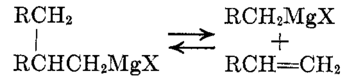
Taken with an estimate of 21.7 kcal/mol[5] for the bond cleavage process



$$\underset{\text{RCHCH}_2\text{MgX}}{\overset{\text{RCH}_2}{|}} \rightleftharpoons \text{RCH}_2\text{MgX} + \text{RCH}{=}\text{CH}_2$$

a ring strain of 24 kcal is derived. A value of 23 kcal is obtained from data at 160°.[6]

The estimates of ring strain obtained are in approximate agreement with the heat of combustion value of 26.2 kcal/mol.[7] The discrepancy, amounting to a factor of 10 to 40 in equilibrium or rate constants, could be the summation of errors from various sources in the kinetics and the estimation procedures, or it may represent the limits of applicability of the thermochemical approach to solution reactions. It could also result from some additional stabilization of the four-membered ring in the cyclobutylmethyl Grignard reagent, or from the incidence of a new, higher activation energy mechanism at the higher temperatures.[8] In any event, the current results provide a clear example of the quantitative influence of the thermochemical strain energy of a cyclobutane ring on the equilibrium constant for a chemical reaction.

Experimental Section

Nmr spectra were obtained on a Varian Associates HA-100 nmr spectrometer. Boiling points are uncorrected.

Cyclobutylmethylmagnesium chloride in tetrahydrofuran was prepared as described previously.[2b] Samples in nmr tubes were heated for approprirate times, and the extent of rearrangement was determined by integration of the signals at δ -0.35 and -0.66 ppm, corresponding to Grignard reagents **1** and **2**, respectively.[2b] Rate constants obtained were 2.55×10^{-6} sec^{-1} at 59.6°; 2.76×10^{-5} sec^{-1} at 80.2°, and 2.18×10^{-4} sec^{-1} at 99.9°. Derived activation parameters were $\Delta H^{\ddagger} = 26.55 \pm 0.2$ kcal/mol and $\Delta S^{\ddagger} = -4.6 \pm 0.5$ eu.

4-Penten-1-ol-*1,1*-d_2 was prepared by reduction of methyl 4-pentenoate with lithium aluminum deuteride in diethyl ether, bp 137–140° (lit.[9] bp 141–141.5°° for isotopically normal compound).

5-Chloro-1-pentene-*5,5*-d_2 was prepared from the alcohol with thionyl chloride and tri-*n*-butylamine in ether by a procedure similar to one described previously:[2b] bp 98–103° (lit.[9] bp 103–104° for isotopically normal compound). The nmr spectrum showed no detectable absorption (<0.5%) at δ 3.5 ppm, where the α hydrogens of the isotopically normal compound absorb.

Grignard Reagent from 5-Chloro-1-pentene-*5,5*-d_2.—A Grignard reagent was prepared from 0.679 g of the chloride and 0.21 g of magnesium in 3 ml of tetrahydrofuran, and sealed in nmr tubes. After heating for several hours at 140°, a triplet signal, $J = 8$ Hz, appeared at δ -0.66 ppm. Poorly defined changes occurred in the olefinic absorption, and a new signal appeared at δ 6.45 ppm, attributable to ethylene formed from attack on the solvent.[10] At long reaction times, the α-hydrogen absorption reached a maximum of about 60% of one hydrogen (relative to the olefinic protons) and then decreased in size, while the ethylene absorption continued to increase. By using the appearance of ethylene as a measure of the amount of Grignard reagent destroyed by reaction with solvent, the spectra obtained for shorter reaction times were corrected for the loss of total organometallic. The rate of loss appeared to be about 20–30% of the rearrangement rate. The best rate measurements were made using a similar sample of concentration 0.92 *M* supplied by H. G. Richey, Jr., and T. C. Rees.

A sample which had been heated for four half-lives was hydrolyzed with water. The volatile materials were transferred from the residue under vacuum and gas chromatographed. The collected 1-pentene, the only detected reaction product, was analyzed by nmr. Integration yielded the following: δ 0.92 (t, 1.8, $J \cong 7.1$ Hz, CH_3 and CHD_2), 1.4 (q, 2, $J \cong 7.2$ Hz, CH_2), 2.02 (q, 1.2, $J \cong 7.2$ Hz, allylic CH_2), 4.95 (m, 2, $=CH_2$), and 5.7 ppm (m, 1, $=CH$).

Registry No.—**1**, 32251-57-3; **2**, 30090-51-8; **8**, 32251-59-5; **10**, 32251-60-8.

Acknowledgment.—We are grateful to H. G. Richey, Jr., and T. C. Rees of the Pennsylvania State University for communication of their earlier results, and for the gift of a sample of deuterated Grignard reagent used for kinetics studies.

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[5] S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, **69**, 279 (1969).

[6] It might be more valid to use only one-half of the rate of ring opening in calculating an equilibrium constant, since the observed ring cleavage is the sum of cleavages of two ring bonds. Such a treatment would lower the strain energy estimated by about 0.5 kcal/mol.

[7] S. Kaarsemaker and J. Coops, *Recl. Trav. Chim. Pays-Bas*, **71**, 261 (1952).

[8] The latter is consistent with preliminary results of T. C. Rees (Ph.D. thesis, Pennsylvania State University, communicated to us by Professor H. G. Richey, Jr.) in which no reaction was found after 170 hr at 110°.

[9] A. Juvala, *Chem. Ber.*, **63**, 1989 (1930).

[10] E. A. Hill, *J. Org. Chem.*, **31**, 20 (1966).

9-Anthroxy. A Protecting Group Removable by Singlet Oxygen Oxidation

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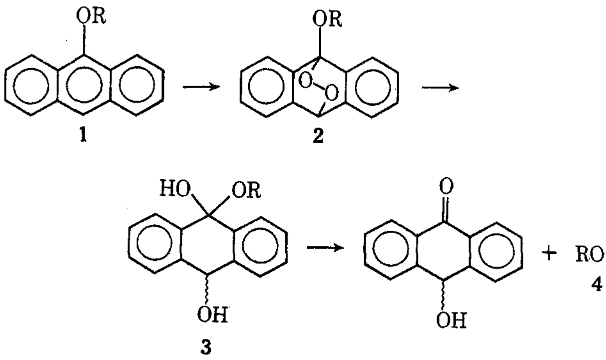
Aromatic ethers have not often[1,2] been used as protecting groups because of problems associated with attachment and removal by making and breaking the aromatic carbon–oxygen bond. We recently reported[3] that 9-anthroxy alkyl ethers **1** are useful protecting groups which can be readily cleaved at the aromatic carbon–oxygen bond by a sequence using low temperature (−30°) singlet oxygen oxidation[4] to an anthracenyl peroxide[5] (**2**) followed by mild catalytic reduction[6] of the weak oxygen–oxygen single bond. The initial reduction product is presumably the hemiketal **3**, which spontaneously eliminates the alcohol **4**. We report here some experimental details for cleaving 9-anthroxy ethers and a new method for synthesizing them.



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[1] J. F. W. McOmie in "Advances in Organic Chemistry—Methods and Results," Vol. 3, Interscience, New York, N. Y., 1963, p 191.

[2] For a listing of protecting groups devised after McOmie's review see W. Theilheimer, "Synthetic Methods," subject indexes to Vol. 24, 23, and 20.

[3] W. E. Barnett and Larry L. Needham, *Chem. Commun.*, 1383 (1970).

[4] R. W. Murray and M. L. Kaplan, *J. Amer. Chem. Soc.*, **91**, 5358 (1969).

[5] W. Bergmann and M. J. McLean, *Chem. Rev.*, **28**, 367 (1941).

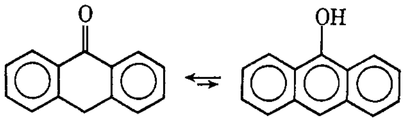
[6] C. Dufraisse and J. Houpillart, *C. R. Acad. Sci.*, **205**, 740 (1937).

In order for a protecting group to be generally useful it should be easily attached, it should survive reactions used for transforming other parts of the molecule, and it should be easily removed, preferably by some highly specific reaction. In this context, the singlet oxygen method for cleaving an aromatic ether is notable for its mildness. In a more general sense though, it is important because it has introduced a new kind of reagent for removing protecting groups. Thus in addition to protecting groups removable under acidic, basic, reductive,[1,2] and photochemical[7-10] conditions, we have a group removable under highly specific, and highly selective, oxidative conditions.[11] The result of singlet oxygen oxidation is to generate a labile peroxide which can be cleaved by a variety of reactions[12] to produce the alcohol **4** or a derivative thereof.

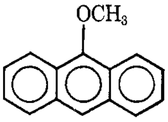
Singlet oxygen can be generated in a variety of ways. The removal scheme we use employs triphenyl phosphite[4] to generate singlet oxygen. This method is convenient and has the advantage that stoichiometry can be controlled better than by most other methods, but the triphenyl phosphate formed is a nuisance to separate from relatively nonpolar alcohols such as 1-hexadecanol. Hexadecanol and triphenyl phosphate have remarkably similar R_f values in several solvent sysems. Although the boiling points differ widely, we have preferred, for small-scale work, a chemical separation rather than distillation. In such a case, mild base-catalyzed hydrolysis can be employed to free the alcohol from phosphate ester. Obviously this difficulty can be corrected by modification of the phosphite for generating singlet oxygen, thus allowing the phosphite method to be used without the hydrolysis step. This would be necessary for 9-anthroxy cleavage in the presence of other esters whose hydrolysis is undersirable. In the case of water-soluble alcohols, no difficulty is experienced as shown by the isolation of butane-1,4-diol from its 9-anthroxy ether. The by-product triphenyl phosphate is easily separated by virtue of its water insolubility.

By choosing 9-anthroxy as the aromatic ether protecting group we were able to develop a mild method of regenerating the protected alcohol. We were, however, still faced with the problem of synthesizing these ethers. The usual way to construct aromatic–aliphatic ethers is by the Williamson synthesis. With a few special exceptions,[3] this turns out to be an effective method for attaching the 9-anthroxy group. The alcohol to be protected is changed into its tosylate, which is in turn converted into the 9-anthroxy ether by displacement with the phenolate ion from anthrone.[3] Obviously this method involves attachment by making the alkyl carbon–oxygen bond. It is desirable, however, to have a method for attaching the goup *via* the aromatic carbon–oxygen bond, a method which would be useful in cases where tosylate displacement is ineffective. It was noted that, although the 9-anthroxy group is stable to a variety of reaction conditions, in very strong acid[13] it will undergo hydrolysis to anthrone and an alcohol. We hoped to employ the reverse of this reaction as a method of synthesizing 9-anthroxy ethers *via* aromatic carbon–oxygen bond formation. However, using *p*-toluenesulfonic acid as catalyst we have been unable to force this reaction completely in the direction of ether formation. Prolonged refluxing of equimolar amounts of an alcohol and anthrone in benzene or toluene under conditions where water could be removed by azeotropic distillation gives mixtures containing starting materials as well as the desired ether.

Although these results were not fully understood, it was speculated that the difficulty might involve the unfavorable anthrone–9-anthrol, **5–6**, equilibrium. A way of eliminating this probem would be to O-methylate anthrone and to use the resulting methyl ether, **7**, in acid-catalyzed exchange reactions with other higher boiling alcohols. In practice this works well. Equimolar amounts of 9-methoxyanthracene[14] and of the alcohol to be protected, **8**, are refluxed in benzene containing a catalytic amount of tosyl acid. The condensate is collected in a Dean–Stark trap containing calcium chloride to trap some of the methanol. The trap is drained periodically over a period of 24–63 hr until almost all of the benzene and methanol have been removed from the system. Primary alcohols give excellent yields of ethers, **1**, by this method. Secondary alcohols react only partially. Some examples are shown in Table I.



5 **6**



7

$+ \underset{\mathbf{8}}{\text{ROH}} \longrightarrow \mathbf{1} + CH_3OH$

TABLE I

9-ANTHROXY ETHERS FROM 9-METHOXYANTHRACENE

9-Anthroxy ether	Decrease[a] in 9-methoxy-anthracene, %	Reflux time, hr	Yield of ether,[b] %
1′-Hexadecanyl	Quantitative	62	83
1′-Dodecanyl	Quantitative	21	90
1′-Octanyl	Quantitative	22	91
4′-Hydroxy-1′-butanyl	Quantitative	62	85
2′-Octanyl	63	62[c]	
Cyclohexanyl	66	63[c]	
3′-Cholesteryl	45	63[c]	

[a] Measured by nmr. [b] After chromatography. [c] Longer times do not result in a further decrease of 9-methoxyanthracene.

Experimental Section

Nmr spectra were taken on a Varian HA-100 spectrometer. Melting points were taken on a Thomas–Hoover capillary tube melting point apparatus and are uncorrected. Except where indicated, all infrared spectra were taken in $CHCl_3$ solution on a Perkin-Elmer Model 257 spectrometer. They were calibrated at 1603 cm^{-1} with a polystyrene film.

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(7) J. A. Barltrap and P. Schofield, *J. Chem. Soc.*, 4758 (1965).

(8) D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *ibid.*, 3571 (1965).

(9) J. W. Chamberlin, *J. Org. Chem.*, **31**, 1658 (1966).

(10) A. J. Kirby and A. G. Varvoglis, *Chem. Commun.*, 406 (1967).

(11) Oxidation has been used as a secondary step in removing a protecting group. In strongly basic media, allyl ethers are isomerized to enol ethers which can be cleaved by acid or by oxidation: R. Grigg and C. D. Warren, *J. Chem. Soc.*, 2205 (1965).

(12) W. E. Barnett and L. L. Needham, results to be published.

(13) E. deB. Barnett, J. W. Cook, and M. A. Matthews, *J. Chem. Soc.*, **123**, 1994 (1923).

(14) J. S. Meek, P. A. Monroe, and C. J. Bouboulis, *J. Org. Chem.*, **28**, 2572 (1963).

Methyl tosylate was prepared according to an "Organic Syntheses" procedure;[15] an 88% yield of crude tosylate was obtained.

9-Methoxyanthracene was prepared from crude methyl tosylate according to the method of Barnett, *et al.*,[13] total yield 60%, mp 93–94° (lit.[13] mp 94°).

9-Hexadecyloxyanthracene.—A mixture of 2.08 g (0.010 mol) of 9-methoxyanthracene, 2.42 g (0.010 mol) of hexadecanol, and 0.020 g of *p*-toluenesulfonic acid in 50 ml of benzene was refluxed for 62 hr. Throughout this period, a Dean–Stark trap containing approximately 10 g of $CaCl_2$ was attached. Periodically, benzene was removed so that the final volume was about 10 ml. The mixture was then cooled and diluted to 75 ml with ether. This solution was washed with 5 ml of 2 *N* NaOH and 5 ml of water. The organic layer was dried ($MgSO_4$), filtered, and evaporated to give 3.92 g (96%) of a crystalline solid. Nmr analysis showed this material to be greater than 90% pure hexadecyloxy ether. The material was recrystallized from EtOAc–hexane (5 ml–20 ml) to give 2.31 g of white powder, mp 58–59.5°. The mother liquors were evaporated to dryness and triturated with 5 ml of pentane. On cooling (−5°) white crystals precipitated but some dark material coprecipitated. The pentane was removed and the residue was dissolved in 20 ml of warm hexane. This homogeneous solution was filtered through 10 g of activity I Woelm alumina, using additional hexane. The first three 50-ml fractions gave white crystalline residues weighing 0.982, 0.084, and 0.012 g, respectively. The total yield of ether isolated was thus 3.37 g (83%). Elution with 50 ml of ether gave 0.213 g of a red oil which was not further investigated. Pure hexadecyloxy ether gave the following nmr ($DCCl_3$): δ 5.60 (t, 2 H), 7.34–8.30 (m, 9 H), 0.87–2.09 (m, 31 H).

Anal. Calcd for $C_{30}H_{42}O$: C, 86.07; H, 10.11. Found: C, 86.21; H, 10.11.

9-Dodecyloxyanthracene.—A procedure and apparatus similar to that used for the preparation of the hexadecyl ether were used. A benzene solution of 1.86 g (0.010 mol) of dodecanol, 2.08 g (0.010 mol) of 9-methoxyanthracene, and 0.020 g of *p*-toluenesulfonic acid was refluxed for 21 hr *with periodic removal of benzene.* After the usual work-up with base and water, the reaction mixture was dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo.* The crude yield was 3.53 g. Nmr analysis showed nearly quantitative formation of the dodecanyl ether. The crystalline material was dissolved in the minimum amount of warm hexane and filtered through a column containing 10 g of alumina. Additional hexane was added so that three 50-ml fractions were collected. The respective weights were 2.98, 0.55, and 0.08 g. The first fraction was recrystallized from a small amount of pentane: yield 2.68 g; mp 48–49°; nmr ($DCCl_3$) δ 7.6–8.34 (m, 9 H), 4.17 (t, 2 H), 0.90–2.10 (m, 23 H).

Anal. Calcd for $C_{26}H_{34}O$: C, 86.13; H, 9.45. Found: C, 86.31; H, 9.65.

9-Dodecycloxyanthracene.—The amounts of reagents used were the same as in the preceding experiment. The reflux time was 44 hr and *no benzene* was drained from the Dean–Stark trap. The work-up was as usual; the crude yield was 3.52 g. The nmr spectrum, however, showed only about a 50% decrease in the intensity of the methoxy singlet.

9-(4-Hydroxybutoxy)anthracene.—A mixture of 6.28 g (0.0302 mol) of 9-methoxyanthracene, 54.3 g (0.604 mol) of 1,4-butanediol, and 0.090 g of *p*-toluenesulfonic acid in benzene (120 ml) was refluxed for 62 hr with periodic draining of the Dean–Stark trap, which contained *ca.* 10 g of $CaCl_2$. After cooling, benzene (50 ml) was added along with 2 *N* NaOH (20 ml). After separating the layers, the organic layer was washed twice with water (50 ml) in order to rid the product of unreacted diol. The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed *in vacuo.* The product (7.116 g) was dissolved in the minimum amount of methylene chloride. This solution was then preadsorbed onto 3 g of basic alumina (activity I). The preadsorbed material was added to alumina (30 g), and the product was eluted with light petroleum containing increasing amounts of ether. The 9-(4-hydroxybutoxy)anthracene was collected in fractions varying in ether percentage from 15 to 100. The total yield was 6.77 g (84.5%), mp 77–81°. A 100% ether fraction was recrystallized from an ethyl acetate–hexane mixture: mp 81–82°; nmr ($DCCl_3$) δ 7.20–8.31 (m, 9 H), 4.18 (t, 2 H), 3.78 (t, 2 H), 1.85–2.20 (m, 4 H).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.25; H, 6.81.

Cleavage of the Hexadecanyl Ether.—A solution of triphenyl phosphite (3.1 g, 0.010 mol) in methylene chloride (100 ml) was ozonized for 45 min at the rate of 100 mmol/min. After purging the blue solution with nitrogen, a heterogeneous mixture of the 9-hexadecyloxyanthracene (2.09 g, 0.005 mol) in methylene chloride (50 ml) at approximately −78° was added to the ozonolysis flask. The reaction temperature was allowed to rise slowly until it reached 25°. Methylene chloride was removed *in vacuo.* The residue was dissolved in ethyl acetate (125 ml) and 0.52 g of 10% Pd/C was added. The hydrogenation was carried out at a pressure of 43.8–43.4 psi for 30 min. The hydrogenated turquoise solution was then filtered through 3 g of Celite. The Celite was washed repeatedly with ethyl acetate. The filtrate was concentrated *in vacuo* to give a crude yield of crystalline material, 5.2 g. The nmr of this material showed no $-OCH_2-$ triplet in the ether region (4–4.1 ppm), but there was a triplet at 3.6 ppm where the triplet in an authentic sample of hexadecanol is located. An attempt was made to separate the hexadecanol from triphenyl phosphate *via* column chromatography. However, an efficient separation was not possible.

In another run the crude Pd reduction product (from 0.003 mol of 9-decyloxyanthracene) was treated with 6 equiv of KOH in 100 ml of methanol in order to hydrolyze the triphenyl phosphate. The reaction mixture was stirred magnetically overnight at room temperature. The methanol was removed *in vacuo* and water (200 ml) was added. This basic mixture was extracted twice with ether (100 ml). The combined ether layers were dried (Na_2SO_4), and the ether was evaporated *in vacuo.* Nmr analysis of the yellowish material indicated that the products were hexadecanol and a small amount of aromatic material. This material was then treated with hot hexane (10 ml) and filtered with suction. The insoluble material was washed twice with hot hexane (5 ml). The hexane layers were combined and the solvent was removed *in vacuo.* The yield was 0.63 g (87%) of beige crystalline material. Spectral data were almost identical with those of authentic hexadecanol. In order to purify this material further, it was dissolved in warm hexane (20 ml) and filtered through neutral alumina (5 g). Fractions (40 ml) of hexane and varying amounts of ether (from 0 to 36%) were taken. These five fractions weighed 0.48 g (68%). The nmr spectrum and the melting point were identical with those of hexadecanol.

Cleavage of 9-(4-Hydroxybutoxy)anthracene Ether.—The apparatus used was similar to that used previously. However, this time the procedure was slightly different. Methylene chloride (100 ml) was ozonized at −78° until the solvent was saturated with ozone (detected by blue coloring of CH_2Cl_2). The cold triphenyl phosphite in methylene chloride was added until the blue color disappeared. The ozonolysis was repeated until the appearance of a blue coloration again; then more of the triphenyl phosphite was added. This continual ozonolysis and addition was repeated until all the triphenyl phosphite (3.10 g, 0.010 mol) had been added. After purging with nitrogen, the 9-(4-hydroxybutoxy)anthracene (1.33 g, 0.005 mol) was added in a methylene chloride solution. The yellow solution was then allowed to warm to room temperature. The methylene chloride was removed *in vacuo* and the yellow residue was dissolved in ethyl acetate (100 ml). It was transferred to a Paar hydrogenation bottle and 0.52 g of 10% Pd/C was added as a slurry with ethyl acetate to the bottle. After hydrogenation for 30 min and filtration through Celite, the solvent was evaporated *in vacuo.* In order to extract the water-soluble diol, distilled water (200 ml) was added. After filtering through a Büchner suction filter, the water was evaporated to a volume of about 70 ml. This aqueous solution was cooled at 5°. The contents again were filtered and the water was evaporated *in vacuo,* yield 0.31 g. Nmr analysis indicated that the product still contained some water and that the per cent yield of diol was 47.

Registry No.—9-Hexadecyloxyanthracene, 30253-18-0; 9-dodecyloxyanthracene, 31734-34-6; 9-(4-hydroxybutoxy)anthracene, 31734-35-7.

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(15) "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 146.