A NOTE ON THE OXIDATIVE CAPACITY OF BENZOFURAZAN OXIDE

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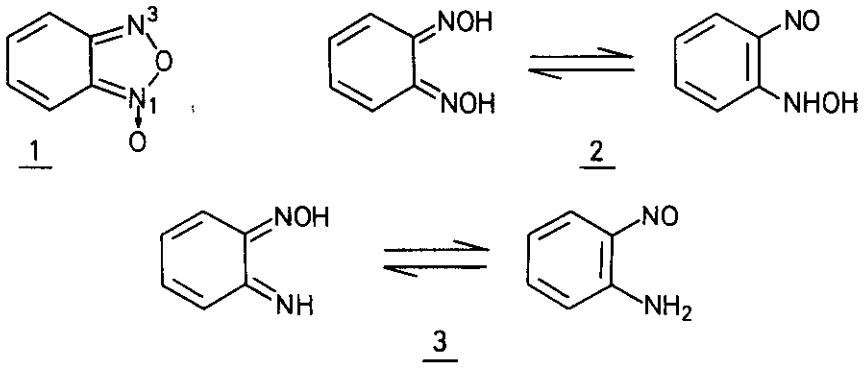
Abstract - A method is described for the preparation of o-quinone dioximes from the reaction of benzofurazan oxide (or its congeners) with sodium dithionite, thiophenols, phenylhydroxylamine, and hydrazine derivatives. These, and other related reactions reported in the literature, are interpreted as two-electron transfer processes from reductant to benzofurazan oxide (oxidant), leading to the o-quinone dioxime anion.

Benzofurazan oxide (BFO, 1) reacts readily with electron-rich systems, such as enamines and enolate anions, to give a variety of heterocyclic compounds[1]. Recent work from several laboratories indicates that in the course of these synthetically valuable reactions, BFO may also act as an oxidizing agent, thereby occasionally giving rise to unexpected or undesirable by-products, including two reduction products of BFO: o-benzoquinone dioxime (2, tautomeric with o-hydroxylaminonitrosobenzene; one oxidation level below BFO) and o-nitrosoaniline (3, two



1 2 3

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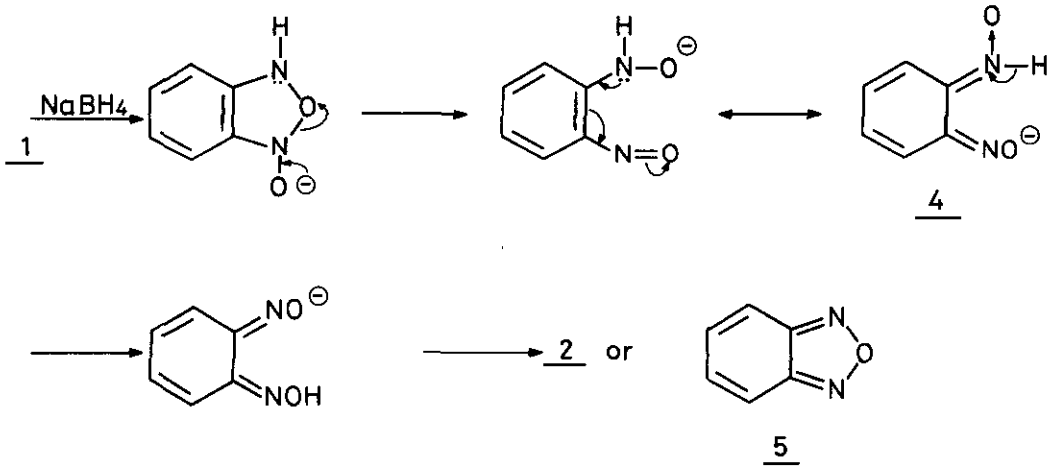
oxidation levels below BFO). As 2 and 3 are quite reactive, their formation is often masked by subsequent reactions[2].

The propensity of BFO for accepting electrons is manifested by its well-known reduction by sodium borohydride[3] (Scheme 1) to give, depending on the experimental conditions, either 2 (as the anion) or benzofurazan (5, at the same oxidation level as 2). The reaction probably entails attack by the hydride on N-3 of 1, followed by ring opening to intermediate 4[4], which finally gives 2 (after acidification) or its dehydration product 5.

Scheme 1

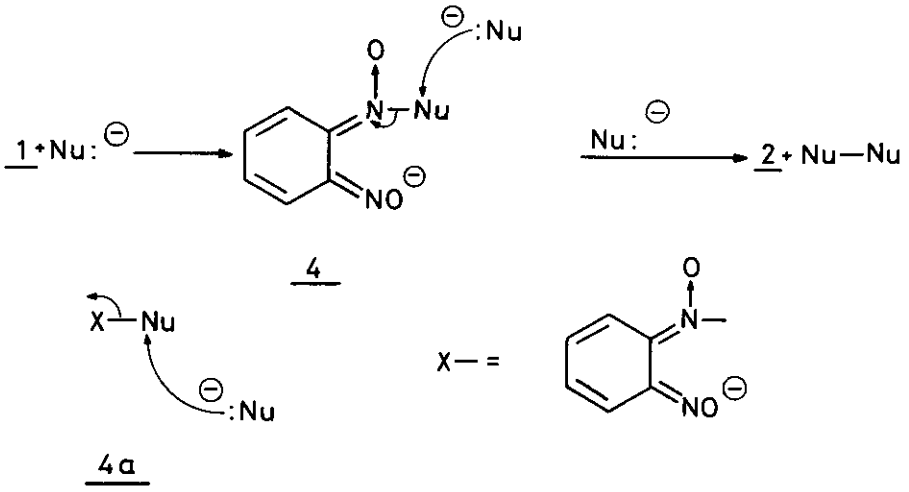


In this paper we report some oxidations by BFO performed in our laboratory (Table I) and suggest that they, as well as other similar oxidations reported in the literature, may be regarded as two-electron transfers from reductant to oxidant (BFO) via displacement (Scheme 2) or elimination (Scheme 3) processes. The reductants listed in Table I include sodium dithionite, thiophenols, phenylhydroxylamine, and hydrazine derivatives. Although anyone of these reductants, as shown in Table I, provides a general route to o-quinone dioximes, we particularly recommend semicarbazide hydrochloride for this purpose because of its efficacy and relatively low cost.

In Scheme 2, the reductant ($Nu:^-$) and BFO give intermediate 4 (cf Scheme 1), from which the anion of o-benzoquinone dioxime is displaced by attack of a second reductant molecule. Two electrons are fully transferred to the oxidant during

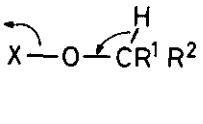
this process, a typical example of which is the oxidation of thiophenols by BFO in the presence of base to give disulfides and 2 (Scheme 2, $Nu:^- \equiv ArS^-$). The reaction of BFO with thiourea to give 2 probably follows a similar mechanism (see Table I, reactions with $p\text{-}CH_3C_6H_4SH$, $o\text{-}NH_2C_6H_4SH$, NH_2CSNH_2). For convenience, intermediates such as 4 hereafter will be shown as 4a, where $\overset{\curvearrowleft}{X}^-$ represents the incipient leaving group (o-benzoquinone dioxime anion).

Scheme 2

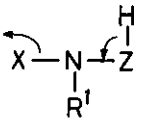


Scheme 3 depicts a pathway entailing attack on BFO by the reductant via one of the latter's nucleophilic atoms (commonly oxygen or nitrogen) to give intermediates such as 6 or 7, from which the o-benzoquinone dioxime anion arises by an elimination process. Early preparations of o-benzoquinone dioxime from BFO and alcoholic potassium hydroxide[5] or hydroxylamine in basic solution[6,7] probably involve intermediates such as 6 or 7a. In our laboratory we have prepared 2 by simply treating an ethanolic solution of BFO at room temperature with phenylhydroxylamine (Table I). The by-product that we isolated from this reaction, azoxybenzene, evidently arises from the (expected) further reaction of nitrosobenzene (arising from 7b) with excess phenylhydroxylamine. We have also utilized the reaction of BFO (or its congeners) with a number of hydrazine derivatives to prepare o-quinone dioximes in moderate to good yields (Table I). In the case of hydrazobenzene, we isolated the expected dioxime as well as the azobenzene (arising from the decomposition of 7c)[8].

Scheme 3



6

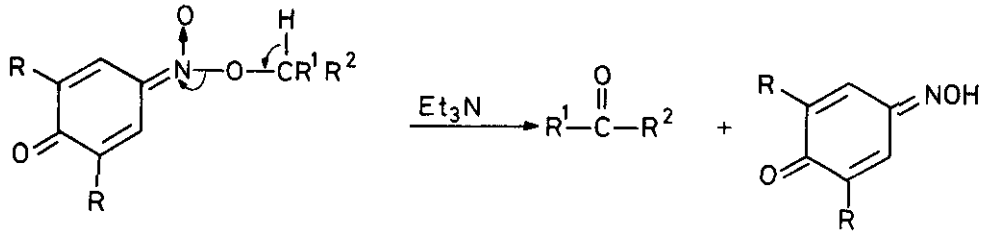


7

	a	b	c	d
R^1	H	Ph	Ph	R^1
Z	O	O	NPh	CHR^2

That 6 and, by analogy, 7 are indeed plausible intermediates in these reactions is corroborated by the recently reported[9] facile conversion of acinitroesters (8; note structural relationship to 6) into carbonyl compounds by treatment with base (Scheme 4). Our further finding that BFO and its congeners can

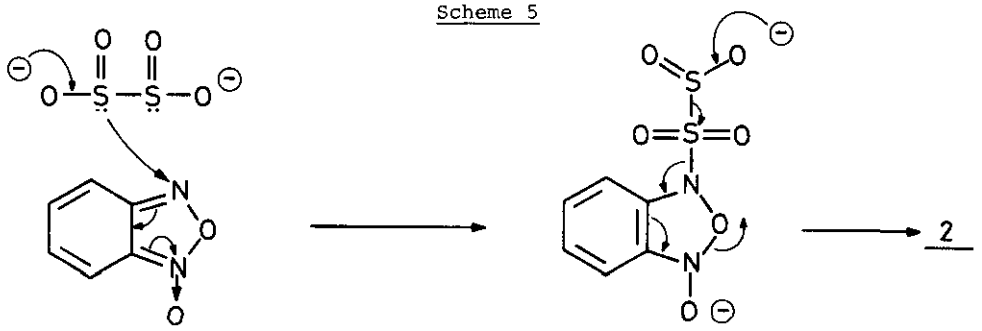
Scheme 4



8 (R = tert. butyl)

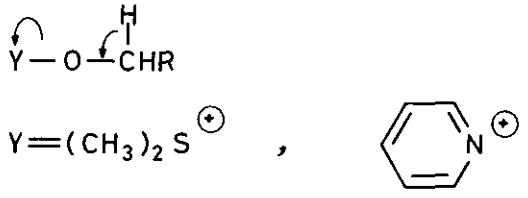
be reduced to o-quinone dioximes by sodium dithionite (Table I) is consistent not only with the mechanism shown in Scheme 3 but also with the mode of reduction of other systems by dithionite[10] (Scheme 5). Moreover, the previously reported

Scheme 5



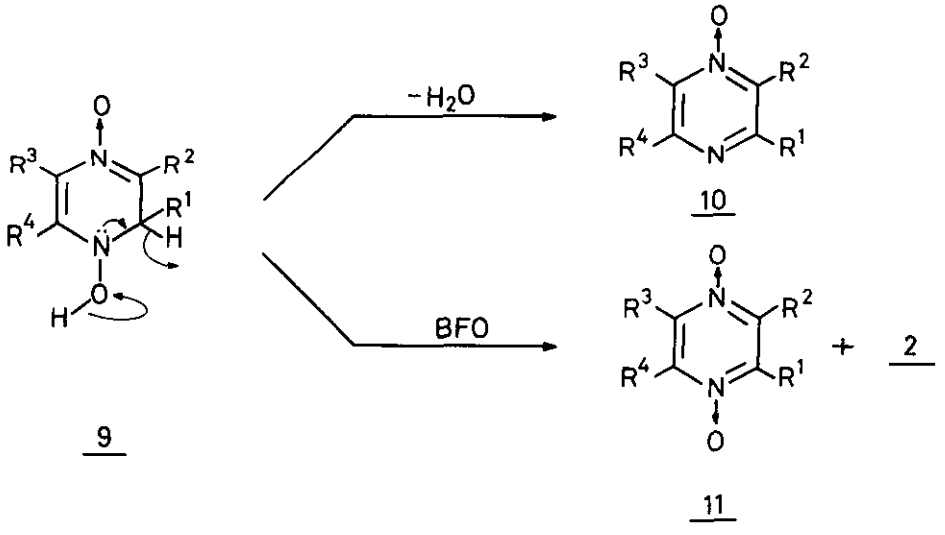
reaction of BFO with secondary amines to give imines[2] also conforms with the pattern of Scheme 3 (intermediate 7d), as also does the reported oxidation of certain hydroquinones by BFO to give p-quinones and 2[11]. It should be noted that the reactions of Schemes 3 and 4 are mechanistically related to the Kornblum oxidation[12] of alcohols to carbonyl compounds by base-catalyzed elimination on appropriately substituted onium salts (Scheme 6).

Scheme 6



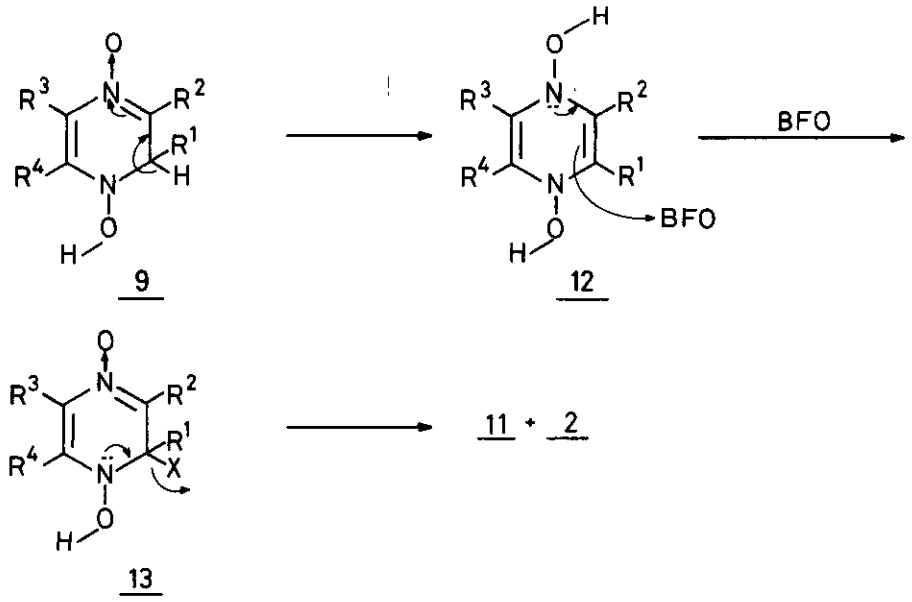
In concluding, we should like to propose that certain recently reported oxidations of systems such as 9, in the presence of BFO, may also be interpreted in terms of the mechanism depicted in Scheme 3. Although these systems may, in principle, undergo dehydration to the corresponding monoxide (9 ⟶ 10, Scheme 7), they often follow an oxidative pathway leading to the dioxide (9 ⟶ 11). The

Scheme 7



transformation of 9 into 11 formally amounts to transfer of a hydride from 9 (Scheme 7, arrows), but the relatively mild conditions of the reaction suggest the possibility of an alternative pathway (Scheme 8), whereby electrons are transferred to BFO by a process compatible with that described in Scheme 3. The salient feature of Scheme 8 is a prototropic shift to give 12 (analogous to an enamine), which attacks BFO in the manner[1] expected of enamines to give 13, in which the incipient anion of o-quinonedioxime serves as the leaving group. Scheme 8 would account for the oxidation of dihydro intermediates to phenazinol-5,10-dioxides during the reaction of BFO with appropriately substituted phenols[11]. The recent finding[13] that quinoxaline di-N-oxides may appear as products of certain BFO reactions that normally lead to monoxides, may also be interpreted in terms of Scheme 8.

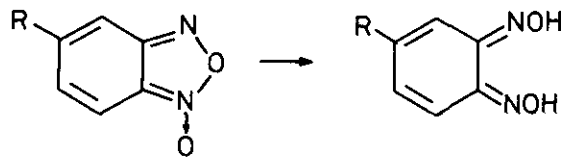
Scheme 8



Experimental

1. Phenylhydroxylamine. A solution of phenylhydroxylamine (2.2 g) and BFO (1.4 g) in ethanol (20 ml) was allowed to stand overnight in a stoppered flask. The solvent was evaporated to dryness and the residue was treated with ammonium hydroxide (10 ml conc. NH_4OH and 40 ml water), stirred well, and filtered. The filtrate, upon acidification with acetic acid, gave 0.50 g of o-benzoquinone dioxime, melting at 145-146° (dec.). The solid on the filter paper was treated with hot ethanol (30 ml) and filtered. The hot filtrate was decolorized with

Table I



Reductant	R	Moles of Oxidant	Moles of Reductant	EtOH (ml)	H_2O (ml)	25% alc. KOH (ml)	Temp. (°C)	Time	Yield (%)
$pCH_3C_6H_4SO_2NHNH_2$	H	0.015	0.016	15	20	10	25	0.5 hr	90
$NH_2NHCONH_2.HCl$	H	0.015	0.02	15	10	10	25	0.5 hr	90
NH_2CSNH_2	H	0.015	0.03	15	10	10	25	0.5 hr	55
$NH_2NH_2.2HCl$	H	0.015	0.02	15	15	20	60	0.5 hr	50
$pCH_3C_6H_4SH$	H	0.015	0.03	25	5	5	50	0.75 hr	25[a]
PhNHNHPh	H	0.015	0.02	25	10	10	25	0.5 hr	60[b]
$o\text{-}NH_2C_6H_4SH$	H	0.015	0.03	30	10	10	30	0.5 hr	40[a]
$Na_2S_2O_4$	H	0.022	0.023	50	10	10	70	2 min	75
$pCH_3C_6H_4SO_2NHNH_2$	Cl	0.012	0.013	15	20	5	25	0.3 hr	80
$NH_2NHCONH_2.HCl$	Cl	0.012	0.02	15	10	5	25	0.3 hr	75
NH_2CSNH_2	Cl	0.012	0.02	15	10	5	25	0.3 hr	40
$pCH_3C_6H_4SO_2NHNH_2$	CH_3	0.007	0.008	15	10	5	35	0.5 hr	70
$NH_2NHCONH_2.HCl$	CH_3	0.007	0.009	15	10	5	35	0.5 hr	60
NH_2CSNH_2	CH_3	0.006	0.012	15	10	5	35	0.5 hr	50
PhNHOH	H	0.01	0.02	20	-	-	25	16 hr	36[c]

a. After completion of the reaction, 50 ml of ice-water was added and the disulfide was filtered off before acidification. b. Same as in a, the precipitate being azobenzene. c. Azoxybenzene was also isolated as a by-product. See experimental section.

charcoal, filtered, and cooled to give azoxybenzene (1.0 g) melting at 36°.

2. General procedure for other reductants. The reactions were carried out in aqueous ethanolic potassium hydroxide using the amounts of reductant and oxidant specified in the Table, and with constant stirring. Upon completion of the reaction (Table I), the intensely red solution was concentrated under reduced pressure at room temperature to half the original volume, diluted with 25 ml water, cooled to 0°, and filtered. Upon acidification of the filtrate with acetic acid, the red color disappeared and the o-quinone dioxime precipitated. The product was collected, washed with 10 ml of ice-cold water, and dried at room temperature for 48 hours. Purification was effected by dissolving the oxime in ammonium hydroxide, filtering the solution, and acidifying the filtrate with acetic acid. Melting points: o-benzoquinone dioxime: 145-146° dec. (lit.[6] 142°, dec.); 4-methyl-o-benzoquinone dioxime: 129-130° (lit.[6] 127-128°); 4-chloro-o-benzoquinone dioxime: 129-130° (lit.[14] 128°).

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