

# Reversibility and Isotope Effects in the Homolytic Substitution of Benzoquinone and Pyridine. Mechanism of Homolytic Substitution

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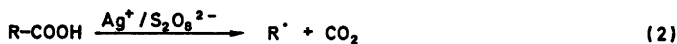
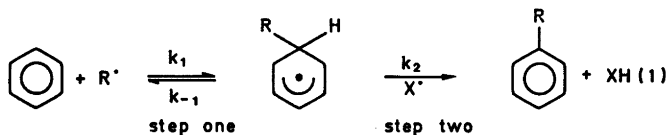
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The mechanism of radical substitution is a delicate balance between a first step that in principle is reversible, and an irreversible second step comprising competitive H abstraction by radicals and electron transfer. In the specific cases of alkylation of quinone or pyridinium ion with the  $\text{Ag}^+/\text{S}_2\text{O}_8^{2-}$  couple and carboxylic acids reversibility of the first step is demonstrated. The second step consists of an H-abstraction by  $\text{SO}_4^{\cdot-}$ . Benzoquinone shows an isotope effect of  $k_{\text{H}}/k_{\text{D}} = 1.9$  (phoxymethylation) and pyridine  $k_{\text{H}}/k_{\text{D}} = 2.2$  (2-position, methylation), 1.1 (4-position, methylation), 4.2 (2-position, *t*-butylation) and 5.5 (4-position, *t*-butylation).

The aromatic homolytic substitution is formulated according to (1) by analogy with electrophilic substitution.<sup>1a,b</sup> The existence of the  $\sigma$ -intermediate is well documented but evidence for the equilibrium is circumstantial, rates ( $k_1$ ,  $k_{-1}$ , and  $k_2$ ) are only approximately known<sup>2</sup> and no equilibrium constant has ever been measured. The C—H bond is strong and elimination of a hydrogen atom needs the assistance of other radicals or an oxidant, *i.e.*  $k_2$  is an expression for competing reactions.

In that respect homolytic substitution is more complicated than electrophilic substitution where the second step involves heterolytic dissociation of a proton, an energetically more favourable process. The interception of the  $\sigma$  intermediates<sup>3-6</sup> and the observation of isotope effects<sup>4,6-9</sup> usually in the range of 1–3, are indicative of a reversible first step followed by a rate-determining second step. Isotope effects are not necessarily synonymous with reversibility of step one because they can be explained by diversion of the  $\sigma$  complex into side products.<sup>10,11</sup> In several cases no, or very small, isotope effects ( $k_{\text{H}}/k_{\text{D}} < 1.3$ ) have been observed<sup>5,12-15</sup> indicative of a comparatively slow first step. Generation of cyclohexadienyl radicals by an independent route has shown that negligible fragmentation occurs,<sup>16</sup> *i.e.* insignificant reversibility, whereas studies of the reactions of 4-phenylbutyl radicals have shown that the spirocyclization is reversible.<sup>17,18</sup> Some circumstantial evidence for reversibility in step one has been derived from product studies of phenylation of dichlorobenzenes at different



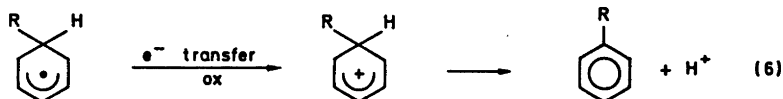
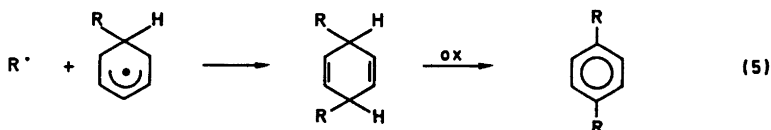
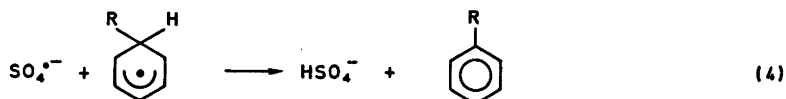
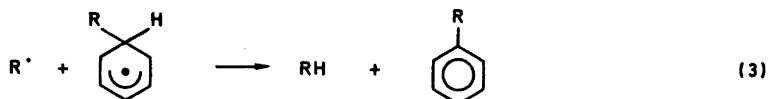
temperatures.<sup>19</sup> The overall picture of the mechanism of homolytic substitution is thus not wholly clear. The reactivity of the attacking radical(s), the relative strength of the  $sp^3$  bonds in the  $\sigma$  complex, and the efficiency of the competing reactions of step two influence strongly the magnitude of the  $k$  values in (1).

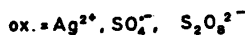
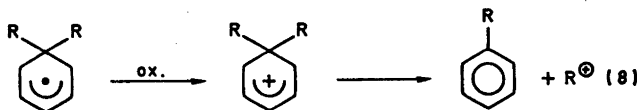
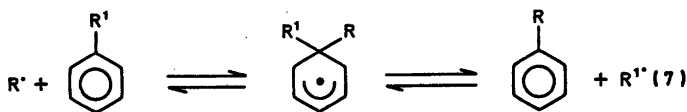
In a preceding paper<sup>20</sup> we offered evidence for the equilibrium in step one in homolytic quinone alkylation. It was found that when 2-benzyl-1,4-naphthoquinone was ethylated with ethyl radicals, 2-benzyl-3-ethylnaphthoquinone, 2,3-di-benzyl-naphthoquinone and 2,3-diethylnaphthoquinone were formed in the proportion 10:1:1. This is only compatible with a radical exchange and reversibility of step one which in this case starts with an *ipso* attack, (7). The expulsion of the benzyl radical is favoured by *ca.* 54 kJ/mol because of its weaker bond strength.<sup>24</sup> Similar exchanges of alkyl and acyl groups were observed by other workers<sup>21-23</sup> in radical alkylation of pyridines. This work is now followed up by an investigation of the isotope effects for alkylation of benzoquinone and the pyridinium ion. The radicals were generated by silver ion-catalyzed peroxydisulfate oxidation of carboxylic acids (2). No scrambling in either the pyridine or quinone reactions was observed.

Several processes are conceivable for the second step of (1) under the prevailing conditions. The alkylation of quinone and the pyridinium ion is generalized in eqns (3)–(8)

as a radical alkylation of an aromatic system.

The high yield of monoalkylated products obtained on several occasions with near equimolecular proportions of reactants in the alkylation of both benzoquinone<sup>25</sup> and pyridinium ions<sup>26</sup> and the absence of *ortho* or *para* disubstituted pyridine, render (3) and (5) unimportant and no dimers were noticed. One cannot completely discard the possibility of "disproportionation", *i.e.* R' in (3) is just another  $\sigma$ -complex. The dihydro product formed can subsequently be oxidized to the aromatic compound. At the first sight (6) seems to be a most reasonable pathway for terminating the oxidative alkylation.  $Ag^{2+}$  and  $SO_4^{\cdot-}$  are reactants with high oxidation potentials which can produce the carbonium ion easily. It has been shown by pulse radiolysis experiments<sup>27</sup> that  $SO_4^{\cdot-}$  and  $Ag^{2+}$  react rapidly with easily oxidizable methoxy-substituted aromatics ( $k$  *ca.*  $5 \times 10^9$  l M<sup>-1</sup> s<sup>-1</sup> and  $5 \times 10^7$  l M<sup>-1</sup> s<sup>-1</sup>, respectively) but in our case an electron transfer will create an unfavourable positive charge  $\alpha$  to the carbonyl group in the quinone and a doubly charged pyridinium species, circumstances that will lower the rate of this reaction considerably. The formation of alcohols or aldehydes is negligible, *i.e.* (8) or dissociation of R<sup>+</sup> from (6) are unimportant, and electron transfer is a comparatively inefficient process here. That leaves the H abstraction (4) as the dominating second step, a reaction that has been reported to be very fast<sup>28</sup>





(2-propanol +  $\text{SO}_4^{\cdot-}$ ,  $k = 8.8 \times 10^7 \text{ l M}^{-1} \text{ s}^{-1}$ ). The overall rate of reaction of alkyl radicals with benzoquinone was recently determined ( $k = 2.0 \times 10^7 \text{ l M}^{-1} \text{ s}^{-1}$ ).<sup>29</sup> This value is a minimum value since reversibility was not considered. Since the reaction of ethyl radicals with 2-benzyl-naphthoquinone gave in addition to 2-benzyl-3-ethylnaphthoquinone considerable amounts of 2,3-dibenzyl- and 2,3-diethylnaphthoquinone, it is clear that  $k_{-1}$  must be large and at least of the same order of magnitude as  $k_2$ . Thus, in the quinone system,  $k_1$ ,  $k_{-1}$ ,  $k_2$  are of comparable magnitude and an isotope effect is expected. The relative rate,  $k_{\text{H}}/k_{\text{D}} = 1.9 \pm 0.1$  for phenoxymethylation of benzoquinone and benzoquinone- $d_4$ , was determined mass spectrometrically. Methylation of the pyridinium ion (ca. 25 % conversion) gave pyridine (69 %), 2-methylpyridine (15 %), 3-methylpyridine traces, 4-methylpyridine (15 %), 2,6-dimethylpyridine (0.1 %), 2,4-dimethylpyridine (0.6 %). The crude mixture was analyzed by the GC-MS. A complicating factor in the calculation of the isotope effect is the slight separation of the protium and deuterium derivatives within the peak of the isomer that has to be considered and corrected for. The isotope effect showed clearly a positional dependence.  $k_{\text{H}}/k_{\text{D}}$  for the 4-position of the pyridinium ion was  $1.1 \pm 0.1$  and for the 2-position  $2.2 \pm 0.2$ . There seems to be no obvious explanation for this difference in isotope effect. The amount of the 3-isomer was too small to be determined. These results differ from arylation of 4-methylpyridine by benzoyl peroxide<sup>11</sup> where  $k_{\text{H}}/k_{\text{D}} = 3.7$  for the 3-position and 1.0 for the 2-position. This isotope

effect vanished on addition of another oxidant, nitrobenzene, which probably acts as an electron transfer agent, and the effect is explained by selective diversion of the  $\sigma$  complex into side-products.

It was reasoned that use of a more stable radical, such as *t*-butyl instead of methyl would drive the equilibrium of step one towards the reactants;  $k_{-1}$  is expected to be larger because of the lower  $E_a$  of the reverse reaction, with a larger isotope effect as a consequence. This was, in fact, found when a mixture of pyridine- $d_5$  and pyridine was *t*-butylated by pivalic acid and  $\text{Ag}^+/\text{S}_2\text{O}_8$ .  $k_{\text{H}}/k_{\text{D}}$  for the 2-position increased to 4.2 and for the 4-position to 5.5 which is a large value showing that the second step in now rate-determining (Table 1).

**Conclusion.** Eqn. (1) describes well the mechanism of homolytic substitution. For the pyridinium ion and quinone the first step is reversible. The rate constants are of comparable magnitude. For the *t*-butyl radical the second step is clearly rate-determining. H-abstraction by the  $\text{SO}_4^{\cdot-}$  radical determines the second step, eqn. (4).

Table 1. Isotope effect of homolytic alkylation of aromatics. Solvent  $\text{H}_2\text{O}$ , temperature  $80 \pm 5$  °C.

Substrate	Radical	$k_{\text{H}}/k_{\text{D}}$
Benzoquinone <sup>a</sup>	$\text{C}_6\text{H}_5\text{OCH}_2^{\cdot}$	$1.9 \pm 0.1$
Pyridine, 2-pos <sup>†</sup>	$\text{CH}_3^{\cdot}$	$2.2 \pm 0.2$
— 4-pos <sup>†</sup>	$\text{CH}_3^{\cdot}$	$1.1 \pm 0.1$
Pyridine, 2-pos <sup>†</sup>	$(\text{CH}_3)_3\text{C}^{\cdot}$	$4.2 \pm 0.4$
— 4-pos <sup>†</sup>	$(\text{CH}_3)_3\text{C}^{\cdot}$	$5.5 \pm 0.6$

<sup>a</sup> Temperature  $65 \pm 5$  °C.

## EXPERIMENTAL

**Methylation of pyridine.** To pyridine (0.185 g, 2.33 mmol), pyridine- $d_5$  (99 % purity)/(0.426 g, 5.06 mmol), acetic acid (0.88 g, 14.8 mmol), silver nitrate (100 mg) in 15 ml 0.5 N sulfuric acid, sodium peroxydisulfate (2.25 g, 10.0 mmol) in water (10 ml) was added drop by drop with stirring at 80 °C. After 1 h the solution was cooled, neutralized with conc. ammonia, extracted with methylene chloride, and solvent evaporated. *Ca.* 25 % conversion was obtained. GC on a glycerol column showed that only traces of 3-methylpyridine were present. Pyridine, 2- and 4-methylpyridine, 2,4- and 2,6-dimethylpyridine were separated on a 10 % PEG column, 20 m, 1 % KOH, at 75 °C. The 2- and 4-methylpyridine peaks were analyzed by MS. The parent peaks were used for measuring the relative amounts of products. It was found that the isotopic pyridines had slightly different retention times and this effect was corrected for by the measurements of the intensities of the  $M^+$  peaks of protonated and deuterated methylpyridines on several positions of the peak. It was separately checked that the intensities of the  $M^+$  peaks of pyridine and pyridine- $d_5$  were proportional to the molar fraction injected.

***t*-Butylation of pyridine** was carried out similarly<sup>26</sup> and the product was analyzed by GC-MS (10 % PEG column). In order to obtain *ca.* 25 % conversion of pyridine the following molar proportion of reactants was used in aqueous sulfuric acid and at *ca.* 80 °C: Pyridine, pivalic acid, ammonium peroxydisulfate, 1:1.1:0.4.

**Phenoxy-methylation.**<sup>30</sup> To a mixture of benzoquinone (108 mg), benzoquinone- $d_4$  (111.9 mg), silver nitrate (50 mg), and phenoxyacetic acid (80 mg) in water (6.5 ml), ammonium peroxydisulfate (116 mg) in water (1 ml) was added with stirring at 65 °C. After cooling, filtration, and dissolving the precipitate on the filter in methylene chloride, 77 mg of crystalline phenoxy-methylquinone was obtained on evaporation of the solvent. The conversion was *ca.* 25 %. The intensities of the  $M^+$  and  $(M+3)^+$  peaks were determined and corrected for 0 % conversion.

**Benzoquinone- $d_4$**  was prepared according to the method of Charney and Becher.<sup>31</sup> The isotopic purity was better than 98 %.

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