COMMUNICATION

New insights into the mechanism of phenolic oxidation with phenyliodonium(III) reagents

László Kürti,[a] Pál Herczegh,[b] Júlia Visy,[c] Miklós Simonyi,[c] Sándor Antus *[a] and Andrew Pelter *[d]

[a] *Department of Organic Chemistry, Lajos Kossuth University, PO Box 70, H-4010 Debrecen, Hungary*
[b] *Research Group for Antibiotics, Hungarian Academy of Sciences, PO Box 70, H-4010, Debrecen, Hungary*
[c] *Institute of Chemistry, CRC Hungarian Academy of Sciences, PO Box 17, H-1525 Budapest, Hungary*
[d] *Department of Chemistry, University of Wales Swansea, Swansea, UK SA2 8PP*

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Calculations indicate that the position of oxidation of substituted phenols is in accord with the intervention of phenoxenium ions as intermediates. The lack of induction of chirality in the reaction whether using a preformed chiral iodonium reagent or a homochiral alcohol as the medium also supports this hypothesis.

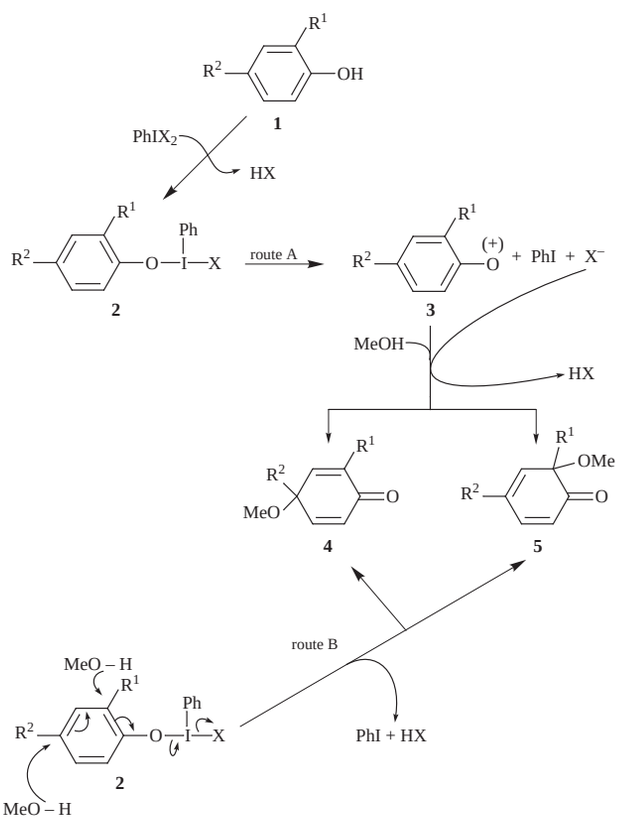
Hypervalent iodine compounds have become widely used and important synthetic reagents.[1] In particular phenyliodonium(III) diacetate (PIDA) and phenyliodonium(III) bis(trifluoroacetate) (PIFA) are efficient reagents for the preparation of *o*- or *p*-quinones,[2] dialkoxycyclohexadienones (quinone ketals), alkoxyalkyldienones[3] and 4-hydroxy-4-alkylcyclohexadienones[3g,h] from phenols.

Cyclohexadienones are important synthetic intermediates[3b–j] and the mechanism of their formation is therefore of interest. As a continuation of previous studies[4,3a] we chose to investigate this oxidation, for which two main pathways have been proposed[3c] (Scheme 1).

Common to both postulates is intermediate **2**. Hypothesis A postulates dissociation to give solvated phenoxenium ions **3** as intermediates. These react further with methanol to give **4** and/or **5**. In hypothesis B, products **4** and **5** arise by direct attack of methanol on **2**. For hypothesis A the site of reaction, *e.g.* C-2 or C-4 would mainly be electronically controlled and even if the iodine atom of **2** were in a chiral environment there could be no chiral induction. For hypothesis B attack on the comparatively non-polar **2** would be strongly influenced by steric factors and if the iodine were in a homochiral environment there might be some asymmetric induction, particularly in the production of **5**.

Table 1 shows the calculated (AM1) Mulliken charge distributions of a number of substituted phenoxenium ions whilst Table 2 shows the LUMO coefficients of the same ions. *The experimental results are very much in line with predictions based on charge distributions*[5a] *and size of LUMO*[5b] *coefficients for phenoxenium ions* ***3***.

Phenol itself is substituted at C-4 in line with our Tables and the results of Ohwada.[5a] 4-Methoxyphenol reacts even more rapidly than phenol and again at C-4 as predicted in the Tables. 2-Methoxyphenol is attacked at C-2,[2d,3d] even though this is the most hindered position, and this is also in line with the Tables. Both 3-methyl- and 4-methylphenol should, if a phenoxenium ion is an intermediate, substitute at C-4 as observed.[3d] An important observation is that 3,5-dimethylphenol oxidises at C-4[3a] despite the great hindrance at this position. 2,3-Dimethylphenol substitutes mainly at C-4 but 2-methoxy-4-methylphenol substitutes at C-2,[3d] showing the profound effect of the 2-methoxy group. Both 2- and 4-benzylphenol oxidise at C-4 even though, in the latter case, it is a position subject to severe hindrance.[3a] That steric factors *can* be influential is shown by the oxidation of 4-*tert*-butylphenol to give C-2 and C-4 attack



Scheme 1

in equal ratios.[3d] In the symmetrical 2,4,6-tri-*tert*-butylphenol however, attack is at C-4 exclusively. The concentration of charge at C-4 in the case of the cations derived from phenol and alkylated phenols is interesting and may reflect the difficulty of placing a positive charge at C-2, adjacent to a carbonyl group, in the cyclohexadienone forms of the phenoxenium ions.

In our hands 4-bromophenol was substituted solely at C-4 [but see ref. 3(*d*)] as predicted both by the size of the LUMO coefficients (Table 2) and by the charge distribution (Table 1).

The predictions for dimethylamino substituted phenols are in line for those for the corresponding methoxy compounds. The nitrophenols are of interest because the predicted point of attack is at C-4 for all three isomers.

To examine the influence of chirality we chose to oxidise 2,3-isopropylidenepyrogallol **6a**,[6] knowing that the product, substituted at C-2 would not dimerise due to the substituent at C-3.[7]

The oxidation process was first examined by oxidising **6b**

Table 1 Charge distributions at C-2, C-4, C-6, O-1 of substituted phenoxenium ions

Substituent	C-2	C-4	C-6	O-1
H	0.030	0.213	0.030	0.067
2-Me	0.143	0.184	−0.279	−0.094
3-Me	0.004	0.207	0.029	−0.073
4-Me	0.007	0.282	0.005	0.089
2-OMe	0.235	0.121	−0.010	−0.091
3-OMe	−0.100	0.177	0.030	−0.068
4-OMe	−0.003	0.335	−0.003	−0.110
2-NMe_2	0.108	0.027	−0.156	−0.187
3-NMe_2	−0.162	0.167	0.044	−0.095
4-NMe_2	−0.065	0.217	−0.062	−0.144
2-NO_2	−0.033	0.217	0.071	−0.022
3-NO_2	0.075	0.242	0.048	−0.043
4-NO_2	0.048	0.180	0.048	−0.044
2-Br	0.052	0.189	0.007	−0.070
3-Br	0.035	0.229	0.042	−0.063
4-Br	0.015	0.181	0.015	−0.007

Table 2 LUMO coefficients for substituted phenoxenium ions

Substituent	C-2	C-4	C-6
H	−0.476	0.606	−0.477
2-Me	0.535	−0.573	0.409
3-Me	0.471	0.608	0.479
4-Me	−0.451	0.618	−0.444
2-OMe	0.558	0.505	0.329
3-OMe	0.466	−0.610	0.484
4-OMe	−0.437	0.588	−0.401
2-NMe_2	−0.566	0.411	−0.267
3-NMe_2	0.424	−0.621	0.509
4-NMe_2	0.383	−0.542	0.382
2-NO_2	−0.449	0.601	−0.501
3-NO_2	−0.470	0.599	−0.482
4-NO_2	0.472	−0.600	0.472
2-Br	−0.518	0.574	−0.427
3-Br	−0.466	0.607	−0.484
4-Br	−0.446	0.618	−0.446

6 **7**

(a) $R^1 = CMe_2$
(b) $R^1 = Me$

	R^1	R^2	config. at C-2
(a)	CMe_2	Me	*R/S*
(b)	CMe_2	$CH_2C^*H(Me)Et$	*R/S*
(c)	Me	Me	
(d)	Me	Ac	*R/S*

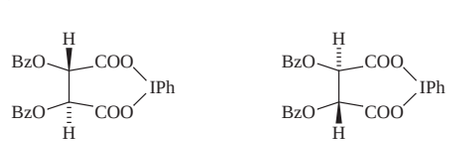
Scheme 2

with PIDA in CH_2Cl_2 containing 2 mole equivalents of methanol. This gave a mixture of **7c** and **7d**, the latter arising most probably from the increasing amount of acetic acid released during the oxidation. Racemic mixture **7a** was prepared first by oxidation of **6a** with PIDA in methanol[8] and was baseline resolved using a homochiral protein column.[9]

As chiral oxidants we chose **8** and **9** prepared by Merkhusev's method[10,11] from dibenzoyl-D-tartaric acid and dibenzoyl-L-tartaric acid respectively.

Oxidation[8] *of* ***6a*** *with either* ***8*** *or* ***9*** *gave racemic mixture* ***7a*** *in each case, whatever conditions were used*. There are a variety of explanations of these results including the intervention of **3**. It is also possible that there is rapid displacement by methanol of dibenzoyltartaric acid from **8** and **9** to give achiral PhI-$(OMe)_2$ as the effective oxidant. We therefore used (*S*)-(−)-2-methylbutan-1-ol as solvent so that ligand displacement would give homochiral $PhI(OCH_2C^*H(Me)Et)_2$. However, even in this medium, only the diastereoisomeric mixture **7b** was obtained, each diastereoisomer being present in equal amounts. We then examined the oxidation using racemic 2-methylbutan-1-ol and obtained equal amounts of all four possible diastereoisomers, as shown by chiral HPLC.[9]

Thus there is a total lack of diastereo- and enantioselectivity in the oxidations examined. Whilst these negative results must be treated with caution, they are in full accord with reaction proceeding *via* phenoxenium ions **3** (route A) and cast doubt on route B. This, taken together with the concordance of experimental results and theory for the prediction of the position of substitution based on phenoxenium ions **3** as intermediates, strongly favours route A for the oxidation of phenols with PIDA.



8 **9**

Acknowledgements

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8 The general procedure was to dissolve the phenol (5 mmol) in a mixture of dry CH_2Cl_2 (10 ml) and the alcohol (100 mmol) and add the phenyliodonium reagent (5 mmol) in dry CH_2Cl_2 (40 ml) over 5 min at room temperature. The reaction was stopped after 20 min and worked up in the usual way.
9 Chiral-AGP from Chrom Tech AB (Hägerstrom/Sweden) using 0.01 M phosphate buffer (pH = 7.0) containing 2% (or 4% v/v) propan-2-ol at 360 mm. Retention times for the two isomers of **7a** were 2.8 and 5.3 min and for **7b** were 11.5 and 27.5 min.
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11 A solution was made of the corresponding dibenzoyltartaric acid (25 mmol) and PIDA (25 mmol) in chlorobenzene (250 ml). The chlorobenzene was slowly removed under reduced pressure at 55 °C. The residue was taken into CH_2Cl_2 and precipitated with ether to give **8** and **9** as white powders, mp 130–135 °C, $[\alpha_D] = 41.54$ (*c* 0.5 in CH_2Cl_2) for **8**, δ_H 5.60 (s, 2H), 6.80–8.00 (m, 15H).

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