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THE REMARKABLE NUCLEOPHILICITY OF SUPEROXIDE ANION RADICAL.

RATE CONSTANTS FOR REACTION OF SUPEROXIDE ION WITH ALIPHATIC BROMIDES.

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We wish to report rate constants for the reaction of superoxide anion radical, $O_2^{\overline{\cdot}}$, with various aliphatic bromides in dimethylsulfoxide (DMSO) solution. The results suggest that $O_2^{\overline{\cdot}}$ is one of the most potent nucleophiles yet studied.

Superoxide ion is the radical anion derived by adding an electron to molecular oxygen and is suspected of having a widespread, albeit transitory, existence in nature. The elegant pioneering work of Fridovich and his group has demonstrated that all aerobic organisms studied possess a defense mechanism against $O_2^{\overline{\cdot}}$ in the form of superoxide dismutase.[1] These biological findings have prompted investigations of the chemical behavior of this unique anion radical and a number of such studies have been reported recently.[2] Although $O_2^{\overline{\cdot}}$ is capable of exhibiting nucleophilic, radical, and redox behavior, the nucleophilic and reducing electron-transfer processes appear to predominate. It has been demonstrated that $O_2^{\overline{\cdot}}$ reacts readily with aliphatic halides[3-6] to produce the corresponding alcohols in DMSO[3] and that the transformations occur with essentially complete inversion[3,4] of configuration typical of a S_N2 Walden inversion mechanism. It is quite likely that the main course of reaction of $O_2^{\overline{\cdot}}$ with RX in DMSO involves an initial rate limiting displacement of X^- by $O_2^{\overline{\cdot}}$ to generate an intermediate peroxy radical ROO· (eq. 1) and that this species is rapidly reduced by a second $O_2^{\overline{\cdot}}$ (eq. 2). It has been

$$RX + O_2^{\overline{\cdot}} \longrightarrow RO_2\cdot + X^- \qquad (1)$$

$$RO_2\cdot + O_2^{\overline{\cdot}} \longrightarrow RO_2^- + O_2 \qquad (2)$$

$$RO_2^- + CH_3SOCH_3 \longrightarrow RO^- + CH_3SO_2CH_3 \qquad (3)$$

recently demonstrated by Gibian and Ungermann[7] that alkyl peroxide anions react rapidly with solvent DMSO to produce the corresponding alcohol and dimethylsulfone (eq. 3). We have verified the stoichiometry required by eqs. 1-3. Reaction of 1-bromobutane with excess KO_2 in DMSO and titration[8] of unreacted KO_2 indicated 1.9 ± 0.2 equivalents of KO_2 were consumed per equivalent of 1-bromobutane.

By means of stopped-flow kinetic techniques we have determined the rate constants for the reaction of KO_2 with representative aliphatic bromides in DMSO at 25.0°. The reactions were conducted under pseudo-first-order conditions with the disappearance of $O_2^{-\cdot}$ monitored at 275 nm. Typical experimental concentrations were 10^{-3}M KO_2 and 10^{-1}-10^{-2}M alkyl bromide; the alkyl bromide was always present in at least 10-fold excess. The reactions were shown to exhibit first-order kinetics in $O_2^{-\cdot}$ for over 70% reaction. Second-order rate constants were obtained by dividing the observed pseudo-first-order values by two times the concentration of the alkyl bromide. The factor of two takes into account the $O_2^{-\cdot}$ consumed in eq. 2. The concentration of each bromide was varied by at least 10-fold with minimal effect on the second-order rate constant. The results are recorded in Table 1.

Table 1

Rate Constants for the Reaction of KO_2 with Alkyl Bromides in DMSO at 25.0°

Alkyl Bromide	k_2 (M^{-1} sec^{-1})
CH_3Br	$(6.7 \pm 0.2) \times 10^2$
CH_3CH_2Br	$(3.5 \pm 0.2) \times 10^2$
$CH_3(CH_2)_3Br$	$(1.5 \pm 0.1) \times 10^2$
$(CH_3)_2CHBr$	$(6.5 \pm 0.1) \times 10^1$
1-bromoadamantane	<1.0[a]

[a] Too slow to measure by the stopped-flow technique.

The usual reactivity order[9] characteristic of an S_N2 process is evident: MeBr > ETBr > i-PrBr >> 1-bromoadamantane. The first four entries in this series reflect the increasing inaccessibility of the carbon atom undergoing displacement although the spread in reactivities is smaller than frequently observed.[9] The unreactivity of the bridehead bromide demonstrates the absence of any appreciable electron transfer type substitution process (e.g., eq. 4). The differences in reduction potentials between $O_2^{-\cdot}$ and aliphatic bromides are apparently too

$$R\text{-}Br \xrightarrow[-O_2]{O_2^{-\cdot}} [RBr^{-\cdot}] \xrightarrow[-Br^{-}]{} R\cdot \xrightarrow{O_2} RO_2\cdot \longrightarrow \text{Products} \qquad (4)$$

great to allow such a transfer to take place even though such behavior is observed with the more easily reduced nitroaromatic halides.[2a]

A comparison of the present kinetic values for $O_2^{-\cdot}$ (Table 1) with other nucleophiles reacting with the same substrate bromides (Table 2) reveals that $O_2^{-\cdot}$ is an extremely potent nucleophile. It is seen to react typically several orders of magnitude more rapidly than the acclaimed iodide, thiophenoxide, and thiocyanate ions. However, the difficulty in comparing the nucleophilicities of different anions is demonstrated by the reactivity order $I^- > SCN^-$, $CN^- > N_3^-$, $Br^- > Cl^- > CH_3CO_2^-$ with methyl iodide in protic solvents which becomes $CN^- > CH_3CO_2^-$ $> Cl^-$, Br^-, $N_3^- > I^- > SCN^-$ in dipolar aprotic solvents.[10a] The last three entries in Table 2 are included because there are no comparable data for the CN^- and $CH_3CO_2^-$ nucleophiles with the substrate bromides of the present study. The available data[10a] suggest that CH_3I should be roughly 5-20 times more reactive than CH_3Br with a given nucleophile under similar conditions. Although there are relatively few data in DMSO solution for direct comparison, the available evidence suggests that the dipolar aprotic solvents DMSO, DMF, and CH_3CN should exert similar effects on reaction rates.[11] Although more directly comparable data would be highly desirable, the conclusion appears inescapable that $O_2^{\bar{\cdot}}$ is, indeed, a powerful nucleophile.[12]

Table 2

Rate Constants for Reactions of Various Nucleophiles with Organic Bromides in Dipolar Aprotic Solvents at 25°.[10a]

Reactants	Solvent	k_2 (M^{-1} sec^{-1})
$CH_3Br + Cl^-$	DMF	4.0×10^{-1}
$CH_3Br + N_3^-$	DMF	4.0×10^{-1}
$CH_3Br + SCN^-$	DMF	1.3×10^{-2}
$CH_3Br + I^-$	Me_2CO	4.0×10^{-1}
$CH_3(CH_2)_3Br + N_3^-$	CH_3CN	4.0×10^{-2}
$CH_3(CH_2)_3Br + N_3^-$	DMSO	1.0×10^{-2}
$CH_3(CH_2)_3Br + C_6H_5S^-$	DMF	5.0×10^{1}
$(CH_3)_2CHBr + N_3^-$	DMF	4.0×10^{-3}
$(CH_3)_2CHBr + C_6H_5S^-$	DMF	2.0×10^{-1}
$CH_3\text{-}I + CN^-$	DMF	3.2×10^{2}
$CH_3\text{-}I + AcO^-$	DMF	2.0×10^{1}
$CH_3\text{-}I + CH_3O^-$	DMSO	6.3×10^{1}

Why is $O_2^{\bar{\cdot}}$ such a potent nucleophile? Unfortunately, no simple explanation can be given at the present time. The relative nucleophilicities of anions toward organic substrates has been the subject of much research over the years and the topic has been thoroughly reviewed.[9,14] There are numerous factors (Bunnett[14a] lists 17) which must be considered in an assessment of nucleophilic reactivity including solvation, basicity, polarizability, and the α-effect. The effect of solvent was noted above. The $O_2^{\bar{\cdot}}$ ion, the conjugate acid of which exhibits $pK_a = 4.88$[15], is not very basic and, being comprised of two electronegative second-row oxygen atoms, is not expected to be particularly polarizable. With a second oxygen atom and its attendant non-bonded electron pairs adjacent to the nucleophilic site, $O_2^{\bar{\cdot}}$ is an α-effect nucleophile.[13] Although such an electronic arrangement is known to produce exceptional nucleophilic reactivity, the reason(s) for the α-effect are not well understood. It is plausible that the super nucleophilicity of $O_2^{\bar{\cdot}}$ can, perhaps, be at least partially attributed to a significant electron-transfer contribution in the transition state (eq. 5). Although

$$O_2^{\bar{\cdot}} + RBr \longrightarrow \left[O_2^{\bar{\cdot}}\text{---}R\text{---}Br \longleftrightarrow O_2\text{---}\dot{R}\text{---}\bar{Br}\right]^{\ddagger} \longrightarrow RO_2\cdot + Br^- \qquad (5)$$

such contributions can be drawn for all nucleophiles, it may be particularly important for $O_2^{\bar{\cdot}}$ because of the inherent stability of molecular oxygen.

We are examining the kinetics of reaction of $O_2^{\cdot -}$ with other organic substrates under various conditions. Results will be reported in future publications.

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