1282 J. Org. Chem. 1984, 49, 1282-1284

of EtOH and benzene (1:1) as solvent. The crude product was purified by preparative thin-layer chromatography on silica gel with hexane–$CHCl_3$ as solvent to yield a solid: mp 137–139 °C; IR 1660, 1540, 1365 cm^{-1}; NMR δ 8.24–7.36 (m, 9 H); CIMS, *m/e* (relative intensity) 268 (M^+ + 1, 100), 105 (87).

2-(2-Quinolyl)-3-nitro-4*H*-benzopyran-4-one (14). The crude material was recrystallized from MeOH: mp 239–241 °C; IR 1655, 1540, 1360 cm^{-1}; NMR δ 8.46–7.50 (m, 10 H); CIMS, *m/e* (relative intensity) 319 (M^+ + 1, 100).

7,8-Dimethoxy-3-(methoxycarbonyl)-2-(2-quinolyl)-4*H*-benzopyran-4-one (15). The final residue was recrystallized from MeOH: mp 216–217 °C; IR 1730, 1630, 1620 cm^{-1}; NMR δ 8.34–7.69 (m, 6 H), 8.02 (d, 1 H, *J* = 9.0 Hz), 7.08 (d, 1 H, *J* = 9.0 Hz), 4.06 (s, 3 H), 4.05 (s, 3 H), 4.02 (s, 3 H); CIMS, *m/e* (relative intensity) 392 (M^+ + 1, 100), 360 (74).

7,8-Dimethoxy-3-nitro-2-(2-quinolyl)-4*H*-benzopyran-4-one (16). The magnesium chelate of the nitro ketone **11** was prepared by using a mixture of EtOH and benzene (1:1) as solvent. The crude product was recrystallized from a mixture of MeOH and $CHCl_3$: mp 236–237 °C; IR 1640, 1590, 1535, 1365, 1280, 1090 cm^{-1}; NMR δ 8.41 (d, 1 H, *J* = 9.2 Hz), 8.16 (d, 1 H, *J* = 9.7 Hz), 8.06 (d, 1 H, *J* = 9.8 Hz), 8.20–7.64 (m, 4 H), 7.14 (d, 1 H, *J* = 9.2 Hz), 4.06 (s, 3 H), 4.03 (s, 3 H); CIMS, *m/e* (relative intensity) 379 (M^+ + 1, 100).

7,8-Dimethoxy-3-nitro-2-[5-(benzyloxy)-6-methoxy-2-quinolyl]-4*H*-benzopyran-4-one (17). In this case, the magnesium chelate was prepared by using a benzene–EtOH mixture (1:1) as solvent. The crude product was recrystallized from MeOH: mp 236–237 °C; IR 1650, 1590, 1280, 1080 cm^{-1}; NMR δ 8.57 (d, 1 H, *J* = 8.9 Hz), 8.06 (d, 1 H, *J* = 9.0 Hz), 8.05 (d, 1 H, *J* = 9.1 Hz), 7.91 (d, 1 H, *J* = 9.3 Hz), 7.59 (d, 1 H, *J* = 9.3 Hz), 7.50–7.30 (m, 5 H), 7.12 (d, 1 H, *J* = 9.1 Hz), 5.21 (s, 2 H), 4.06 (s, 3 H), 4.05 (s, 3 H), 4.03 (s, 3 H); CIMS, *m/e* (relative intensity) 515 (M^+ + 1, 100), 482 (12), 424 (19), 91 (32).

7,8-Dimethoxy-3-(methoxycarbonyl)-2-[5-(benzyloxy)-6-methoxy-2-quinolyl]-4*H*-benzopyran-4-one (18). The final residue was recrystallized from MeOH: mp 210–211 °C; IR 1725, 1720, 1630, 1590 cm^{-1}; NMR δ 8.55 (d, 1 H, *J* = 9.5 Hz), 8.11 (d, 1 H, *J* = 8.8 Hz), 8.01 (d, 1 H, *J* = 8.8 Hz), 7.86 (d, 1 H, *J* = 9.2 Hz), 7.57 (d, 1 H, *J* = 9.6 Hz), 7.51–7.27 (m, 5 H), 7.05 (d, 1 H, *J* = 9.1 Hz), 5.22 (s, 2 H), 4.06 (s, 3 H), 4.04 (s, 6 H), 4.01 (s, 3 H); CIMS, *m/e* (relative intensity) 528 (M^+ + 1, 100), 437 (30), 91 (67).

Anal. Calcd for $C_{30}H_{25}NO_8$: C, 68.31; H, 4.78; N, 2.66. Found: C, 68.50; H, 5.00; N, 2.71.

Acknowledgment. This investigation was supported by Grant No. GM30932, awarded by the National Institute of General Medical Sciences, DHHS, and by Grant No. CA27517, from the National Cancer Institute, DHHS.

Registry No. **6**, 10524-88-6; **7**, 98-88-4; **8**, 50342-01-3; **9**, 88685-87-4; **10**, 29378-60-7; **10** (Mg chelate), 88685-95-4; **11**, 82222-78-4; **11** (Mg chelate), 88685-96-5; **12**, 88685-88-5; **12** (Mg chelate), 88685-97-6; **13**, 88685-89-6; **14**, 88685-90-9; **15**, 88685-91-0; **16**, 88685-92-1; **17**, 88685-93-2; **18**, 88685-94-3.

Base-Catalyzed Autoxidation of Weak Carbon Acids Using Poly(ethylene glycols) as Phase-Transfer Catalysts

Ronny Neumann and Yoel Sasson*

Casali Institute of Applied Chemistry, School of Applied Science, The Hebrew University of Jerusalem, 91904 Jerusalem, Israel

Received September 27, 1983

Base-catalyzed autoxidations using phase-transfer catalysts are known only for relatively strong carbon acids, p*K* < 25. Cryptands, crown ethers,[1] and quaternary ammonium salts[2] have been used as catalysts for this reaction. Oxidation of weaker carbon acids, p*K* $\gtrsim$ 30, is unknown under these conditions. Previously, oxidations of this type have been preformed by using expensive aprotic polar solvents. Picolines, p*K* $\sim$ 30, have been oxidized by using DMF as solvent and potassium *tert*-butoxide as base.[3] Diphenylmethane, p*K* $\sim$ 33, and triphenylmethane, p*K* $\sim$ 32, have been oxidized by using the same base in solvents such as Me_2SO[4] and HMPA.[5]

Scheme I

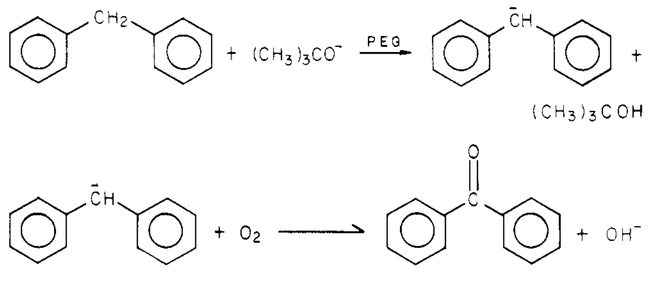


Table I. Autoxidation of Various Carbon Acids[a]

substrate	p*K*	conversion,[b] %	product
fluorene	22.5	87	fluorenone
α-picoline	31	30	picolinic acid
β-picoline	30	36	nicotinic acid
γ-picoline	29	48	isonicotinic acid
diphenylmethane	34	50	benzophenone
triphenylmethane	32	62	triphenylcarbinol
toluene	35	0	
ethylenebenzene	35	0	

[a] Reaction conditions: *T* = 25 °C, 0.025 mol of substrate, 0.05 mol of potassium *tert*-butoxide, 0.00033 mol of PEG 6000, 30 mL of benzene, P_{O_2} = 75 psi, time 2 h. [b] These are fundamentally maximum conversion because after 2 h there was no further absorption of oxygen.

Poly(ethylene glycols) and their alkyl ethers, $RO(CH_2CH_2O)_nR$ (R = H, alkyl), have received attention in recent years as phase-transfer catalysts in a variety of reactions, for example, aliphatic nucleophilic substitution,[6] oxidation by permanganate,[7] reductions,[8] and Williamson ether syntheses,[9] but have never been used in autoxidation reactions.

We have oxidized weak carbon acids in simple nonpolar solvents, e.g., benzene, by using solid potassium *tert*-butoxide as base and various poly(ethylene glycols) (PEG) as phase-transfer catalysts at ambient temperatures. In a solid–liquid phase-transfer system the general reaction scheme using diphenylmethane as the substrate is shown in Scheme I. We have investigated the scope of the reaction and the effect of the catalyst's molecular weight and compared alkylated and nonalkylated catalysts. In addition a comparison has been made with other common phase-transfer catalysts.

Results and Discussion

The results of the autoxidation of a variety of carbon acids are summarized in Table I. Significant yields were

---

(1) Dietrich, B.; Lehn, J. M. *Tetrahedron Lett.* **1973**, *15*, 1225–1228.

(2) Alneri, E.; Bollaccio, G.; Carletti, U. *Tetrahedron Lett.* **1977**, *24*, 2117–2118.

(3) Bartok, W.; Rosenfeld, D. D.; Schriesheim, A. *J. Org. Chem.* **1963**, *28*, 410–412.

(4) Russell, G. A.; Janzen, E. G.; Becker, H. D.; Smentowsky, F. J. *J. Am. Chem. Soc.* **1962**, *84*, 2652–2653.

(5) Hofmann, J. E.; Rosenfeld, D. D.; Schriesheim, A. *Prepr. Pap.-Am. Chem. Soc., Div. Fuel Chem.* **1965**, *10*, 183–186.

(6) Lehmkuhl, H.; Robet, F.; Hauschild, K. *Synthesis* **1976**, 184–186.

(7) Lee, D. G.; Chang, V. C. *J. Org. Chem.* **1978**, *43*, 1532–1536.

(8) Zupancic, B. G.; Kokalj, M. *Synth. Commun.* **1982**, *12*, 881–886.

(9) Hirao, A.; Nakahama, S.; Takahashi, M.; Yamazaki, N. *Makromol Chem.* **1978**, *179*, 1735–1741.

0022-3263/84/1949-1282$01.50/0 © 1984 American Chemical Society

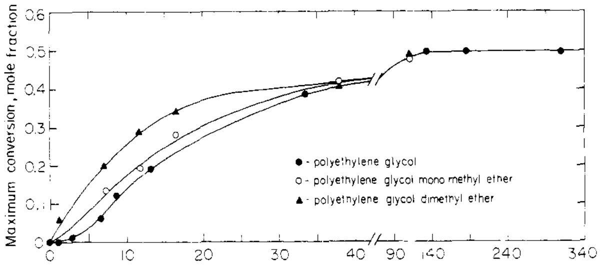


Figure 1. Maximum conversion for the autoxidation of diphenylmethane with nonalkylated and mono- and dimethyl ethers of poly(ethylene glycols) of various molecular weights. Reaction conditions: T = 25 °C, time 2 h, P_{O_2} = 75 psi, 0.025 mol of diphenylmethane, 0.05 mol of potassium *tert*-butoxide, 30 mL of benzene, and 2 g of catalyst.

obtained for compounds having a p$K < 35$, whereas for compounds with a p$K \gtrsim 35$ the reaction fails. The selectivity of the reaction is 100%, and no side products were found. As soon as the catalyst was added to the reaction mixture the organic phase changed color (usually bright red), indicating the presence of the carbanion. In reactions that failed no such color changes were observed. This supports the general reaction scheme as presented above. It is interesting to note that the picolines had lower conversions than the di- and triphenylmethanes though their pKs are lower. We attribute this to the formation of acid salts, which lowers the concentration of the *tert*-butoxide ion in the reaction system and halts the reaction. In general, we attribute the nonquantitative conversions to several factors. First, as one can see in Scheme I, as the reaction progresses the *tert*-butoxide ion is replaced by the hydroxide ion, which was found to be inactive under these conditions in a separate experiment. On the other hand, it was found that by using a large excess of potassium *tert*-butoxide the reaction could be completed. Second, the catalyst itself undergoes a slight amount of autoxidation, causing chain degradation and thereby lowering the catalyst's activity. This is especially true for substrates with p$K \gtrsim 35$ where there was only autoxidation of the catalyst. However, the catalyst was not totally degraded. This was proven by adding diphenylmethane to the reaction mixture (attempted oxidation of toluene) as the new substrate and continuing the reaction. Benzophenone was found as the oxidation product. From this experiment, catalyst degradation was estimated to be approximately 10% by extrapolation.

In a previous article[10] dealing with aromatic nucleophilic substitution we already noticed that the molecular weight of the catalyst had significant influence on its activity. Similar measurements for this system, i.e., the effect of molecular weight on the final or maximum conversion were made for the diphenylmethane oxidation system. In addition, we compared the effectiveness of mono- and dimethylpoly(ethylene glycol) ethers to those of nonalkylated poly(ethylene glycols). From the results as shown in Figure 1, one notices several trends. First, the molecular weight of the catalyst has a considerable effect on the catalytic activity. It is important to realize that the effect is much stronger than would appear from the graph because with rising molecular weight the mole percentage of catalyst dropped in the reaction system (constant weight of catalyst was used). A plateau is reached at a molecular weight of 6000 or about 130 oxyethylene units. We have attributed this effect to increased complexation of the potassium cation with increased molecular weight.[11] The advantage of increased complexation by increasing chain length above PEG 6000 is offset by the lowering of the molar concentration. The addition of oxyethylene groups on the same molecule is not equivalent to increased molar concentration. The use of mono- and dialkylated catalysts sheds new light on this system. Since the free hydroxyl group of PEG certainly undergoes ionization by the *tert*-butoxide ion, it probably causes the catalyst to become less soluble in the nonpolar solvent, thereby reducing its effectiveness. By alkylating the free hydroxyl groups we eliminate the possibility of ionization, and therefore the catalyst retains its solubility. With increased molecular weight the differences between alkylated and nonalkylated catalysts diminishes and disappears because of the large chain bulk vs. the small chain ends. We, therefore, stipulate that the increased activity of high molecular weight catalysts is due to increased complexation on the one hand (with dimethyl ethers the high molecular weight catalysts are still more effective) and to decreasing chain end effects on the other hand, which in ionized form reduce the solubility of the catalyst. It is interesting to note that these results are in contrast to results obtained in the dehydrobromination of 2-bromoctane[12] under similar conditions where dialkylated PEG was found to be a totally inactive catalyst.

Table II. Autoxidation of Diphenylmethane with Various Phase-Transfer Catalysts[a]

catalyst	conversion, %
18-crown-6	36.5
tetrabutylammonium bromide	1.0
Aliquat 336	<1.0
PEG 400	7.5
PEG 6000	67.0
PPG 2000	2.5

[a] Reaction conditions: T = 25 °C, time 2 h, P_{O_2} x 75 psi, 0.025 mol of diphenylmethane, 0.05 mol of potassium *tert*-butoxide, 0.0005 mol of catalyst, 30 mL of benzene.

In order to judge poly(ethylene glycol) as a phase-transfer catalyst for this system, comparative runs were made with other common phase-transfer catalysts. The results are tabulated in Table II. As one can see, quaternary ammonium salts are ineffective catalysts for this reaction. They immediately undergo Hoffman degradation rendering them inactive. Poly(propylene glycol) (PPG) is also inactive. The oxypropylene unit is apparently incapable of complexing the potassium cation, making PPG an ineffective catalyst. Crown ethers have fair activity, better than low molecular weight PEG but poorer than those of high molecular weight. It is therefore apparent that high molecular weight poly(ethylene glycols) are the catalyst of choice for base-catalyzed autoxidations of weak carbon acids.

Experimental Section

Materials. All chemicals were standard laboratory chemicals from various commercial companies (Baker, Fluka, Merck, BDH, and Aldrich). All were of the highest purity available and used without further purification. The single exception is the poly(ethylene glycol) dimethyl ethers, which were prepared from the corresponding monomethyl ether by the following procedure. Monomethyl ether (20 g) was dissolved in 80 mL of methylene chloride with 0.005 mol of tetrabutylammonium bromide, 10 g of sodium hydroxide was dissolved in 100 mL of water and added to the reaction mixture. Dimethyl sulfate (10 mL) was added

---

(10) Neumann, R.; Sasson, Y., *Tetrahedron* **1983**, *39*, 3437–3440.

(11) Liu, K. J., *Macromolecules* **1968**, 1, 308–311. Chaput, G.; Jeminet, G.; Juillard, J. *Can. J. Chem.* **1975**, *53*, 2240–2246.

(12) Kimura, Y.; Regen, S. L. *J. Org. Chem.* **1983**, *48*, 195–198.

dropwise while stirring the reaction during 30 min. The mixture was stirred for an additional 12–16 h to ensure complete conversion. The reaction was stopped and the remaining dimethyl sulfate was neutralized with dilute ammonia. The organic phase was separated, washed, and evaporated, leaving the dimethyl ether as product.

Oxidation Procedure. The oxidations were performed in a 500-mL Parr hydrogenation apparatus (Model 3921). The reaction vessel was charged with substrate, solvent (benzene), catalyst, base, and internal GLC standard if necessary. The vessel was flushed five times with oxygen and then brought to a pressure of 75 psi. The reaction commenced by starting the shaker. After 2 h no further oxygen uptake was observable and the reaction was stopped. The reaction mixture was neutralized by 5% aqueous H_2SO_4 and then analyzed.

Analysis. In general, conversions were computed by GLC analysis. For reactions where the products were acids, dodecane was used as an internal standard. The column used was 15% OV-17 on acid-washed Chromosorb W with a Packard 427 gas chromatograph with FID detectors, column length 2 m, column temperature 100–200 °C at 10 °C/min. For all substrates the product was isolated at least once. For fluorenone and benzophenone, the water phase was separated and the benzene was evaporated. The remaining benzophenone and fluorenone were identified by IR and by their dinitrophenylhydrazine derivatives; benzophenone mp 236-237 °C, fluorenone mp 282-283 °C. For picolinic, nicotinic, and isonicotinic acids, water only was added to the reaction mixture and the benzene phase was separated. The water phase was then acidified with dilute HCl and the water was evaporated. From the remaining solid the carboxylic acid was dissolved in ethanol, which was then evaporated to leave the respective acid: picolinic acid, mp 135-136 °C; nicotinic acid, mp 233-234 °C; and isonicotinic acid, mp 314-315 °C.

Registry No. PEG, 25322-68-3; fluorene, 86-73-7; α-picoline, 109-06-8; β-picoline, 108-99-6; γ-picoline, 108-89-4; diphenylmethane, 101-81-5; triphenylmethane, 519-73-3.

Mechanism for the *m*-Chloroperbenzoic Acid Oxidation of Trialkyl-Substituted Furans

Samuel B. Gingerich and P. W. Jennings*

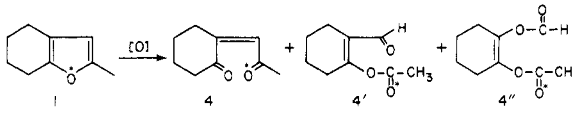
Department of Chemistry, Montana State University, Bozeman, Montana 59717

Received November 30, 1983

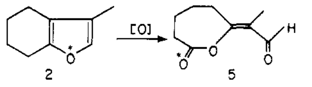
The impetus for investigating the oxidation of furan-containing compounds is derived from their potential toxicity.[1] They are known to be toxic to animals and man and in several cases have been shown to give enhanced activity when oxidized by the mixed function oxidase (MFO) enzyme system.[2]

We began our study on the oxidation of model furan compounds by investigating several reported chemical mimics of the MFO enzyme system. Of these, *m*-chloroperbenzoic acid (mCPBA) is the most readily available and easily controlled reagent[3] and was, therefore, our choice. There may be some question as to whether or not the peracid is, in fact, a reasonable mimic of the MFO. Nevertheless, the results gained in this study are intriguing and useful. In this paper, we present some new results that tie the previous papers together into a general reaction sequence for the peracid oxidations of these types of alkylated furan compounds.

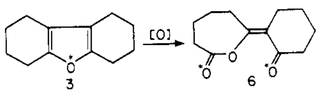
In previous work,[4,5] we have investigated the peracid oxidations of three compounds: 2-methyl- and 3-methyl-4,5,6,7-tetrahydrobenzofuran and perhydrodibenzofuran (eq 1–3). Further, through the use of ^{18}O label (shown as an asterisk in eq 1), the pathway for the oxidation of compound 1 was elucidated and has been discussed in detail previously.[5] Briefly, compound 1 was shown to react with the first mole of mCPBA to form an epoxide at the *internal* and *more substituted olefin.* This epoxide then rearranges rapidly to the *enedione* 4 shown in eq 1 with the labeled oxygen going to the methyl ketone moiety. A second mole of mCPBA reacts at the methyl ketone moiety to form the acetate which rearranges to acetate 4′. Finally, a third mole of mCPBA reacts with the aldehyde functionality to form the formate ester shown as 4″. It is important to remember this sequence as reference is made to it later in the paper. For compounds 2 and 3, we had not executed any ^{18}O-labeling studies at the time of their publication and suggested in those two cases that an alternative diepoxide pathway might be a reasonable means to the observed products.



(1)



(2)



(3)

Results and Discussion

3-Methyltetrahydrobenzofuran (2). Compound 2 was readily labeled with ^{18}O by a method that has been published elsewhere.[6] It contained 43% ^{18}O label as determined by NMR spectroscopy. The ^{13}C NMR resonances for the atoms adjacent to ^{16}O were at 150.9 and 136.7 ppm, and the ^{13}C–^{18}O resonances occurred 0.039 and 0.036 ppm upfield, respectively.[7]

On oxidation with 2 equiv of mCPBA in CH_2Cl_2 at 0 °C, a nearly quantitative yield of lactone 5 was obtained (eq 2). NMR spectral analysis showed that >98% of the ^{18}O label was contained in the lactone carbonyl oxygen. The ^{13}C–^{16}O resonance for 5 was at 170.7 ppm with the ^{13}C–^{18}O resonance occurring 0.04 ppm upfield. This result is not definitive and is consistent not only with the diepoxide intermediate, which was proposed earlier,[4] but also with an enedione intermediate in analogy with the 2-methyl case.

Perhydrodibenzofuran (3). As in the previous example compound 3 was labeled with ^{18}O by a method published elsewhere.[6] It contained 39% ^{18}O as determined by NMR spectral analysis and 41% by mass spectral analysis. On oxidation with 2 equiv of mCPBA in CH_2Cl_2 at 0 °C,

---

[1] (a) Jennings, P. W.; Reeder, S. K.; Hurley, J. C.; Caughlan, C. N.; Smith, G. D., *J. Org. Chem.* **1974**, *39*, 3392. (b) Jennings, P. W.; Hurley, J. C.; Reeder, S. K.; Holian, A.; Lee, P.; Caughlan, C. N.; Larsen, R. D. *Ibid.* **1976**, *41*, 4078. (c) Jennings, P. W.; Reeder, S. K.; Hurley, J. C.; Robbins, J. E.; Holian, S. K.; Holian, A.; Lee, P.; Pribanic, J. A. S.; Hull, M. W. "Effects of Poisonous Plants on Livestock"; Academic Press: New York, 1978; pp 217–228.

[2] Holian, S. K., M.S. Thesis, Montana State University, 1975.

[3] Hanzlik, R. P.; Westkaemper, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 2465.

[4] Gingerich, S. B.; Campbell, W. H.; Bricca, C. E.; Jennings, P. W. *J. Org. Chem.* **1981**, *46*, 2589.

[5] Gingerich, S. B.; Jennings, P. W. *J. Org. Chem.* **1983**, *48*, 2606.

[6] Gingerich, S. B.; Jennings, P. W., *J. Labelled Compd. Radiopharm.* **1983**, *20*, 591.

[7] Vederas, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 374.