Phase transfer catalysis by tetraethylammonium bromide: Nucleophilic opening of anhydrides using potassium superoxide in aprotic medium

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Tetraethylammonium superoxide, generated in situ by the phase transfer reaction of potassium superoxide and tetraethylammonium bromide, brings about a clean cleavage of various anhydrides, particularly those with high molecular weight in dry dimethylformamide. As an outcome, succinic anhydride 1; glutaric anhydride 2; 3,3-dimethylglutaric anhydride 3; phthalic anhydride 4; diphenic anhydride 5; 1,2,3,4-tetrahydro-9-oxo-1,4-ethano naphtalene-2,3-endodicarboxylic anhydride 6; 1,4,5,6,7,7-hexachloro-5-norbornene-2,3-endodicarboxylic anhydride 7; endo-bicyclo [2.2.1] heptan-2-one-5,6-dicarboxylic anhydride 8; cis-5-norbornene-endo-2,3-endodicarboxylic anhydride 9 and trans-1,2-cyclohexane endodicarboxylic anhydride 10 have been transformed into their corresponding dicarboxylic acids in fairly good yields. The report demonstrates the applicability of tetraethylammonium bromide as a phase transfer catalyst for efficient superoxide studies.

The focal role played by molecular oxygen and oxygen species in living systems has been realised almost from two centuries. The continuing interest in oxygen stems from the complicated role it plays not only in the breath of life but also more interestingly in oxygen toxicity. One of the most active oxygen species implicated in this detrimental process is the ubiquitous one-electron reduction product of molecular oxygen, i.e., superoxide anion radical (O$_2^-$). Superoxide ion plays an important role in various diseases such as carcinogenesis, ischemia, inflammation, diabetes and aging. During the past two decades, considerable interest has been paid to the chemistry and the reactivity of O$_2^-$ by a host of interdisciplinary researchers. Since O$_2^-$ has radical as well as anionic characters, it is capable of exhibiting nucleophile, radical, oxidant and reductant behaviours.

Currently, two basic approaches are in use for the generation of O$_2^-$ in aprotic media. The first approach involves the cathodic reduction of molecular oxygen at a constant potential of $-1.0 \text{V vs SCE}$ in aprotic media. However, the concentration of O$_2^-$ resulting from electrochemical method is too small ($<10^{-3} \text{M}$) for efficient product studies. The second method utilizes commercially available potassium superoxide (KO$_2$) which is solubilized through the agency of 18-crown-6-ether. But, since crown ethers are expensive reagents, their use for the large scale preparation has yet limited applications. In lieu of KO$_2$/18-crown-6 combination, the use of tetraethylammonium superoxide (Et$_4$NO$_2$), obtained by the phase transfer reaction of KO$_2$ and tetraethylammonium bromide (Et$_4$NBr), has recently been recognized as a useful alternative. As a part of our ongoing programme on superoxide research, it is our current endeavour to extend the applicability of Et$_4$NBr as an inexpensive alternative to 18-crown-6 for superoxide reactions from a functional group perspective.

Acid anhydrides are, as a rule, only slightly soluble in water and are hydrolysed comparatively slowly in cold. The stability of anhydrides towards water increases with increasing molecular weight. The scanning of literature on the chosen field of investigation reveals that there exist only a few reports describing the reactivity of anhydrides with O$_2^-$, but as the studies are confined to limited substrates and the results being complex too, there is enough room for further investigation in this direction. With a view to investigating the behaviour of Et$_4$NO$_2$ towards simple organic molecules, which is of importance in itself and further to assess its synthetic scope, the reactions of this novel reagent with anhydrides having variant structural features (Scheme I) were studied.

Various anhydrides viz., succinic anhydride 1; glutaric anhydride 2; 3,3-dimethylglutaric anhydride 3; phthalic anhydride 4; diphenic anhydride 5;
Scheme I

1,2,3,4-tetrahydro-9-oxo-1,4-ethanonaphthalene-2, 3-endo-dicarboxylic anhydride 6; 1,4,5,6,7, 7-hexachloro-5-norbornene-2,3-dicarboxylic anhydride 7; endo-bicyclo [2.2.1] heptan-2-one-5,6-dicarboxylic anhydride 8; cis-5-norbornene-endo-2,3-dicarboxylic anhydride 9 and trans-1,2-cyclohexanedicarboxylic anhydride 10 were subjected to the reaction with in situ generated Et₄NO₂ in dry DMF at room temperature to give their corresponding dicarboxylic acids namely, succinic acid 1a; glutaric acid 2a; 3,3-dimethylglutaric acid 3a; phthalic acid 4a; diphenic acid 5a; 1,2,3,4-tetrahydro-9-oxo-1, 4-ethanonaphthalene-2,3-dicarboxylic acid 6a; 1,4,5,6,7,7-hexachloro-5-norbornene-2,3-dicarboxylic acid 7a; endo-bicyclo [2.2.1] heptan-2-one 5,6-dicarboxylic acid 8a; cis-5-norbornene-endo-2,3-dicarboxylic acid 9a; and trans-1,2-cyclohexanedicarboxylic acid 10a respectively, in fairly good yields (Table I).

In an effort to maximize the yield of the product, the reaction was investigated in detail by varying a number of solvents viz., acetonitrile, DMSO and DMF in the presence as well as in the absence of Et₄NBr. It is important to note that in the absence of Et₄NBr, only a negligible transformation of the substrate was observed which may be attributed to the

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield* (%)</th>
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<tbody>
<tr>
<td>(1)</td>
<td>(1a)</td>
<td>28</td>
</tr>
<tr>
<td>(2)</td>
<td>(2a)</td>
<td>64</td>
</tr>
</tbody>
</table>

*Isolated mass yields are based on anhydrides 1-10.
least solubility of KO$_2$ in aprotic media. As regards the effect of solvents, while acetonitrile gave rather intractable products, the use of DMSO was refrained owing to a lower yield of the isolated product. The yields of the products (Table I) were obtained employing a 3.2 times molar excess of KO$_2$ and a 1.6 times excess of Et$_4$NBr over the substrate 1-10 in dry DMF. Generally, the anhydrides 1-10 were subjected to the reaction for 8-12 hr at room temperature under dry nitrogen. The reaction was then quenched and worked-up to afford the products 1a-10a. The completion of reaction was monitored on TLC. All the products exhibited physical and spectral data consistent with their structures (cf. Table II). The IR spectra of the products showed a strong C=O stretching band in the region 1650-1720 cm$^{-1}$ instead of two absorption bands in the region 1740-1870 cm$^{-1}$ for the anhydride linkage. Further, a broad O-H stretching band in the region 3200-3600 cm$^{-1}$ coupled with the above carbonyl stretching clearly represented the COOH function. The $^1$HNMR spectra of the products displayed a characteristic resonance signal at $\delta$ 8.5-12.5 ppm ascribed to the carboxylic proton which is D$_2$O exchangeable.

Based on product isolation and existing literature on the chemistry of superoxide ion in aprotic media, the following mechanism may be hypothesized (Scheme II). The reaction is proposed to be initiated by the nucleophilic attack of O$_2$ at one of the carbonyl carbons of anhydride linkage to give an anion radical A which accepts an electron from another molecule of O$_2$ to provide a dianionic species B. This species B attacks another molecule of the substrate giving rise to the peroxide C which after necessary oxygen-oxygen bond scission via electron transfer from O$_2$ to the peroxide linkage gets converted into the dicarboxylate anion of products 1a-10a.

The present report demonstrates the synthetic potential of tetraethylammonium superoxide, a novel reagent, for a clean hydrolysis of anhydrides, particularly with high molecular weight, under significantly mild reaction conditions in aprotic medium.

**Experimental Section**

Melting points were measured with a Buchi apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer ($v_{\text{max}}$ in cm$^{-1}$) and $^1$HNMR spectra on a JEOL FT-NMR spectrometer FX-90Q (the chemical shifts in $\delta$, ppm, downfield relative to tetramethylsilane as internal reference).

Potassium superoxide and tetraethylammonium bromide were procured from E. Merck, Germany and

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**Table II—Physical and spectral data of compounds 1a-10a**

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p. ($^\circ$C)</th>
<th>IR($v_{\text{max}}$ in cm$^{-1}$)</th>
<th>$^1$H NMR ($\delta$, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>185</td>
<td>640, 803, 920, 1178, 1203, 1312, 1420, 1695, 2500-3550</td>
<td>2.45 (t, 4H, 2×CH$_2$)</td>
</tr>
<tr>
<td>2a</td>
<td>97.97-97.98</td>
<td>920, 1165, 1210, 1268, 1307, 1410, 1435, 1698, 2500-3500</td>
<td>1.8 (m, 2H, C=CH$_2$-C=O)</td>
</tr>
<tr>
<td>3a</td>
<td>103-04</td>
<td>700, 931, 1188, 1203, 1438, 1710, 1740, 2500-3400</td>
<td>1.1 (s, 6H, 2×CH$_2$); 2.35 (s, 4H, 2×CH$_2$)</td>
</tr>
<tr>
<td>4a</td>
<td>228-30</td>
<td>740, 798, 907, 1070, 1280, 1402, 1585, 1682, 2300-3200</td>
<td>7.20-8.00 (m, 4H, ArH)</td>
</tr>
<tr>
<td>5a</td>
<td>226-28</td>
<td>750, 762, 1270, 1300, 1405, 1580, 1595, 1685, 2300-3250</td>
<td>6.9-8.1 (m, 8H, ArH)</td>
</tr>
<tr>
<td>6a</td>
<td>187-89</td>
<td>815, 960, 1022, 1220, 1300, 1410, 1700 (br), 2700-3600</td>
<td>2.0-2.9 (m, 2H, O-CH$_3$); 3.2-4.2 (m, 4H, 4×-CH$_2$); 7.4 (m, 4H, ArH); 12.3 (s, 2H, COOH, D$_2$O exchangeable)</td>
</tr>
<tr>
<td>7a</td>
<td>228</td>
<td>820, 890, 1060, 1170, 1220, 1350, 1420, 1600, 1710, 2500-3550</td>
<td>4.1 (s, 2H, 2×-CH$_3$); 8.15 (s, 2H, COOH, D$_2$O exchangeable)</td>
</tr>
<tr>
<td>8a</td>
<td>163</td>
<td>1708(br), 2600-3550</td>
<td>2.0-2.4 (m, 4H); 3.15 (m, 2H); 3.95-4.20 (m, 2H); 11.95 (s, 2H, COOH)</td>
</tr>
<tr>
<td>9a</td>
<td>192-94</td>
<td>1595, 1705, 2500-3450</td>
<td>1.45-1.90 (m, 2H); 3.3-3.7 (m, 4H); 6.2 (t, 2H, CH=CH)</td>
</tr>
<tr>
<td>10a</td>
<td>219-21</td>
<td>905, 970, 1026, 1220, 1700, 2550-3400</td>
<td>0.9-2.7 (m, 10H, CH$_2$-CH); 11.8 (s, 2H, COOH)</td>
</tr>
</tbody>
</table>
were used as such. Dry DMF of Aldrich, USA was stored over 4Å molecular sieves prior to use. Succinic anhydride 1 and glutaric anhydride 2 were prepared by the reaction of acetic anhydride with succinic acid and glutaric acid respectively, according to a literature procedure. The substrates, 3,3-dimethylglutaric anhydride 3; phthalic anhydride 4; diphenic anhydride 5; 1,4,5,6,7,7-hexachloro-5-norbornene-2,3-dicarboxylic anhydride 7 and trans-1,2-cyclohexane dicarboxylic anhydride 10 were of Aldrich, USA and used without further purification. The compound 1,2,3,4-tetrahydro-9-oxo-1, 4-ethanonaphthalene-2,3-endodicarboxylic anhydride 6 was obtained from β-naphthol and maleic anhydride adopting the procedure of Takeda and Kitahonoki whereas endo-bicyclo[2.2.1]heptan-2-one-5,6-dicarboxylic anhydride 8 was prepared by the reaction of cyclopentanone and maleic anhydride using the method of Cimastis and Wolinsky.  

cis-5-Norbornene-endo-2,3-dicarboxylic anhydride 9 was prepared by the Diels-Alder reaction of cyclopentadiene and maleic anhydride. The nitrogen gas was dried by passing through a wash bottle filled with an alkaline solution of pyrogallol.

**Reaction of in situ generated tetrathyammomium superoxide with anhydrides 1-10 : General procedure.** Potassium superoxide (1.17g, 0.016 mole) and tetrathyammomium bromide (1.68g, 0.008 mole) were weighed under nitrogen atmosphere using atmobag and transferred into a three-necked round bottom flask equipped with a magnetic stirrer, N2 inlet and Leibig condenser protected by calcium chloride drying tube. Dry dimethylformamide (30 mL) was added to it and the mixture was agitated magnetically for ~15 min to facilitate the formation of tetrathyammomium superoxide. Finally, the substrate (1-10, 0.005 mole) was admitted to it and the stirring
was continued for 8-12 hr at room temperature. The nitrogen gas was bubbled throughout to avoid atmospheric moisture. The completion of reaction was monitored by TLC.

After the reaction was over, the mixture was successively treated with saturated aq. sodium chloride solution (10 mL) and saturated sodium hydrogen carbonate solution (15 mL). It was then extracted with diethyl ether (3 x 20 mL) to remove the unreacted substrate. Aqueous layer was acidified with concentrated hydrochloric acid and extracted with diethyl ether/dichloromethane (4 x 20 mL). The organic layers were combined, washed with water (2 x 15 mL), and dried over anhyd. sodium sulphate. It was filtered and evaporated to furnish a residue, which was recrystallised and identified.

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References