in special cases which involve deactivation of the reacting species by the solvent, the graphs of log λ against $-H_0$ will have a slope close to unity over a very wide range of composition, so that extrapolation will certainly give fairly accurate comparisons between compounds studied in different acid regions, nevertheless how far such graphs may be extrapolated without *any* error cannot be stated. (It was hoped that the study of the *meta*-isomer would throw some light on this, but unfortunately it did not.) Clearly, the smaller the extrapolation the smaller the uncertainty introduced. In the present case an extension of the anisole plots over one H_0 unit towards higher acidities seems unlikely to introduce any great error, and the same is probably true for an extension of the benzene graph over one, or even two, H_0 units in the opposite direction. Hence the partial rate factors for the *ortho*- and *para*-positions of anisole in, say, 8·53M-aqueous sulphuric acid ($H_0 = -4{\cdot}0$) can be

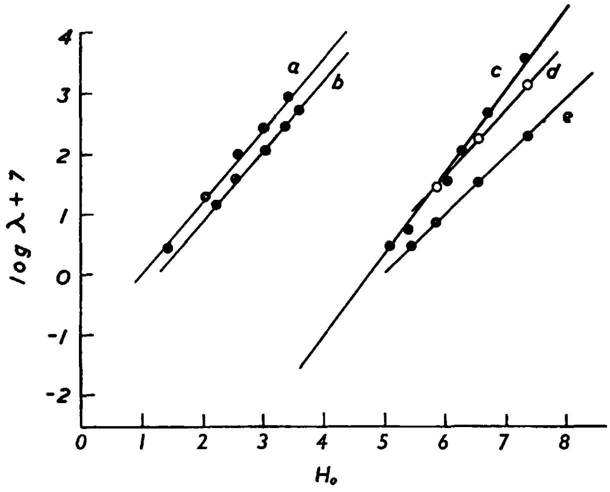

FIG. 1. *Variation of exchange rate with acidity in aqueous sulphuric and perchloric acid.*

a, [*p*-$^2H_1$]Anisole; *b*, [*o*-$^2H_1$]anisole; *c*, [$^2H_1$]benzene; *d*, [$^2H_1$]benzene; *e*, [*m*-$^2H_1$]anisole. *a*—*c*, in H_2SO_4; *d*, *e*, in $HClO_4$.

TABLE 1. *Rate of loss of deuterium from* [p-$^2H_1$]*anisole in aqueous sulphuric acid at* 25°.

H_2SO_4 (M)	3·51	4·86	5·95	6·77	7·59
$-H_0$ (7)	1·44	2·05	2·59	3·00	3·44
$10^7\lambda$ (sec.$^{-1}$)	2·93	18·5	88·0	255	839

TABLE 2. *Rate of loss of deuterium from* [o-$^2H_1$]*anisole in aqueous sulphuric acid at* 25°.

H_2SO_4 (M)	5·18	5·90	6·82	7·34	7·88
$-H_0$ (7)	2·22	2·55	3·06	3·34	3·60
$10^7\lambda$ (sec.$^{-1}$)	14·9	36·3	121	291	521

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[10] Gold and Satchell, *J.*, 1955, 3622.

calculated with some confidence. However, in the general case of a comparison of the reactivities of compounds studied in widely different acidity regions, *i.e.*, compounds of widely different reactivity, our present ignorance as to how much the slopes of the graphs will alter with changes in medium makes such a comparison somewhat uncertain. Further work should provide information serving to make such comparisons more precise.

The partial rate factors for the *ortho*- and *para*-positions of anisole in 8·53M-aqueous sulphuric acid are found to be $2{\cdot}3 \times 10^4$ and $5{\cdot}5 \times 10^4$ respectively at 25°. The *ortho*/*para* rate ratio has the constant value of 0·42 between 3·5M- and 7·5M-acid. The partial rate factors for bromination by molecular bromine are $0{\cdot}8 \times 10^8$ and 70×10^8 at the *ortho*- and *para*-positions respectively.[11] The difference from exchange is marked. As for toluene,[8b] the exchange behaviour of anisole is more like that found for its nitration, which [12] involves an *ortho*/*para* rate ratio of the same order as 0·42.

Another comparison of interest is that between the reactivities of [o-$^2H_1$]anisole and p-methyl[o-$^2H_1$]phenol (for which see Part II [1]). In 8·53M-sulphuric acid the rate ratio is 6·5, *p*-cresol reacting the faster. The partial rate factor for the *meta*-position in toluene in this medium will be close [8b] to 1·9. If the hydroxyl and the methyl group be supposed to activate the position *ortho* to the hydroxyl group in *p*-cresol independently and additively, then the hydroxyl group is found to activate an *ortho*-position 3·4 times more than a methoxyl group. Thus the partial rate factor for the *ortho*-position in phenol would, on this basis, be expected to be about $7{\cdot}8 \times 10^4$. (How far, and in what circumstances, partial rate factors found for monosubstituted benzenes can be used in this way to reproduce the reactivities of polysubstituted molecules is not yet known. That the procedure is admissible in some cases seems, however, quite likely.)

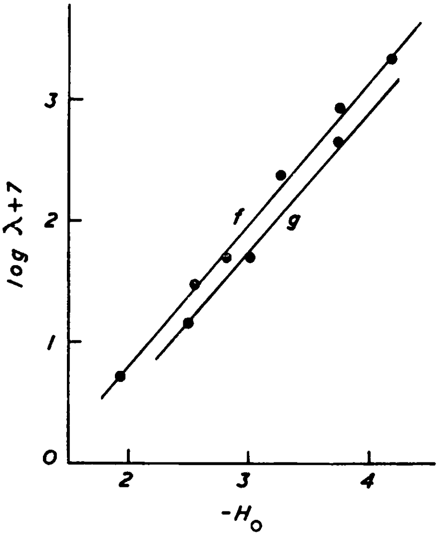

FIG. 2. *Variation of exchange rate with acidity in acetic acid–sulphuric acid.*
f, [p-$^2H_1$]Anisole; *g*, [o-$^2H_1$]anisole.

(b) *Sulphuric acid–acetic acid media.* In these media the rate of destruction of anisole was found to be not entirely negligible compared with the exchange rate. For instance, in the most acidic mixture used it was about one-twentieth of the exchange rate. In calculating the exchange rate constants (λ) small corrections were made to allow for this loss. The values of these constants for the *ortho*-and the *para*-isomer, given in Tables 3 and 4, are regarded as accurate to ±10%. The fate of the lost anisole is unknown.

The values of H_0 quoted in Tables 3 and 4 were taken from Hall and Spengeman's data,[13] it being assumed, for lack of quantitative information to the contrary, that the addition of 1 ml. of anisole to 100 ml. of an acetic acid–sulphuric acid mixture will cause no

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[11] de la Mare and Vernon, *J.*, 1951, 1764.
[12] Bunton, Minkoff, and Reed, *J.*, 1947, 1416.
[13] Hall and Spengeman, *J. Amer. Chem. Soc.*, 1940, **62**, 2487.

change in its H_0 value. (The actual change is probably quite small.) In Fig. 2, log λ for both isomers is plotted against $-H_0$. The resulting graphs are parallel straight lines with a slope of 1·18. This slope is identical with that found in aqueous sulphuric acid where, as has been seen, parallel straight-line plots are also obtained. The behaviour in the two media is therefore very similar. The only differences are that the exchange rate in acetic acid mixtures is slightly smaller that that in the aqueous solvent with the same H_0 value, and that the *ortho/para* rate ratio is somewhat larger in acetic acid, being 0·55 instead of 0·42.

TABLE 3. *Rate of loss of deuterium from* [p-$^2H_1$]*anisole in acetic acid–sulphuric acid media at* 25°.

H_2SO_4 (M)	0·232	0·632	0·916	1·72	2·68	3·52
$-H_0$ (13)	1·93	2·56	2·80	3·28	3·76	4·18
$10^7\lambda$ (sec.$^{-1}$)	5·0	30·0	50·0	230	820	2100

TABLE 4. *Rate of loss of deuterium from* [o-$^2H_1$]*anisole in acetic acid–sulphuric acid media at* 25°.

H_2SO_4 (M)	0·550	1·23	2·64
$-H_0$ (13)	2·49	3·00	3·73
$10^7\lambda$ (sec.$^{-1}$)	14·0	51·0	450

The kinetic behaviour in acetic acid–sulphuric acid media is clearly exactly analogous to that found to be characteristic in aqueous acidic media in general.[1, 8] The mechanism of the exchange in the non-aqueous solvent must therefore be similar to that operative in aqueous media. That suggested [1] on the basis of the parallelism with H_0 remains satisfactory. The aromatic species is considered to take up a proton from the solvent in a rapid pre-equilibrium and then to undergo a slow intramolecular rearrangement, finally relinquishing a deuteron to the medium. Such a mechanism is clearly possible in any acidic solvent containing ionisable hydrogen.

For a medium for which the H_0 values have not been measured, the variation in the rate of exchange should give an approximate indication of how the acidity function for the medium varies with its composition. In a solvent containing both Lewis and Brönsted acids, the variation in the exchange rate should reflect only the potency of the latter.

The differences between the behaviour found in the acetic and aqueous sulphuric acid media have been mentioned. Differences in detailed behaviour in different acidic media have been found before and are discussed elsewhere.[10] At least three distinct effects appear to be involved. First, differences in slope shown by the same compound in different media are thought to arise largely from the change in those solvent properites which affect solubility.[10] Secondly, part at least of any difference in exchange rate shown by the same compound in different media at the same H_0 value is probably due to the non-coincidence of the measured H_0 scales at present available. When these scales receive their definitive mutual adjustment some of the detailed differences in exchange behaviour found at present will probably be reduced. In the present work a third effect has been met for the first time in connection with hydrogen exchange: it appears that the relative displacement of the rates of reaction of two deutero-isomers of the same aromatic molecule, on change from one medium to another, is not necessarily the same. In the present case this gives rise to a higher *ortho/para* rate ratio in acetic acid than in aqueous media. Quite why *ortho*-substitution should be favoured in acetic acid media is not clear.

There is a possible discrepancy between the present results and those of Lauer and Day.[4] These authors found values for the *ortho/para* rate ratio in acetic acid–sulphuric acid media which imply a value of 0·1 or less at 25°. This value is in only qualitative agreement with 0·55. How much of the difference can be attributed to the fairly large difference of medium is not known.

Behaviour of the meta-*Isomer*.—(a) *Sulphuric acid–water media*. It has unfortunately not been possible to measure the exchange rate of [*m*-$^2H_1$]anisole in aqueous sulphuric acid. When this compound was studied by the methods described there appeared to be exchange, but when the rate of destruction was measured in the same media it became apparent that the measured exchange could be completely accounted for by this alone, *i.e.*, the rate of loss of anisole in these solutions was the same, within experimental error, whether it was calculated from the results of experiments in which the deutero-isomer was dissolved, assuming no exchange, as when calculated on the basis of experiments in which the light compound was dissolved.

To obtain conveniently measurable reaction rates the media used had H_0 values ranging between $-4{\cdot}78$ and $-6{\cdot}23$. The anisole solutions became pink after a time and some solid was precipitated. The destruction rates were, somewhat surprisingly, roughly of the first order. The approximate (±20%) first-order constants (k) are given in Table 5. The rate is seen to increase steeply with acidity. If log k is plotted against $-H_0$ the graph has a slope of about 1·7. It is probable that the most important process removing anisole is sulphonation. That other, though possibly subsequent, processes are involved is, however, evident from the examination of solutions kept for some time.

TABLE 5.* *Rate of destruction of anisole in aqueous sulphuric acid at 25°.*

H_2SO_4 (M)	10·09	11·00	12·91
$-H_0$ (7)	4·78	5·27	6·23
10^7k_H (sec.$^{-1}$)	0·84	5·9	230
10^7k_D (sec.$^{-1}$)	0·81	6·0	210

* k_H and k_D = rate constants calculated from experiments in which the light and the heavy compound, respectively, were dissolved.

That the rates of destruction based on experiments with heavy and light isomers agree, if exchange is assumed absent, means in practice that the exchange rate in all the media studied must be at least about five times slower than the destruction rate. Examination of Fig. 1, which contains the benzene exchange data, the values given in Table 5 being borne in mind, shows that where $H_0 = -5{\cdot}0$, and probably in higher acidities also, the *meta*-position in anisole must be appreciably deactivated towards exchange in aqueous sulphuric acid.

(b) *Perchloric acid–water media.* By using concentrated perchloric acid media instead of sulphuric acid, sulphonation could be avoided. Anisole, however, still proved unstable. When it was dissolved a yellow-green colour was immediately formed; the colour darkened with time and solid was eventually precipitated. The origin of the colour (which was different from that which eventually formed in the sulphuric acid media) is unknown. The precipitate was presumably anisole which had undergone oxidation or polymerisation. Once a small amount of precipitate had formed it became difficult to separate the anisole and acid phases after the equilibration process, so that study of the rate of reaction of anisole in these media was restricted to the period during which the solutions remained clear. Experiment showed, somewhat surprisingly, that the rate of destruction of anisole was negligible up to the point when solid began to be precipitated. After this point visual examination indicated that, at any rate in the most concentrated acids used, decomposition was rapid. The destruction is therefore possibly autocatalytic. The period which elapses before appreciable decomposition sets in is shorter the stronger the acid. During this period, for acid mixtures having H_0 values between $-5{\cdot}45$ and $-7{\cdot}35$, it was possible to follow the exchange reaction of [*m*-$^2H_1$]anisole over about a quarter of its life in each case. It is usually desirable in kinetic work to follow reactions further than this, but the first-order rate constants obtained (Table 6) were reproducible to ±10%, and are regarded as reliable.

In order to discover whether the *meta*-isomer was deactivated towards exchange in these media compared with benzene, it was necessary to measure the benzene exchange rates. Benzene is much more stable than anisole in perchloric acid and the exchange reaction can be followed over many half-lives without complication arising from appreciable destruction of benzene. The results for three acidities are given in Table 7. It is clear from the values given in Tables 6 and 7 that the *meta*-position in anisole is deactivated towards exchange in concentrated aqueous perchloric acid.

The H_0 values quoted in Tables 6 and 7 were obtained from an extrapolation of Hammett and Deyrup's data [14] which only extend to 10·15M-acid. They are probably accurate to better than $\pm 0{\cdot}2$ unit. The plot thus obtained of log λ against $-H_0$ for benzene in aqueous perchloric acid has a slope of 1·12 compared with 1·36 in aqueous sulphuric acid (Fig. 1). The exchange rate in the two media is the same when $H_0 = -5{\cdot}80$.

TABLE 6. *Rate of loss of deuterium from* [m-$^2H_1$]*anisole in aqueous perchloric acid at* 25°.

$HClO_4$ (M)	10·04	10·43	11·01	11·71
$-H_0$ (14)	5·45	5·85	6·55	7·35
$10^7\lambda$ (sec.$^{-1}$)	3·00	7·20	32·4	200

TABLE 7. *Rate of loss of deuterium from* [$^2H_1$]*benzene in aqueous perchloric acid at* 25°.

$HClO_4$ (M)	10·43	11·01	11·71
$-H_0$ (14)	5·85	6·55	7·35
$10^7\lambda$ (sec.$^{-1}$)	28·2	175	1350

The plot of log λ against $-H_0$ for [*m*-$^2H_1$]anisole has a slope of 0·98 (Fig. 1). The slope shown by the *ortho*- and the *para*-isomer in sulphuric acid is 1·18. Thus for both benzene and anisole the use of perchloric acid results in a lower slope. The partial rate factor for hydrogen isotope exchange at the meta position is found to be 0·25 in 10·43M-aqueous perchloric acid.

The results described confirm and amplify the tentative deductions which may be drawn from the work of Ingold, Raisin, and Wilson.[2] The conclusion is inescapable: in strongly acidic media the *meta*-position in anisole is deactivated towards hydrogen isotope exchange. This conclusion presents no theoretical anomaly: one simply assumes that the inductive effect of the methoxyl group is sufficiently powerful to deactivate the *meta*-position in spite of any secondary relay of its very strong tautomeric activation of the *ortho*- and *para*-positions. The present work being the only instance of a direct measurement of the reactivity of the *meta*-position in anisole, the results present no real experimental anomaly either. However, two indirect estimates of the *meta*-reactivity are available and they both predict a slight activation. These estimates are based on experiments with dimethoxybenzenes and the assumption that substituents affect reactivity independently and additively. de la Mare and Vernon [11] have argued, on this basis, that for bromination by molecular bromine in acetic acid the partial rate factor at the *meta*-position should be 1·7. Similarly for alkylation by $Ph_2CH_2^+$ in dilute sulphuric acid–acetic acid media a value of 2·7 can be predicted.[15] There seem to be three possible explanations of this descrepancy:

(i) The *meta*-position *is* activated towards bromination and alkylation yet deactivated towards exchange. This is possible but seems unlikely.

(ii) In the strongly acidic media necessary to effect *meta*-exchange, anisole becomes deactivated by the solvent in a way similar to that postulated for nitro-compounds in connection with their nitration in such media.[16] For anisole this deactivation would arise from hydrogen bonding or protonation at the methoxyl oxygen. At first sight this explanation is attractive, but deactivation by this means would presumably increase steeply with increasing acidity and cannot easily be reconciled with the observed linear dependence of exchange rate on H_0, the gradient of which seems very reasonable when compared with that of the benzene plot, the results in sulphuric acid being borne in mind.

(iii) Partial rate factors obtained for monosubstituted benzenes cannot always be used to predict the reactivities of polysubstituted molecules, and *vice versa*. This appears the most likely explanation of the anomaly mentioned. Further experiments on the exchange rates of the dimethoxybenzenes should throw more light on the point.

KING'S COLLEGE, STRAND, LONDON, W.C.2.

[*Received, May* 23*rd*, 1956.]

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[14] Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721.

[15] Personal communication from Dr. V. Gold and Mr. D. Bethell.

[16] Gillespie and Norton, *J.*, 1953, 971.