Tetrahedron Vol. 33, pp. 2119 to 2122 Pergamon Press 1977 Printed in Great Britain

THE HYDROXYLATION OF AROMATIC COMPOUNDS WITH HYPOFLUOROUS ACID†

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(*Received in UK* 18 *February* 1977; *accepted for publication* 9 *March* 1977)

Abstract—The reaction of hypofluorous acid with aromatic substrates (benzene, *p*-xylene, naphthalene, and various monosubstituted benzenes) leads to phenolic products. Isomer distribution studies suggest that the reagent has the characteristics of an electrophilic species which is not the OH radical, and which may be regarded as $HO^{\delta+}$–$F^{\delta-}$. The *p*-methoxyphenol isolated from the *p*-deuterioanisole/hypofluorous acid reaction shows a marked NIH effect (77% incorporation of deuterium). The bearing of these results on microsomal hydroxylation is discussed briefly.

Hypofluorous acid was first prepared by Studier and Appelman[1] in 1971. Nmr[2] and dipole moment[3] measurements suggested that the molecule was polarised in the sense ($HO^{\delta+}$–$F^{\delta-}$) expected on the basis of relative electronegativities. This led us to suppose that the HOF molecule might behave as though it were a source of OH^+, although homolytic processes (to give $OH^\cdot$ and $F^\cdot$; or oxene and HF) appeared in principle to be alternative modes of cleavage. Each of these three pathways generates reactive species which would be expected to lead to hydroxylation of aromatic substrates. This type of reaction is of interest because, although its application is somewhat limited *in vitro* (e.g. Fenton's reagent,[4] the Udenfriend reagent,[5] hydrogen peroxide in acidic media,[6] and peracids[7], especially peroxytrifluoroacetic acid[8]), it is highly important biologically. In the metabolism of aromatic compounds in the liver the key process is hydroxylation, a reaction catalysed by monooxygenases such as cytochrome P_{450}, a haem enzyme which is found in the microsomal fraction when the cells are disintegrated. Reactions of hypofluorous acid with organic substrates have not previously been reported: here we show that with simple aromatic compounds hydroxylation is an important reaction pathway.

The hypofluorous acid used in this work was prepared by the reaction of fluorine gas with ice at approximately −40° in a rapid recirculating flow system as described by Appelman.[9] Hypofluorous acid spontaneously decomposes ($2HOF \rightarrow O_2 + 2HF$, effective $t_{\frac{1}{2}} \approx 30$ min at 25°),[1,9] and on occasion it has detonated. Hence the hypofluorous acid was prepared in small quantities (*ca* 50 mg). In order to carry out a reaction the U-tube in which it had been collected was allowed to warm up from 77° K to room temperature, and, as this happened, the hypofluorous acid was carried by a stream of dry nitrogen or argon into an excess of the aromatic substrate.

In most cases reaction was rapid and obvious: the reaction mixture became warm and more or less discoloured. The phenolic products were generally identified by TLC and GLC, and were estimated by GLC.

The reaction of benzene with hypofluorous acid in this way gave phenol (18.7%) and *o*-catechol (3.9%). *p*-Xylene gave 35.2% of 2,5-xylenol, the identity of which was confirmed by the preparation of the 1-naphthylurethane derivative. The product distribution with certain monosubstituted benzenes is summarised in Table 1. Naphthalene in chloroform gave α-naphthol (14.7%) and β-naphthol (7.7%).

An attempt was made to estimate the relative reactivities (R) of toluene and anisole with respect to benzene by competition experiments. The results are shown, with partial factors (x_f) for *o*- and *p*-substitution, in Table 2. These values are subject to errors arising from (i) alternative reaction pathways (e.g. those leading to di- and polymeric products), (ii) the non-homogeneity (macroscopic and microscopic) of the reaction mixture and (iii) the subsequent reaction of the hydroxylated product, which is, of course, much more reactive towards substitution and oxidation than is the starting material. Such side reactions certainly occurred (as indicated by the formation of coloured by-products, and by the detection of *o*-catechol in the benzene reaction): in an effort to minimise such reactions low mole ratios (0.01–0.02) of reagent to substrate were employed.

Fluorinated products were not observed but we cannot be certain that they are not formed. In the reaction with anisole the *o*- and *p*-fluoroanisoles were sought by GLC, but could not be detected. The yields of hydroxyanisoles (total *ca* 88%) indicate that fluorination can be no more than a minor pathway here. This is in marked contrast to the well known chlorination of aromatic substrates with hypochlorous acid. Here the electronegativities are reversed (O > Cl) and we may expect the molecule to be polarised $HO^{\delta+}$–$Cl^{\delta-}$. The reaction has been shown to be acid catalysed (leading to the supposition that H_2O^+–Cl is the reagent, with the oxygen atom now much the more electronegative) and electrophilic chlorination is the major pathway.[10] Some hydroxylation does occur, but is thought[10] to involve an addition-elimination sequence. Electrophilic *fluorination* has been observed with trifluoromethylhypofluorite, CF_3OF:[11] here the electron-withdrawing effect of the trifluoromethyl group is apparently sufficient to allow the O-F bond to become polarised in the reverse sense.

The data in Tables 1 and 2 accord with the view that the hydroxylation is an electrophilic substitution. Electron donating groups direct mainly ortho/para while the main product from nitrobenzene (which was the only benzene derivative that reacted sluggishly) is *m*-nitrophenol. Some years ago Norman and his colleagues[12,13] made a detailed comparison of the hydroxylation of aromatic systems with peroxytrifluoroacetic acid (which behaved as though it were a source of OH^+) and Fen-

†Dedicated to Robert B. Woodward on the occasion of his 60th birthday.

Table 1. Hydroxylation of monosubstituted benzenes

Substrate	Reagent	Product ratios[a] o	m	p	o/p	Ref
PhMe	HOF	77.5	(3.8)[b]	18.7	4.1	c
	CF_3CO_3H	78.2	2.3	19.5	4.0	13
	Fenton	71	5	24	3.0	12
PhBu-t	HOF	64.9	(1.4)[b]	33.7	1.9	c
PhOMe	HOF	69.5	(2.8)[b]	27.7	2.5	c
	CF_3CO_3H	73.7	0	26.3	2.8	13
	Fenton	84	0	16	5.25	12
PhF	HOF	34.4	nd	65.6	0.52	c
	CF_3CO_3H	17.2	0	82.8	0.21	13
	Fenton	37	18	45	0.82	12
PhCl	HOF	61.2	(2.5)[b]	36.3	1.7	c
	Fenton	42	29	29	1.4	12
$PhNO_2$	HOF	36.7	63.3	nd	-	c
	Fenton	24	30	46	0.52	12

[a]Percentage yields are given in the experimental section.
[b]Peak not resolved on GLC: figures in parentheses refer to estimated upper limits.
[c]Present work.
nd = not detected.

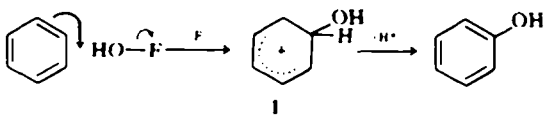
Table 2. Partial rate factors (x_f) and relative reactivities (R) for aromatic hydroxylation with hypofluorous acid

	OMe	Me	
x_f	255 (175)	27 (14)	1.0
R	120 ± 20	12 ± 2	1.0

ton's reagent (regarded as a source of $OH^{\cdot}$, an *electrophilic* radical). Where comparisons are possible (PhMe, PhOMe, PhF: Table 1) the isomer distribution observed with hypofluorous acid more closely resembles that observed by Davidson and Norman[13] for the peracid reagent.

The result with fluorobenzene is particularly indicative: *m*-hydroxylation is not detected with HOF and CF_3CO_3H but is appreciable with the radical reagent. Relative reactivities appear* to point in the same direction: the anisole/benzene ratio is 120 for HOF, 530 for CF_3CO_3H,[13] and 6.35 for Fenton's reagent.[13] These relative reactivities suggest that HOF is more selective (less reactive) than is Fenton's reagent but rather less selective (more reactive) than is CF_3CO_3H.

Since hypofluorous acid reacts with water to give hydrogen peroxide and hydrogen fluoride,[9] it is important to enquire if these compounds could be responsible for the reaction observed, especially since hydroxylation has been carried out with H_2O_2/HF mixtures.[14] However, when toluene was exposed to a HF/H_2O_2 mixture under the conditions of our experiment there was no obvious reaction and no cresols were detected. We conclude that HOF is responsible for the hydroxylation and that the reaction may be most simply formulated as follows:



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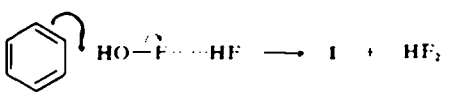
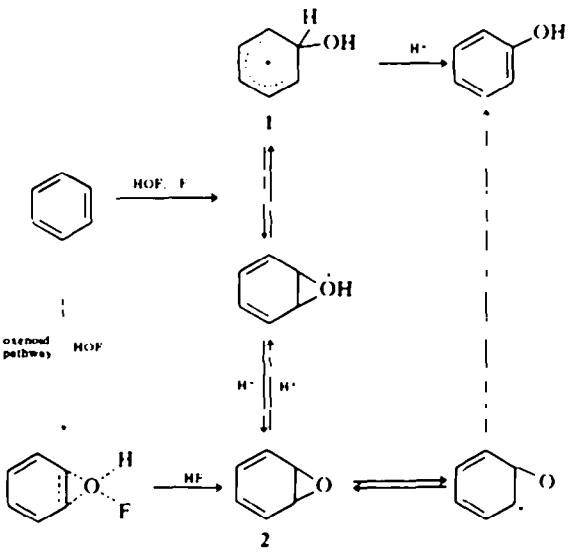
*The note of caution stems from the possibility that reaction with anisole is at or close to the diffusion controlled limit, the rate differences then being principally ascribable to differences in experimental method.

Two developments of this view are worth consideration. Firstly it seems possible that the hydrogen fluoride present as impurity in the reagent (or formed from it in the course of the reaction) may catalyse the reaction, inasmuch as an even better leaving group, HF_2^-, can then be formed.



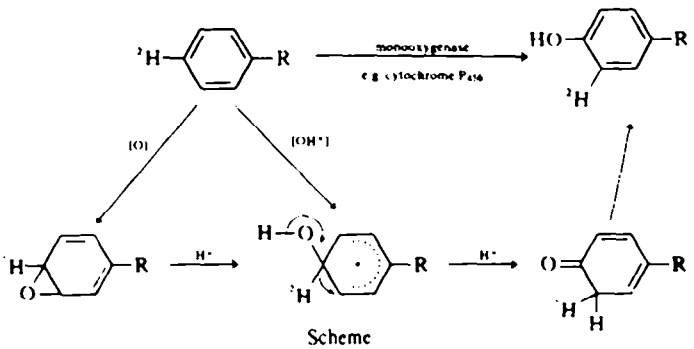
Secondly it is conceivable that the reaction involves an arene oxide (2), which then opens to give the products expected for direct electrophilic substitution. The arene oxide could be generated in various ways, two of which are shown. The observation[15] that arene oxides derived from toluene lead only to *o*- and *p*-cresols argues against



an obligatory arene oxide pathway, since we observe small amounts of *m*-cresol in the hypofluorous acid reaction. (It is worth remarking, however, that the separation of *m*- and *p*-substituted phenols is not always clear cut,[16] and we find that small amounts of the *meta* isomer are sometimes difficult to detect in the presence of much higher yields of the *para* isomer).

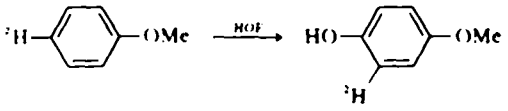
Microsomal hydroxylation. The hydroxylation of toluene by a preparation of liver microsomes gives a mixture of *o*-cresol and *p*-cresol:[15] these are, of course, the predominant products in the chemical hydroxylation of toluene with peroxytrifluoroacetic acid[11] and with hypofluorous acid. However, a remarkable and apparently characteristic feature of the microsomal hydroxylation is that it is attended by an NIH shift,[17] (see Scheme, top of next page).

This rearrangement has been interpreted as shown in terms of an arene oxide intermediate (an intermediate first suggested for biological aromatic hydroxylations by Boyland[18]), and several experimental observations support this view. Thus naphthalene-1,2-oxide has been detected in the microsomal oxidation of naphthalene,[19] and the proportions of NIH shift observed on chemical isomerisation of certain arene oxides resemble those found in the biological hydroxylations of the corresponding hydrocarbons.[20]



Scheme

It was clearly of interest to determine whether or not hypofluorous acid hydroxylation was attended by the NIH rearrangement. *p*-Deuterioanisole was chosen as substrate because *p*-methoxyphenol gives a clean molecular ion, and because microsomal hydroxylation of *p*-deuterioanisole gives a 60% retention of deuterium whereas hydroxylation with peroxytrifluoroacetic acid gives only 8% retention.[21] After reaction of *p*-deuterioanisole with hypofluorous acid, the *p*-methoxyphenol fraction was isolated by preparative TLC. The mass spectrum showed 77% incorporation of deuterium, and the NMR spectrum indicated that the deuterium resided on the benzene ring.



77% NIH rearrangement

On the basis of the findings of Witkop *et al.*,[22] this result indicates that hypofluorous acid is a useful model reagent in the study of microsomal hydroxylation. Whether arene oxides are involved in the reaction of this reagent with aromatic substrates, that is, whether they are obligatory intermediates in the NIH shift, is an open question which we are studying further.

EXPERIMENTAL

Preparation of HOF *and reaction with aromatic compound*

General procedure. Approximately 47 mg batches of hypofluorous acid were prepared by the reaction of fluorine with ice at about −40° in a rapid recirculating flow system. The ice was distributed on a matrix of polytetrafluoroethylene Raschig rings.[1,9] The product was collected at 90°K in a U-tube made of poly(chlorotrifluoroethylene), freed from more volatile impurities such as OF_2 by removal of several volumes of vapour at 194°K, and stored at 77°K until ready for use. This low temperature storage was mandated by the instability of HOF at room temp. The product was contaminated with approximately 0.5 mmole of HF per mmole of HOF.

To carry out a reaction, dry nitrogen or argon was passed through the U-tube containing the HOF and into the substrate (8 ml; either a neat aromatic compound or, in the case of naphthalene, the compound dissolved in CCl_4) in a poly(chlorotrifluoroethylene) vessel. The U-tube was allowed to warm to room temp. over 5–10 min, during which time the volatile HOF (b.p. ~ 10°) was carried into the mixture by the gas stream. In all cases the aromatic substrate was present in substantial excess over the HOF (mole ratio HOF/aromatic usually ~ 0.01–0.02).

The amount of HOF used was estimated by preparing a duplicate sample and transferring it in the same way into an iodide solution. The tri-iodide product was titrated with standard thiosulphate soln.

After all the HOF had been transferred, each mixture was allowed to stand for *ca* 10 mins before being washed with water (8 ml). The aqueous layer was washed with ether (8 ml), which was combined with the original organic soln. (A slightly different procedure was used with *p*-deuterioanisole and nitrobenzene, *vide infra*). The combined organic phase was dried with Na_2SO_4 and subjected to appropriate chromatographic analysis as follows. TLC: Merck silica gel H irrigated with 15% acetone in petroleum (= 60–80° fraction of petroleum ether, throughout) unless otherwise stated. GLC:[16] Varian Aerograph A90-P. Column A—6ft × ¼in, 5% tri-2,4-xylenyl phosphate on 90–100 mesh diatomite; Column B—6ft × ¼in, 0.3% diethyleneglycol succinate + 0.05% phosphoric acid on glass beads. Helium flow rate 60 ml/min. Peak areas were estimated by cutting and weighing: in the reaction mixtures the *m*-isomers of HOC_6H_4Me, $HOC_6H_4Bu^t$, HOC_6H_4OMe, and HOC_6H_4Cl were not sufficiently resolved for accurate estimation, and the values quoted refer to upper limits. GCMS: Perkin Elmer Fractometer; AEI Ltd. MS12 mass spectrometer. HPLC: Waters A202 instrument with 2ft × ¼in Corasil II column, using chloroform as elutrient at 3 ml/min.

Benzene. TLC (5% acetone in petroleum, visualised with diazotised sulphanilic acid) revealed phenol and catechol as products. Phenol (18.7%) was estimated by GLC (column A, 150°); catechol (3.9%) by HPLC.

Toluene. (a) GLC (column A, 150°) showed the products to be *o*-cresol (26.5%), *p*-cresol (6.4%), and *m*-cresol (< 1.3%). The structural assignment of these products was confirmed by mixed TLC (10% acetone in petroleum) and by GCMS. (b) When toluene (8 ml) was agitated under the conditions of the experiment with hydrogen fluoride (40%, 28 mg) and hydrogen peroxide (28%, 50 mg) the solution did not become warm and discoloured after 10 mins, and no phenolic products were detected.

p-Xylene. GLC (column A, 170°) showed that the main product was 2,5-xylenol (35.2%). This was isolated by preparative TLC (after removal of the bulk of the xylene under reduced pressure) and converted into the 1-naphthylurethane, m.p. 171.5° (lit.[26] 172–173°).

t-Butylbenzene GLC (column A, 175°) revealed *o*-t-butylphenol (13.1%) and *p*-t-butylphenol (6.8%) and suggested the presence of *m*-t-butylphenol (< 0.3%).

Anisole. (a) TLC revealed the presence of *o*- and *p*-methoxyphenols. GLC (column B, 190°) gave peaks corresponding to *o*-methoxyphenol (61.6%) and *p*-methoxyphenol (24.6%) and suggested the presence of *m*-methoxyphenol (< 2.5%). (b) The experiment was repeated with *p*-deuterioanisole (5.67 g). The phenolic products were extracted into aqueous sodium hydroxide (10%), which was washed with chloroform (10 ml). The aqueous layer was acidified (2N-H_2SO_4) and extracted with chloroform (5 ml). The chloroform was dried (Na_2SO_4), concentrated, and a portion was submitted to preparative TLC. The *p*-methoxylated fraction was isolated and crystallised from chloroform to give 3-deuterio-4-methoxyphenol (77% deuterium enrichment). δ 6.74 (s, 3H), 4.5 (s, 1H) and 3.72 (s, 3H). m/e (23°) 125($C_7H^2HO_2$, 44), 124 (14), 110 (M-Me, 51). (c) The experiment was repeated with a solution of anisole (0.32 g) in freshly distilled destabilised chloroform (8 ml). The *o*- and *p*-methoxyphenols were detected by TLC together with a minor more polar component.

Nitrobenzene. The reaction mixture did not become noticeably warm, and was kept for 30 min following the introduction of the hypofluorous acid. The mixture was extracted with aqueous

Table 3. Competition experiments

Reactants (mole ratio)	Products	Corrected[a] mole ratio		Partial rate factors	Relative reactivities
(i) PhMe/PhH (1.02)	Phenol	1.0		1.0	
	o-cresol	9.05		$o_f = 26.6$	PhMe/PhH = 12.0
	p-cresol	2.39		$p_f = 14.1$	
	m-cresol	0.56[b]		$m_f = 1.6$[b]	
(ii) PhOMe/PhMe (0.489)	*o*-cresol	1.0	1.0[c]		
	p-cresol	0.27	0.54[c]	$p_f = 14.4$	PhOMe/PhMe = 10.2
	guaiacol	472	9.6[c]	$o_f = 255$	[PhOMe/PhH = 122]
	p-methoxyphenol	1.63	6.6[c]	$p_f = 176$	

[a]From GLC peak areas, corrected for mole response factors.

[b]Peak not resolved: regarded as upper limit. In experiment (ii) *m* isomers could not be adequately estimated.

[c]Partial rate factor with respect to the mono *o*-hydroxylation of toluene.

sodium hydroxide (10%), the aqueous solution being extracted with chloroform before being acidified, and any phenolic products were then re-extracted into chloroform. GLC (column B, 160° and 190°) showed the presence of *o*-nitrophenol (2.9%) and *m*-nitrophenol (5%). *p*-Nitrophenol was not detected.

Fluorobenzene. GLC (column A, 160°) revealed *o*-fluorophenol (18.6%) and *p*-fluorophenol (35.4%).

Chlorobenzene. TLC (petroleum: benzene = 100:25:1) revealed only *o*- and *p*-chlorophenols. GLC (column A, 175°) gave peaks corresponding to *o*-chlorophenol (14.5%) and *p*-chlorophenol (8.6%) and suggested the presence of *m*-chlorophenol (< 0.6%).

Naphthalene. Naphthalene (2 g) in carbon tetrachloride (8 ml) was treated with HOF in the normal way. TLC of the solution after work up showed the presence of 1- and 2-naphthols, together with two minor products. The naphthol fraction was isolated by preparative TLC. GLC (column B, 180°) then showed the presence of 1-naphthol (14.7%) and 2-naphthol (7.7%).

Competition experiments

Hypofluorous acid (47 mg) was reacted with (i) an equimolar mixture (8 ml) of benzene and toluene and (ii) a mixture (8 ml) of toluene (2 mol) and anisole (1 mol) as before. After the passage of HOF the mixture was kept for 10 min, and was then extracted with water (2 × 1 ml). The aqueous soln was extracted with ether (3 ml), the ether was separated, dried and evaporated and the small residue was combined with the main aromatic fraction. After drying (Na_2SO_4) this was submitted to GLC analysis (column A at 150° for (i), column B at 120° for (ii)) with the results presented in Table 3.

Acknowledgements—This work was carried out during the tenure of a British Council Scholarship (to B.M.) and a John Simon Guggenheim Memorial Foundation Fellowship (to E.H.A.). E.H.A. was on leave for Argonne National Laboratory, U.S.A., and acknowledges the support of the U.S. Atomic Energy Commission and the U.S. Energy Research and Development Administration. Certain experiments were repeated and extended at Argonne: a travel grant from the Royal Society (to R.B.) and the hospitality of the Argonne National Laboratory are acknowledged. We are grateful to the Central Research Fund, University of London, for a grant-in-aid (GCMS equipment).

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