STUDIES ON SYNTHESIS AND HYDROLYSIS OF NEW CYCLIC ACETALS

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STUDIES ON SYNTHESIS AND HYDROLYSIS OF NEW CYCLIC ACETALS

（新しい環状アセタール類の合成および加水分解に関する研究）

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PREFACE

The work in this thesis was performed under the guidance by Professor Toshikazu Nagai at the Institute of Chemistry, College of General Education, Osaka University.

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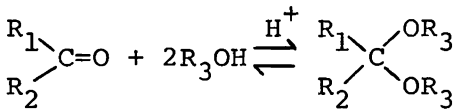
GENERAL INTRODUCTION

Acetals are characterized by the presence of two alkoxy groups attached to a carbon atom. Acetals result from elimination of one molecule of water from a carbonyl compound such as aldehydes and ketones and two molecules of an alcohol or hydroxyl compounds like phenols, being well known as protecting group of carbonyl group in the field of organic chemistry. Particularly cyclic acetals exist in glycosides, in the side chain of steroids and in many alkaloids as well, playing an important role. However, relatively simple acetal and macrocyclic acetals do not seem to occur in nature.[1]

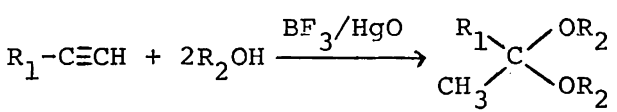
Generally, acetals are obtained by heating carbonyl compounds and alcohols under the influence of various acid catalysts(A). Since this process is an equilibrium reaction, it is not applicable to the synthesis of acetals of low stability. Other known methods of preparation of acetals involve;

Traditional Synthetic Methods of Acetals

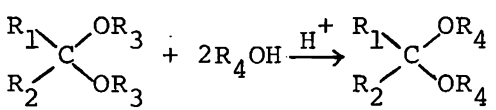
A. Acid Catalyzed Acetal Formation



B. Addition to Alkynes



C. Transacetalization



(B) addition of alcohols to unsaturated bond, (C) transacetalization and so on. But these procedures do not fit to produce cyclic benzophenone acetals and there has been no reports on this subject so far.

In this thesis, the author described the synthesis of cyclic benzophenone acetals using redox reaction of diphenyldiazomethane(DDM) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in the presence of various diols.[2]

A great deal of researches have been made of acid catalyzed hydrolysis of acetals,[1,3] which is regarded as a representing model in order to comprehend acid catalyzed reactions and hydrolytic reactions in aquaous solution in general. Therefore, the author proceeded to obtain further information on hydrolysis reactions using newly prepared benzophenone crown ether acetals and cyclic benzophenone acetals.

Chapter 1 deals with the novel synthesis of benzophenone crown ether acetals possessing the properties of both acetals and crown ethers by using oligoethylene glycol as a diol. The effects of relative amount of glycols used on the product distributions are discussed.

Chapter 2 deals with the synthesis of macrocyclic benzophenone acetals by means of the reaction with α,ω-diols. The relationship between product distribution and the ring size are discussed.

In Chapter 3, influences of ring size and number of oxygen atoms in the ring on the rate are discussed for the hydrolysis of benzophenone crown ether acetals.

In Chapter 4, the effects of ring size and methyl groups

introduced in the methylene ring on the rate for hydrolysis of cyclic benzophenone acetals were investigated. Furthermore, substituents effects were studied in the case of hydrolysis of 2,2-diaryl-1,3-dioxane in the view of structure-reactivity relationship.

Almost parts of the investigation presented in this thesis have now been published by the author in the following papers.

1) A Novel Synthetic Method for Crown Ethers by a Redox Reaction Utilizing the Intermediate from Diphenyldiazomethane and 2,3-Dichloro-5,6-dicyanobenzoquinone
   T. Oshima, R. Nishioka, S. Ueno, and T. Nagai,
   J. Org. Chem., 47, 2114(1982).
2) Syntheses of Macrocyclic Acetals via Cyclization of α,ω-Diols with an Intermediate from Diphenyldiazomethane and 2,3-Dichloro-5,6-dicyanobenzoquinone
   S. Ueno, T. Oshima, and T. Nagai,
   J. Org. Chem., 49, 4060(1984).
3) Substituent Effects in the Acid-Catalyzed Hydrolysis of Cyclic Acetals of Benzophenones
   S. Ueno, T. Oshima, and T. Nagai,
   Bull. Chem. Soc. Jpn., in press.
4) Acid Catalyzed Hydrolysis of Benzophenone Crown Ether Acetals and Analogous Open Chain Acetals
   S. Ueno, T. Oshima, and T. Nagai,
   J. Org. Chem., in contribution.
5) Acid Catalyzed Hydrolysis of Cyclic Benzophenone Acetals
   S. Ueno, T. Oshima, and T. Nagai,
   in preparation.

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1.(a) E. Schmitz and J. Eichhorn, In "The Chemistry of the Ether Linkage", S. Patai, Eds., John Wiley and Sons: London, 1967; chap. 7. (b) R. G. Bergstrom, In "The Chemistry of Ethers, Crown Ethers, Hydroxy Groups and Their Sulphur Analogues", S. Patai, Ed-., John Wiley and Sons: Chichester, 1980; chap. 20.

2. T. Oshima, R. Nishioka and T. Nagai, Tetrahedron Lett., 3919(1980).

3.(a) E. H. Cordes, Progr. Phys. Org. Chem.,4,1(1967).

(b) E. H. Cordes and H. G. Bull, Chem. Rev.,74,581(1974).

Chapter 1

SYNTHESES OF BENZOPHNONE CROWN ETHER ACETALS BY A REDOX REACTION UTILIZING THE INTERMEDIATE FROM DIPHENYLDIAZOMETHANE AND 2,3-DICHLORO-5,6-DICYANOBENZOQUINONE

1-1. Introduction

Since the pioneering work of Pedersen on the preparation and properties of macrocyclic polyethers(crown ethers),[1] there have been numerous reports of syntheses of a wide variety of crowns.[2] The general methods proposed for the synthesis of crown compounds are a modified Williamson ether synthesis by the reactions of oligoethylene glycols with oligoethylene glycol dichlorides or ditosylates[1a,2,3] and of oligoethylene glycols with arenesulfonyl or alkanesulfonyl chlorides,[4] in the presence of suitable template metal cations.

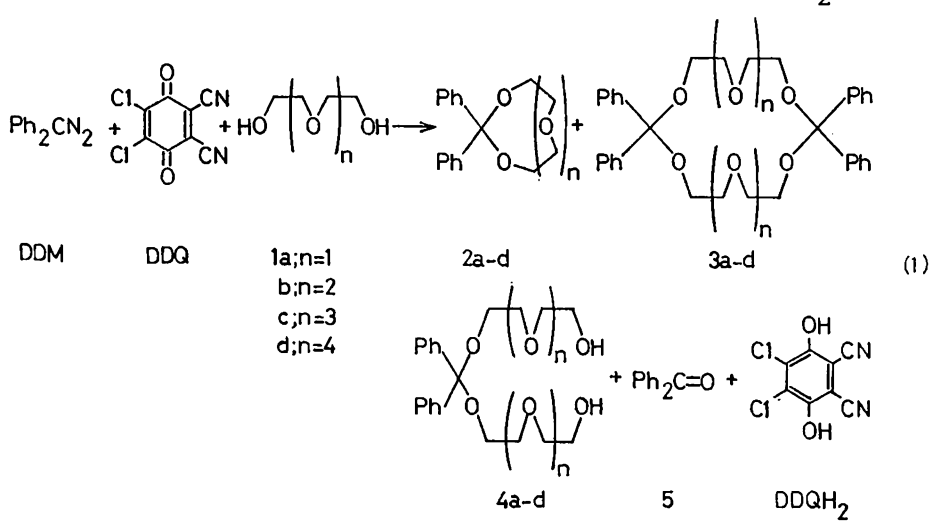
Recently, Nagai et al. reported the synthesis of various cyclic and noncyclic benzophenone acetals and thioacetals in high yields by means of the reaction of diphenyldiazomethane (DDM) with 2,3-dichloro-5,5-dicyanobenzoquinone(DDQ) under the influence of the corresponding alcohols and thiols.[5] The preliminary experiment showed that these redox reactions were also applicable for di- and triethylene glycols to afford so-called crown ether acetals incorporated with a diphenylmethylene unit. Thus the author attempted to extend these simple synthetic methods for preparing crown ether acetals to the

higher series of oligoethylene glycols. In this chapter, the preparation of the desired ethereal macrocycles (2) and (3) derived from di-, tri-, tetra-, penta-, and hexaethylene glycols(1) is described and the effects of the relative amount of glycols used on the product distributions are also discussed.

1-2. Results and Discussion

Reaction of DDM with DDQ in the Presence of Oligoethylene Glycols(Method A).

Reaction of DDM with DDQ in the presence of 1, 3, and 5 equiv of di-, tri-, tetra-, and pentaethylene glycols(1) in dry benzene at 20-25°C gave three macroethereal products, (2), (3), and (4), incorporated with diphenylmethylene moiety together with benzophenone(10-20%) and an almost quantitative amount of 2,3-dichloro-5,6-dicyanohydroquinone($DDQH_2$; eq. 1).



The reaction conditions and the product distributions are seen in Table I. The two macrocyclic products (2) and (3) have structures formally made by the dehydrocyclization of oligo-

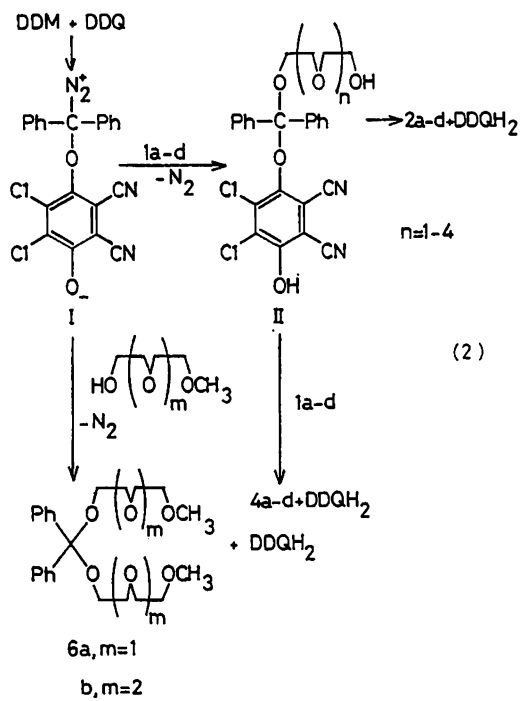
ethylene glycols toward diphenylmethylene with the aid of DDQ; compounds (3) have a dimeric formula of (2). The noncyclic macroethers (4) possess diol structures of two molecules of glycols linked at the central carbon atom of diphenylmethylene.

Table I. Reaction Conditions and Product Distribution

run	glycols[a] (rel equiv)	method	rctn time, h	products,[b] % yield 2	3	4	5
1	1a (1)	A	2	45	5	18	9
2	1a (3)	A	2	38	3	37	9
3	1a (5)	A	2	10	tr	43	3
4	1a (0.5)	B	2	84[c]	0	0	25
5	1b (1)	A	2	27	13	21	16
6	1b (3)	A	2	12	5	52	16
7	1b (5)	A	2	8	tr	68	14
8	1b (0.5)	B	2	79[c]	0	0	27
9	1b (1)	B	2	47	5	6	15
10	1b (3)	B	2	23	8	18	17
11	1c (1)	A	2	38	5	18	18
12	1c (1)	A	4	41	6	15	16
13	1c (3)	A	2	15	2	36	21
14	1c (5)	A	2	7	tr	44	18
15	1c (0.5)	B	2	70[c]	0	0	23
16	1d (1)	A	2	48	tr	19	16
17	1d (0.5)	B	2	89[c]	0	0	22
18	1e (0.5)	B	2	70[c]	0	0	16

[a] 1a; di-, 1b; tri, 1c; tetra-, 1d; penta-, and 1e; hexaethylene glycol. [b] Unless otherwise noted, based on DDM used. [c] Based on glycols.

These overall redox reactions can be explained to proceed via diazonium betaine(I; or carbenium betaine derived from it by the loss of N_2) intermediate as previously demonstrated.[5,6] The nucleophilic attack of the oligoethylene glycols to this intermediate is expected to provide a relatively unstable product(II) which leads to cyclic (2) via an internal S_N2 displacement in competition with an external S_N2 attack of another glycol to afford noncyclic (4)(eq. 2).

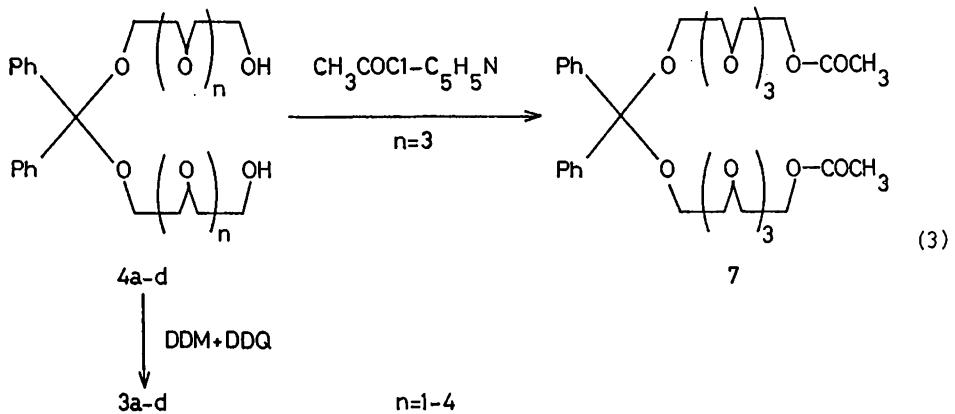


(2)

In accordance with the schematic diagram, reaction with di- and triethylene glycol monomethyl ethers has been found to give only noncyclic macroethers (6). On the other hand, the formation of (3) may be attributed to the nucleophilic attack of the resulting (4) toward the betaine intermediate and the follow-up internal S_N2 displacement as well as the case of (2). The evidence of such an intermediary (4) was realized by the observation that (4) were easily transformed into (3) when treated with DDM and DDQ(see below). As was previously exemplified,[6] the present reaction system is very sensitive to water, so the reagents and the equipment must be carefully dried before use. Thus, the unfortunate occurrence of benzophenone can be ascribed to the residual water.

The purified (2) and (3) were all colorless prisms except for oily (3d), and the structures of these ethereal macrocyclic compounds were ascertained by the IR, NMR, mass spectra, and elemental analyses. A preliminary experiment showed that (2c) remains unchanged on standing overnight in methanol solution containing excess water and CH_3ONa but completely degrades into benzophenone and tetraethylene glycol even when stirred for 5 hr in methanol with a small amount of hydrochloric acid. The IR spectra of oily(4)showed the strong hydroxyl absorption at 3450-3470 cm^{-1} and several characteristic bands assignable to the ethereal bonds at 1020 -1140 cm^{-1}. Mass spectra of (4) revealed $m/e = M^+-(OCH_2CH_2)_n OH$ as the base peaks. Compounds (4) were separated by high-performance liquid chromatography(HPLC), but their elemental analyses deviated due to the hygroscopic property. Therefore,

the diol sraucture were confirmed by acetylation into (7). Further evidence was offered by the cyclization into (3) when treated with DDM and DDQ(eq. 3).



(3)

As seen in Table I, increase of oligoethylene glycols used in method A brings about considerable decrease in the yields of cyclic (2) and (3). But the yields of noncyclic (4) reversely increased with such an increment of glycols. These results mean that the intramolecular cyclization giving (2) was highly disturbed by the growing intermolecular reaction giving (4) with the increasing amounts of glycols.

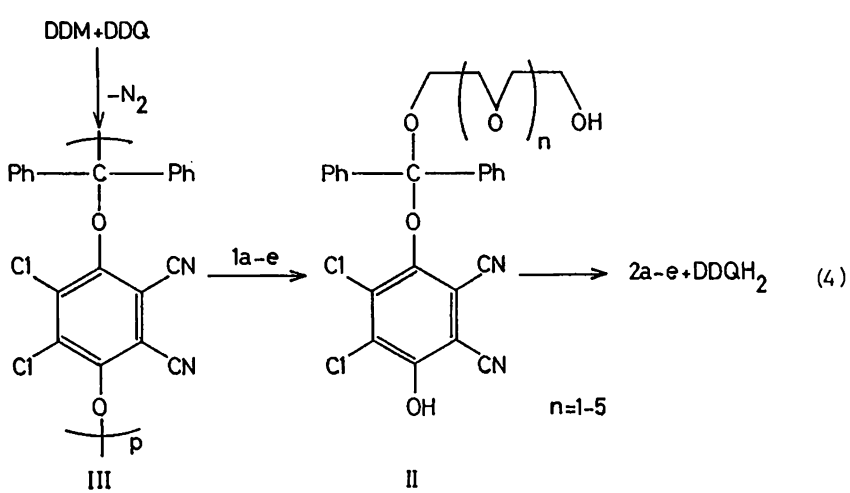
Being markedly different from the conventional synthetic methods of macrocyclic compounds,[7] the present reactions can be made under mild conditions without any special template cation, high dilution technique, or elevated temperature. Also relatively short reaction times(2 hr) are sufficient to complete the reactions. Extended reaction times(4 hr) did not greatly affect the product distributions; essentially similar percentages of (2), (3), and (4) were obtained in the case of triethylene glycol(runs 11 and 12). The facile preparation of these macrocyclic compounds can be essentially

ascribed to the property of DDQ as a good oxidizing agent[8] in addition to the easy formation of diazonium betaine. Indeed, the precipitate of reduced $DDQH_2$ begins to appear at the early stage of the reactions.

Reaction of DDM with DDQ Followed by the Addition of Oligoethylene Glycols(Method B).

The rapid reaction of DDM and DDQ is found to give a resinous poly(2,3-dichloro-5,6-dicyanohydroquinone benzhydryl ether)(III) generated by the successive combination of diazonium betaine, if any hydrolytic or solvolytic additive is absent.[6] Since the polyether undergoes rapid hydrolysis and methanolysis to give the same products as those obtained from the method A treatment,[6] the author attempted to utilize its solvolytic property in the cyclization of oligoethylene glycols.

Dropwise addition of 0.5 equiv of glycols into the reaction solution of DDM and DDQ gave (2) in 70-90% yields(based on glycols used) without any detectable formation of (3) and (4).



(4)

The selective and convenient formation of the desired (2) may be performed by both the slow addition and the small amounts of glycols. Under these conditions, most of glycols exclusively attack the diphenylmethylene moieties in the polyether linkage so that the resulting II has an enough time to undergo internal S_N2 displacement, because free glycols are rarely present in the reaction solutions(eq.4). As represented in the case of triethylene glycol(runs 9 and 10), however, the increased addition(1 or 3 equiv) of glycol resulted in the production of (3) and (4) in addition to the major (2). This phenomenon can be similarly ascribed to the further solvolysis of resulting II by the increased glycol as already demonstrated in method A. The present method B, of course, yields about twice as much cyclic (2) than the corresponding method A(runs 5 and 9), because the former method furnishes the reaction conditions with more II and less glycol especially at the early stage of the reaction.

Although a complete comparison has not been established for the other glycols, method B with 1 equiv of glycols appears to be preferable to method A for the more production of 1:1 macrocyclic (2).

1-3. Experimental Section

All melting points were taken with a Laboratory Devices Mel-Temp instrument and are uncorrected. Infrared spectra were recorded on a Hitachi 260-10 spectrometer. Proton NMR spectra were taken at 90MHz on a Varian EM-390 spectrometer. Mass spectraldata were obtained with a Hitachi RMU-6E mass

spectrometer at ionization potential of 70eV. High-performance liquid chromatography(HPLC) analyses were accomplished with use of naphthalene as an internal standard with a JASCO Trirotor high-pressure liquid chromatograph equipped with a 25 cmx4mm column packed with octadecylsilane on silica gel and with methanol-water(5:1) as an eluent.

Materials.

DDM was prepared according to the procedure described by Smith and Howard[9]; mp 29-30°C(from light petroleum). Oligoethylene glycols were distilled under reduced pressure. DDQ, di-, and triethylen glycol monomethyl ethers were of commercial origin and were used without further purification. Benzene was refluxed over lithium aluminum hydride and was fractionated.

Reaction of DDM with DDQ in the Presence of Oligoethylene Glycols(Method A).

General procedure was described in the case of triethylene glycol. To a stirred suspention of DDQ(1.18g,5.2 mmol) in benzene(20ml) was added dropwise over 1hr at 20-25°C a benzene solution(10ml) of DDM(1.0g,5.2mmol) and 1 equiv of triethylene glycol(0.78g,5.2mmol). After the mixture was stirred for 1 hr, the precipitated $DDQH_2$ was filtered off and was washed with benzene(20mlx3). The washing and filtrate parts were combined, washed with 5% aqueous sodium carbonate (10mlx3) and then with NaCl saturated water(10mlx5), dried over anhydrous sodium sulfate, and concentrated in vacuo to

give a pale-brown viscous oil. The oily products were column chromatographed on alumina. Careful successive elution gave benzophenone with light petroleum-benzene(1:1), 1:1 macrocyclic (2b) with benzene-ether(1:3), 2:2 macrocyclic (3b) with ether, and 1:2 noncyclic (4b) with benzene-methanol(20:1). In the case of diethylene glycol, 2:2 macrocyclic (3a) was eluted with benzene-ether(1:1) before 1:1 product (2a). Column chromatographic separation of (3c) and (4c) or (3d) and (4d) was unsuccessful so that the yields of these compounds were determined by means of the HPLC, using naphthalene as an internal standard. As (4c) and (4d) isolated by the HPLC were colorless hygroscopic oils, structural evidence was demonstrated by conversion into (3c) and (3d) by treatment with DDM and DDQ and also by esterification with acetyl chloride. The structures of 1:1 and 2:2 macrocyclic compounds (2) and (3) were determined as follows.

2,2-Diphenyl-8-crown-3(2a): mp 101-103°C(from ether); IR(KBr) 2910, 1130, 1110cm^{-1}; NMR($CDCl_3$) δ 3.7-3.8(m,OCH_2CH_2O,8H),7.1-7.6(m,aromaticH,10H);MS *m/e* 270(M^+). Anal. Calcd for $C_{17}H_{18}O_3$: C,75.53;H,6.71. Found:C,75.52;H,6.71.

2,2-Diphenyl-11-crown-4(2b): mp 105-106°C(from ether); IR(KBr) 2900, 1128, 1107cm^{-1}; NMR($CDCl_3$) δ 3.7-3.8(m,OCH_2CH_2O,12H), 7.1-7.6(m,aromaticH,10H);MS *m/e* 314(M^+). Anal. Calcd for $C_{19}H_{22}O_4$:C,72.59;H,7.05. Found:C,72.58;H,7.06.

2,2-Diphenyl-14-crown-5(2c): mp 89-90°C(from ether); IR(KBr) 2885, 1132, 1102cm^{-1}; NMR($CDCl_3$) δ 3.8-3.9(m,OCH_2CH_2O,16H), 7.1-7.6(m,aromaticH,10H);MS *m/e* 358(M^+). Anal. Calcd for $C_{21}H_{26}O_5$:C,70.37;H,7.31. Found:C,70.46;H,7.28.

2,2-Diphenyl-17-crown-6(2d): mp 61-62°C(from ether); IR(KBr) 2880, 1138, 1105cm^{-1}; NMR($CDCl_3$) δ 3.5-3.8(m,OCH_2CH_2O,20H), 7.1-7.5(m,aromaticH,10H);MS *m/e* 402(M^+). Anal. Calcd for $C_{23}H_{30}O_6$:C,68.63;H,7.51. Found:C,68.78;H,7.58.

2,2-Diphenyl-20-crown-7(2e): mp 62-63°C(from ether); IR(KBr) 2890, 1140, 1107cm^{-1}; NMR($CDCl_3$) δ 3.7-3.9(m,OCH_2CH_2O,24H), 7.2-7.6(m,aromaticH,10H);MS *m/e* 446(M^+). Anal. Calcd for $C_{25}H_{34}O_7$:C,67.24;H,7.68. Found:C,67.31;H,7.78.

2,2,10,10-Tetraphenyl-16-crown-6(3a): mp 182-183°C(from ether); IR(KBr) 2876, 1090, 1018cm^{-1}; NMR($CDCl_3$) δ 3.3-3.8(m,OCH_2CH_2O, 16H), 7.1-7.6(m,aromaticH,20H);MS *m/e* 540(M^+). Anal. Calcd for $C_{34}H_{36}O_6$:C,75.53;H,6.71. Found: C,75.57;H,6.73.

2,2,13,13-Tetraphenyl-22-crown-8(3b): mp 167-168°C(from dioxane); IR(KBr) 2875, 1096, 1018cm^{-1}; NMR($CDCl_3$) δ 3.3-3.8 (m,OCH_2CH_2O,24H), 7.1-7.6(m,aromaticH,20H);MS *m/e* 628(M^+). Anal. Calcd for $C_{38}H_{44}O_8$:C,72.59;H,7.05; Found:C,72.32;H,6.90.

2,2,16,16-Tetraphenyl-28-crown-10(3c): mp 89-91°C(from ether); IR(KBr) 2875, 1090, 1015cm^{-1}; NMR($CDCl_3$) δ 3.4-3.8(m,OCH_2CH_2O, 32H), 7.2-7.7(m,aromaticH,20H):MS *m/e* 716(M^+). Anal. Calcd for $C_{42}H_{52}O_{10}$:C,70.37;H,7.31. Found:C,70.35;H,7.31.

2,2,19,19-Tetraphenyl-34-crown-12(3d): colorless oil; IR(neat) 2880, 1098, 1025cm^{-1}; NMR($CDCl_3$) δ 3.3-3.7(m,OCH_2CH_2O,40H), 7.1-7.6(m,aromaticH,20H);MS *m/e* 804(M^+). Anal. Calcd for $C_{46}H_{60}O_{12}$:C,68.63;H,7.51. Found:C,68.69;H,7.58.

Reaction with Di- and Triethylene Glycol Monomethyl Ethers.

This reaction was carried out by use of 2 equiv of monomethyl ethers according to method A. Column chromatographic

treatment(on alumina) of the reaction mixtures gave colorless oily (6a) and (6b) with benzene-methanol(20:1) as an eluent 9,9-Diphenyl-2,5,8,10,13,16-hexaoxaheptadecane(6a): 85% yield; IR(neat) 2870, 1095, 1020cm^{-1}; NMR($CDCl_3$) δ 3.35(s,OCH_3,6H), 3.4-3.7(m,OCH_2CH_2O,16H), 7.1-7.5(m,aromaticH,10H);MS *m/e* 285 (M-$(OCH_2CH_2)_2OCH_3$). Anal. Calcd for $C_{23}H_{32}O_6$:C,68.29;H,7.97. Found:C,68.00;H,7.93.

12,12-Diphenyl-2,5,8,11,13,16,19,22-octaoxatricosane(6b): 90% yield; IR(neat) 2875, 1100, 1022cm^{-1}; NMR($CDCl_3$) δ 3.36(s,OCH_3, 6H), 3.4-3.8(m,OCH_2CH_2O,24H), 7.2-7.6(m,aromaticH,10H);MS *m/e* 329(M-$(OCH_2CH_2)_3OCH_3$). Anal. Calcd for $C_{27}H_{40}O_8$:C,65.38;H,8.19. Found:C,65.53;H,8.28.

Reaction of DDM with DDQ Followed by Addition of Oligoethylene Glycols(Method B).

General procedure was described in the case of triethylene glycol. To a stirred suspention of DDQ(1.18g,5.2mmol) in benzene(20ml) was added all at once a benzene solution(10ml) of DDM(1.0g,5.2mmol) at 20-25°C. The reaction was very vigorous with the violent evolution of N_2 and gave a resinous product. The 0.5 equiv of triethylene glycol(0.39g,2.6mmol) in benzene(10ml) was added dropwise over 1 hr to the reaction solution. After the solution was stirred for 1 hr followed by treatment with a small amount of water, the precipitated $DDQH_2$ was filtered off and washed with benzene(20mlx3). The same workup technique as for method A was adopted to give a pale-brown viscous oil. The oily products were column chromatograghed(alumina) with light petroleum-benzene(1:1) as an

eluent to afford benzophenone and then with benzene-ether(1:3) to afford 1:1 macrocyclic (2b), but possible (3b) and (4b) were not detectable when 0.5 equiv of glycol was used. However, 1 or 3 equiv of triethylene glycol brought about the formation of (3b) and (4b) in addition to (2b).

Conversion of (4) into (3).

This reaction was made by employing 0.5 equiv of (4) with respect to DDM and DDQ according to method B. The converted products (3) were isolated by column chromatography on alumina with ether or ether-methanol(20:1) as an eluent. The yields were respectively 65%(3a), 74%(3b), 58%(3c), and 73%(3d).

Acetylation of (4b).

To a benzene solution(10ml) of (4b)(300mg,0.47mmol) was added all at once a benzene solution(10ml) of acetyl chloride (100mg,1.27mmol) and pyridine(150mg,1.9mmol). After the solution stood for 1 hr, precipitated salt was filtered off and washed with benzene(10mlx3). The washing and filtrate were combined, washed with 5% aqueous sodium carbonate(5mlx3) and then with NaCl saturated water(5mlx3), dried over anhydrous sodium sulfate, and evaporated in vacuo at 50°C to give a pale-yellow viscous oil. The oily products were gel chromatographed(Sephadex LH-20,Pharmacia), with methanol as an eluent, to afford (7): colorless oil; 80% yield; IR(neat) 2780, 1735, 1235, 1105cm^{-1}; NMR($CDCl_3$) δ 2.0(s,$COCH_3$,6H), 3.3-3.7(m,OCH_2CH_2O,28H), 4.0-4.2(m,CH_2OCO,4H), 7.1-7.5(m,aromatic H,10H);MS *m/e* 401(M-$(OCH_2CH_2)_4OCOCH_3$). Anal. Calcd for

$C_{33}H_{48}O_{12}$:C,62.24;H,7.60. Found:C,62.07;H,7.60.

1-4. Summary

A synthetic method for the new crown ether acetals possessing a diphenylmethylene moiety by the reaction of diphenyl diazomethane and 2,3-dichloro-5,6-dicyanobenzoquinone under the influence of oligoethylene glycols is described. The two types of crown ether acetals with 1:1 and 2:2 composition of diphenylmethylene/oligoethylene glycol moiety were obtained together with the noncyclic 1:2 compositional acetals. The product distributions were dependent on the relative quantities and the manner of addition of the oligoethylene glycols.

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Chapter 2

SYNTHESES OF MACROCYCLIC BENZOPHENONE ACETALS VIA CYCLIZATION OF α,ω-DIOLS WITH THE INTERMEDIATE FROM DIPHENYLDIAZOMETHANE AND 2,3-DICHLORO-5,6-DICYANOBENZOQUINONE

2-1. Introduction

There are numerous procedures available for the syntheses of acetals.[1,2] Conventional methods include the conversion of aldehydes and ketones into their corresponding acetals by use of alcohols in the presence of acidic catalysts such as *p*-toluenesulfonic acid.[3] These well-known methods, however, fail completely or give low yields when the product is a strained cyclic acetal or an acetal of unusually low stability. Anteunis et al. have reported successful syntheses of strained 1,3-dioxacyclanes by a thermal decomposition of mixed acetals.[4] Acetal exchange reactions are generally used as another method for the preparation of cyclic acetals. As early as 1935, Hill and Carothers[5] prepared the unsubstituted macrocyclic acetals by heating of α,ω-diols with alkyl formal and an acidic catalyst and by depolymerizing the corresponding linear polymers. Dale and Borgen[6,7] synthesized dimethylsubstituted monomeric and dimeric cyclic acetals by heating a mixture of α,ω-diols, 2,2-dimethoxypropane, and an acid ion-exchange resin in benzene and by slowly distillation of an azeotropic mixture of methanol and benzene.

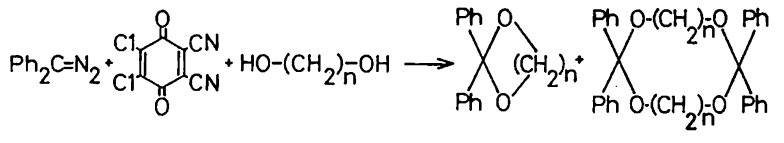
Recently, Nagai et al. developed a new synthetic method for cyclic and noncyclic benzophenone acetals and thioacetals by means of a redox reaction of diphenyldiazomethane(DDM) with 2,3-dichloro-5,6-dicyanobenzoquinone(DDQ) in the presence of suitable alcohols and thiols.[8] The author extended the redox systems to the oligoethylene glycols and succeeded in the preparation of macrocyclic crown ether acetals together with noncyclic macroethereal acetals.[9] The aim of this chapter is to present the possible application of these redox systems to the synthesis of large-ring acetals by employing α,ω-diols, to point out the noticeable difference between α,ω-diols and oligoethylene glycols, and to discuss the effect of chain length on the product distributions.

2-2. Results and Discussion

Product and Mechanistic Studies.

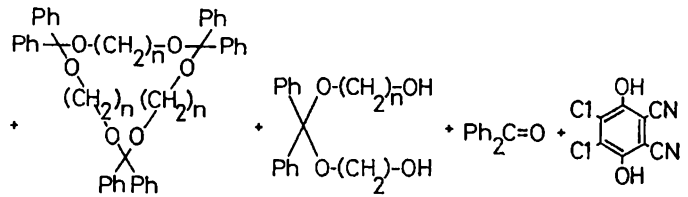
Reaction of DDM with DDQ in the presence of an excess or an equimolar amount of α,ω-diols(1) in dry 1,2-dichloroethane or benzene at 20-25°C gave three types of cyclic acetals,(2), (3), and (4) together with noncyclic acetals(5)(eq. 1). This reaction provided benzophenone(~20%) as by-product and almost quantitative amount of 2,3-dichloro-5,6-dicyanohydroquinone ($DDQH_2$). The acetals (3) and (4) have respectively dimeric and trimeric formula of monomeric acetals(2) with 1:1 composition of diphenylmethylene/diol moiety. The noncyclic acetals(5) consist of two diols and one diphenylmethylene component. These product distributions were dependent on the

chain length of α,ω-diols(Table I).



DDM DDQ 1 2 3

eq.1



4 5 $DDQH_2$

The diols with short chain length such as (1a-c) gave only monomeric cyclic acetals in good yields, while the use of 1,5-pentanediol provided dimeric and a small amount of trimeric cyclic acetal together with noncyclic acetal and monomeric acetal. However, the monomeric acetals were no longer obtained in the higher homologous series for which dimeric and noncyclic acetals were obtained in moderate yields. In the case of 1,3-propanediol and 1,6-hexanediol, solvent variation brought about no essential change in the product distributions.

With respect to the formation of these cyclic and noncyclic acetals, the author can describe the similar sequence of process as was pictured for the case of oligoethylene glycols(eq.2).[9] The nucleophilic attack of diols(1) toward an initially formed diazonium betaine(I) provides II. Because of the strong electron withdrawal of the DDQ moiety, diphenylmethylene site of II was most likely subject to the internal nucleophilic displacement and/or the external attack of

Table I Product Distribution in the DDM-DDQ-Diols Systems

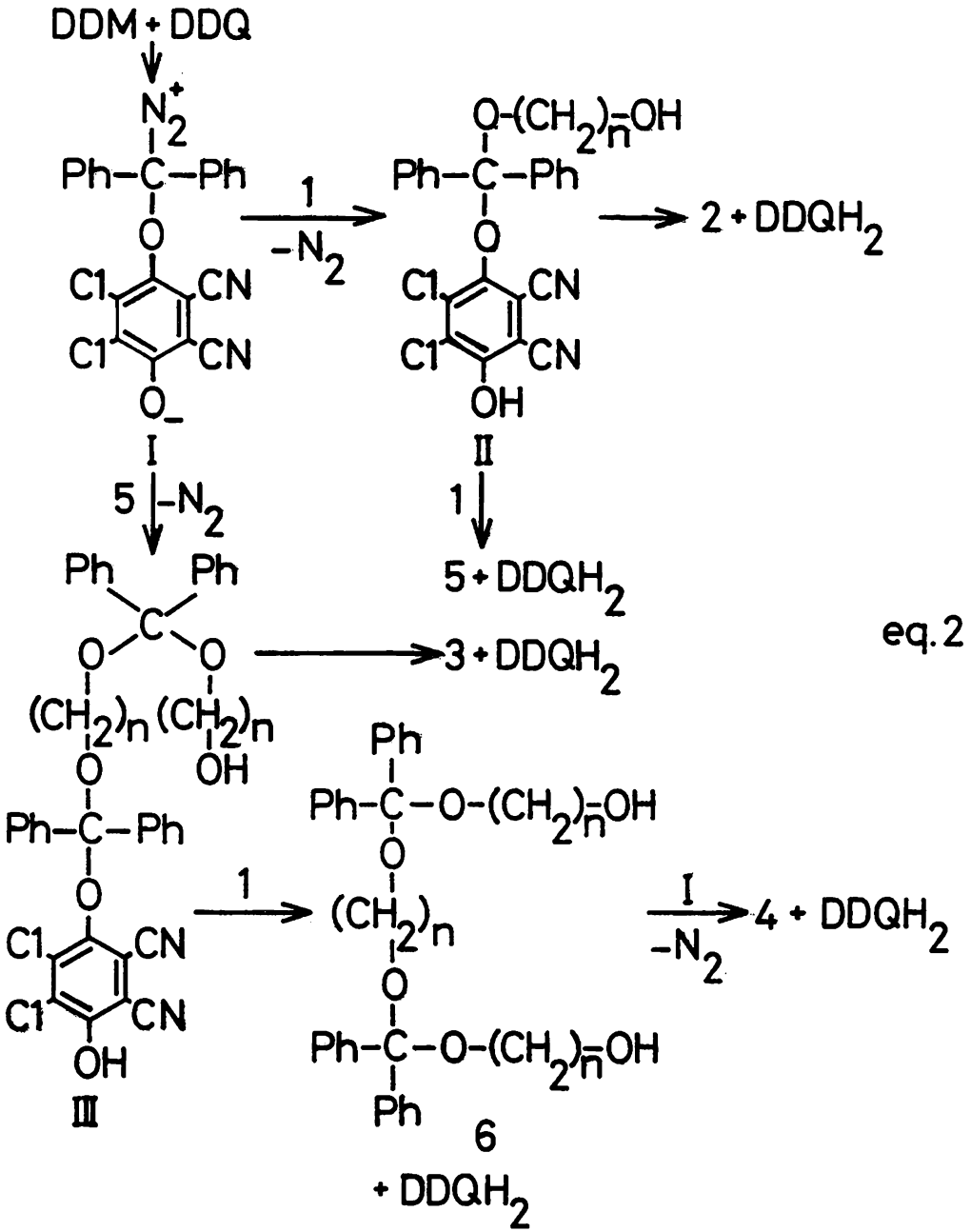
Run[a]	Diols (rel. equiv)	n (number of CH_2 groups)	Products[b] % yield			
			2	3	4	5[c]
1	1a(3)	2	81	0	0	0
2	1b(3)	3	84	0	0	0
3	1b(3)	3	76	0	0	0
4	1c(3)	4	75	0	0	0
5	1d(1)	5	21	18	0.9	30
6	1e(1)	6	0	42	0	12
7	1e(1)	6	0	32	0	17
8	1f(1)	7	0	20	0	43
9	1g(1)	8	0	35	0	30
10	1h(1)	9	0	19	0	49
11	1i(1)	10	0	23	0	50
12	1j(1)	12	0	13	0	40
13	1j(1)[d]	12	0	18	0	44

a) Run 1, 2, 4, and 7 were carried out in 1,2-dichloroethane, others in benzene.

b) Unless otherwise noted, based on DDM used.

c) Based on diols used.

d) Added over 1 hr into the reaction mixture of DDM and DDQ.


DDM + DDQ
N2+
Ph–C–Ph
O
C1
C1
CN
CN
O–
I
1
–N2
O-(CH2)n-OH
OH
II
2 + DDQH2
5 –N2
1
5 + DDQH2
Ph
Ph
C
O
O
(CH2)n
(CH2)n
OH
3 + DDQH2
eq. 2
III
1
Ph
O-(CH2)n-OH
(CH2)n
I
–N2
4 + DDQH2
6
+ DDQH2

another diol. Thus, monomeric cyclic acetals(2) and noncyclic acetals(5) are formed by the respective internal and external acetalization process, both leaving $DDQH_2$. As to dimeric cyclic acetals(3), it is assumed that because of the presence of two OH end groups, (5) further reacts with I and then the resulting III leads to dimeric cyclic acetals and $DDQH_2$ by the internal reaction. This assumption was confirmed by finding that the treatment of (5) with two equiv of DDM and DDQ gave the dimeric acetals in 60-80% yields(see experimental section). Similarly, trimeric cyclic acetal(4d) may be constructed by the action of I toward noncyclic acetal (6d) possibly arising from the reaction of III and (1d). As expected, the formation of benzophenone is responsible for the unfavorable hydrolysis of such intermediates as I, II, and III by residual water, so it is necessary to carefully dry reagents and equipment.

Effect of Chain Length

The yield data from the present work offer some important information in regard to the cycloacetalization processes in eq. 2. Fig. 1 shows a plot of yields of (2), (3), and (5) as a function of number(n) of methylene unit of diols and of number(N) of ring atoms. The lower diols(1a-c) gave only monomeric cyclic acetals of 5-7 ring size in spite of the presence of three-fold excess of diols. This is indicative of the preferential occurrence of intramolecular cycloacetalization of II prior to the attack of these diols, mainly because of the higher ring-closure probabilities for these

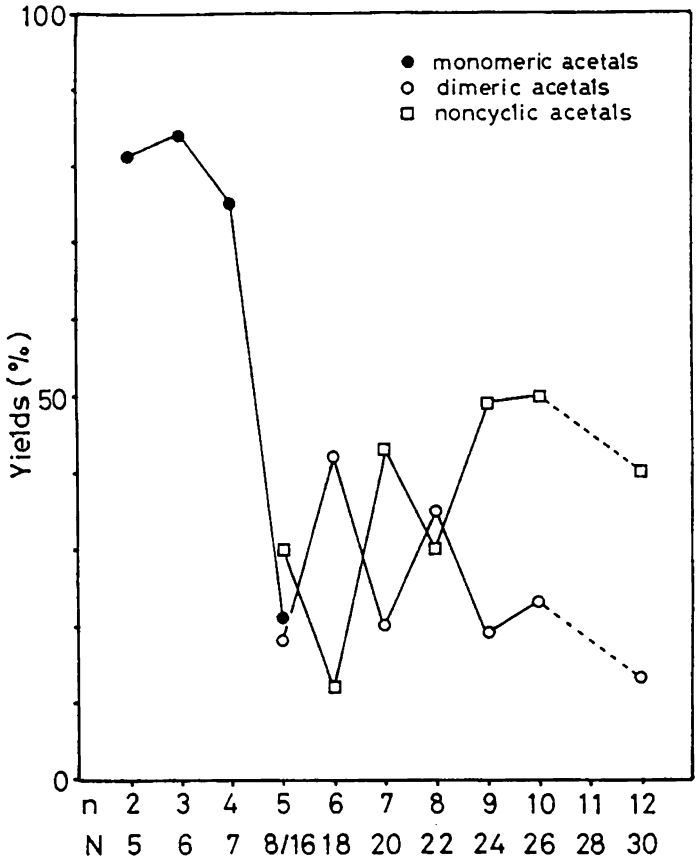


Fig.1 Yields of monomeric(2), dimeric(3) and noncyclic acetals(5). N=total number of atoms in ring, n=number of CH_2 groups in each polymethylene.

common rings. However, as noticed in 1,5-pentanediol, one methylene unit elongation brought about a sudden decrease in the monomeric yield and instead permitted the degradation into (5) by the participation of diol. On going from 1,6-hexanediol to 1,12-dodecanediol, the corresponding monomeric acetals of ring size 9-15 were no longer detected on the careful analysis of the reaction mixtures. These result from the lower ring-closure reactivity of II for medium 8 to 11 membered ring region and beyond owing to the large ring strain and/or lower probabilities of cyclization.[10] The ef-

fects of chain length on the ring-closure reactivities have been considered as an inherent property of the methylene chains connecting the functional groups.[11] The present behavior of diols is strikingly analogous to that observed in the preparation of unsubstituted[5] and dimethylsubstituted macrocyclic acetals[7] by way of acetal exchange reaction of alkyl formal and 2,2-dimethoxypropane with diols.

Here, an interesting question is raised on the ease of cycloacetalization of (5) into (3), because these noncyclic acetals have a diol structure with chain lengths of more than 13 atoms. This can be easily answered by considering the enhancement of ring closure of a long-chain bifunctional compound by the presence of a number of groups composing the chain itself held in the form suitable for ring closure.[12] The bulky *gem*-diphenyl group located in the midst of the chain of (5) was considered as an example of a structural moiety fitting these requirements with the aid of adjacent two ether bonds.

In the previous syntheses of crown ether acetals,[9] both monomeric and dimeric cyclic acetals were obtained together with noncyclic ones. This acetalization was successfully achieved in the glycols which formaly correspond to the α,ω-diols of 5, 8, 11, 14, and 17 methylene units. The yields of monomeric products were improved by the stepwise addition of glycols into the reaction mixture of DDM and DDQ, where free glycols are present in very low concentration relative to I (or its polymerized form). This dilution technique was applied to 1,12-dodecanediol in order to make a large-ring

monomeric acetal, but no essential change was found in the product distributions(Run 12 and Run 13). This result implies that the intermediate II of long chain diol resists the intramolecular cycloacetalization and preferably undergoes the external attack of diol even if the forcing condition is particularly designed to build up a monomeric acetal. Ultimately, the marked difference in the reaction fashion between oligoethylene glycols and α,ω-diols may be attributed to the oxygen atom effect[13] by which transannular -CH···HC- repulsions in polymethylene chain can be relieved.

It is of interest that the dimeric acetals(3) derived from diols with even-methylene unit(n=6, 8, 10) were formed in higher yield than those from diols with odd-methylene unit (n=5, 7, 9). The melting points of dimeric acetals also

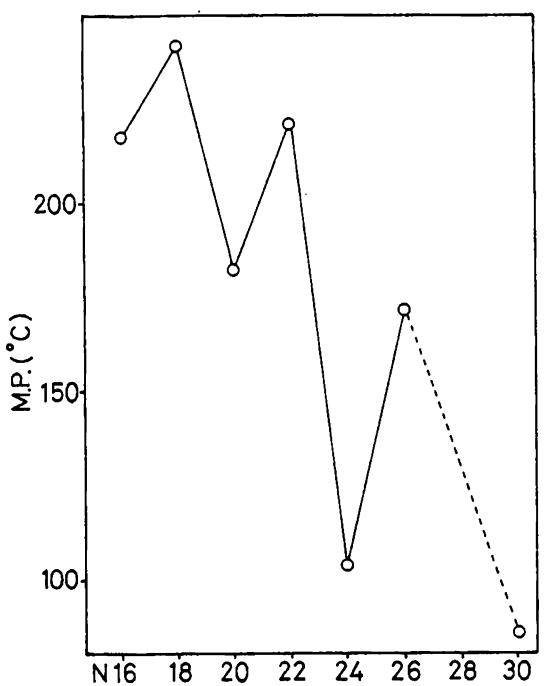


Fig. 2 Melting points of dimeric acetals(3).

showed the similar zig-zag profiles(Fig. 2). However, the

opposite alternation was found in the yields of noncyclic acetals(5) except for a small inversion in 1,9-nonanediol and 1,10-decanediol, strongly supporting the participation of (5) as a precursor of (3). Such alternating effects in the yield data have been widely observed in the various cyclization reactions of bifunctional polymethylene compounds as found in the thermal cyclization of dibasic acids,[14] cyclic ketone formation from dinitriles,[15] acid catalyzed lactone formation from ω-oxy acids.[16]

Borgen has already reported that *gem*-dimethyl substituted dimeric acetals of ring size 16-24 show a similar alternation in yield profiles as the new *gem*-diphenyl substituted ones.[7] He assumed three-bond bridge rectangular conformation with 1,3-dioxa group $^{+}gauche\ ^{+}gauche\ (^{+}g\,^{+}g)$ across corners. According to these conformational restrictions, it is evident that dimeric benzophenone acetals also adopt strain-free diamond lattice type structures for the 18, 22, 26, and 30 membered rings. This is represented in Fig. 3(A) for 2,2,11,11-tetraphenyl-1,3,10,12-tetraoxacyclooctadecane. However, the 16, 20, and 24 membered rings will not have the advantage of being of the diamond lattice type structures in such rectangular conformation as shown in Fig. 3(B) for 2,2,12,12-tetraphenyl-1,3,11,13-tetraoxacycloeicosane. For these reasons, 18, 22, and 26 membered acetal groups are more stable, more predominant, and have higher melting points than 16, 20, and 24 membered ones. To make an experimental justification of the conformational stabilities, a kinetic study of acid catalyzed hydrolysis of these dimeric acetals was attempted.

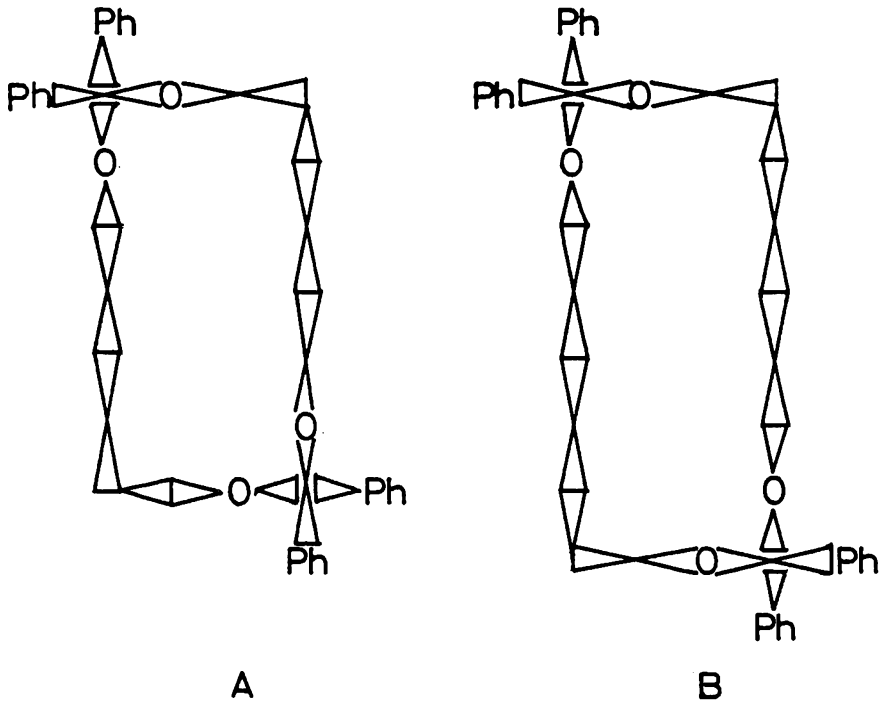


Fig. 3 Wedge-type representation of 2,2,11,11-tetraphenyl-1,3,10,12-tetraoxacyclooctadecane(A) and 2,2,12,12-tetraphenyl-1,3,11,13-tetraoxacycloeicosane(B).

The results shown in Fig. 4 strongly suggest the alternation in the conformational stabilities.

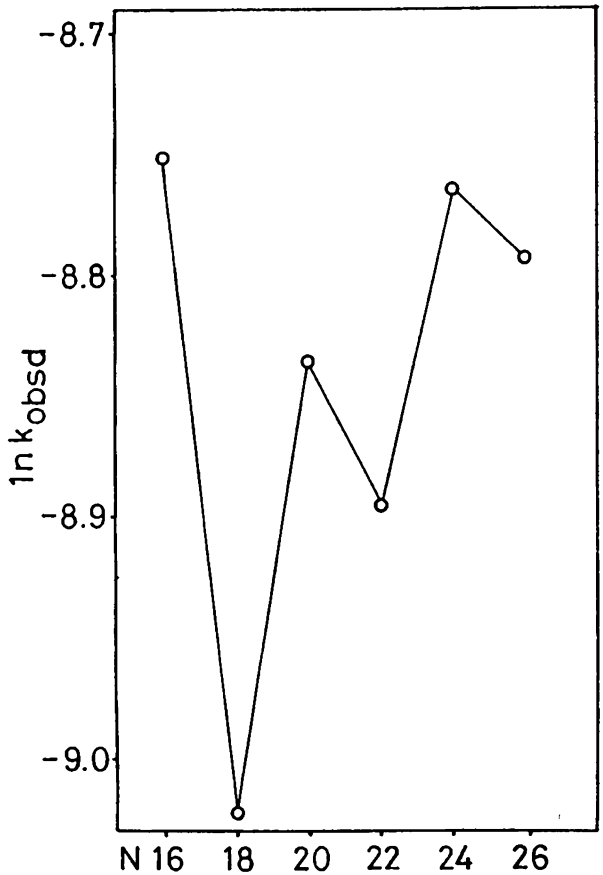


Fig. 4 Rate profiles vs ring size for the hydrolysis of dimeric acetals(3) at 30°C in 95% dioxane-0.1 N hydrochloric acid(v/v). Observed rate constants(k_{obsd}) were determined according to eq. 3 and had values of 1.58×10^{-4} (dm^3/mol) (3d), 1.21×10^{-4} (3e), 1.45×10^{-4} (3f), 1.37×10^{-4} (3g), 1.56×10^{-4} (3h), and 1.52×10^{-4} (3i).

2-3. Experimental Section

All melting points were taken with a Laboratory Devices Mel-Temp instrument and are uncorrected. Infrared spectra were recorded on a Hitachi 260-10 spectrometer. Proton NMR spectra were taken at 90 MHz on a Varian EM-390 spectrometer. Mass spectral data were obtained with a Hitachi RMU-6E mass spectrometer at ionization potential of 70 eV. Molecular weights were obtained with a CORONA 117 Molecular Weight Apparatus. High-performance liquid chromatography(HPLC) analyses were accomplished with a JASCO high-pressure liquid chromatograph equipped with a 10cm x 1cm radial pack chromatography cartridge of octadesyl silane(Waters Associates, INC.)

Materials.

Diphenyldiazomethane(DDM) was synthesized according to the method described by Smith and Howard;[17] mp 29-30°C(from light petroleum). DDQ and all α,ω-diols were commercial origin. DDM, DDQ, and solid diols were dried in vacuo just before use. Oily diols were allowed to stand for several weeks over molecular sieves(4A). Benzene was refluxed over lithium aluminum hydride and fractionated. The 1,4-dioxane was refluxed over sodium for several days and fractionated.

Reaction of DDM with DDQ in the Presence of α,ω-Diols

General procedure was represented in the case of 1,5-pentanediol. The synthetic procedure for 1,2-ethanediol to 1,4-butanediol was described elsewhere.[8] To a stirred sus-

pention of DDQ(1.18g,5.2mmol) and 1,5-pentanediol(0.54g, 5.2mmol) in benzene(20ml) was added dropwise over 10 min at 20-25°C a benzene solution(10ml) of DDM(1.0g,5.2mmol). The DDM immediately reacted with DDQ accompanying the vigogous evolution of N_2 and the precipitation of $DDQH_2$. After the mixture was stirred for 2 hr, the $DDQH_2$ was filtered off and was washed with benzene(20mlx3). The filtrate parts and washing were combined, washed with 5% aquaous sodium carbonate (10mlx5) and then with NaCl saturated water(10mlx5), dried over anhydrous sodium sulfate, and concentrated in vacuo to give a pasty residue. The residue was chromatographed on alumina(300 mesh). Successive elution gave monomeric acetal (2d,296mg,21%), dimeric acetal(3d,240mg,18%), trimeric acetal (4d,12mg,0.9%), and benzophenone(140mg,15%) with light petroleum-benzene mixture(1:20-1:1), and noncyclic acetal(5d,260mg, 30%) with benzene-methanol(100:1). In the case of 1,6-hexanediol, 1,8-octanediol, 1,10-decanediol, and 1,12-dodecanediol, dimeric acetal were partly filtered off together with $DDQH_2$, however these dimers were cleanly recovered by dissolving $DDQH_2$ in a minimum amount of acetone. The structures of monomeric, dimeric and trimeric cyclic acetals were determined by IR, NMR, mass spectra and elemental analyses.

2,2-Diphenyl-1,3-dioxolane(2a): mp 54-55°C(from ether); IR (KBr) 2800, 1450, 1085, 1000cm^{-1}; NMR($CDCl_3$) δ 4.0(s,CH_2,4H), 7.1-7.6(m,aromaticH,10H);MS *m/e* 226(M^+). Anal. Calcd for $C_{15}H_{14}O_2$:C,79.62;H,6.24. Found:C,79.68;H,6.24.

2,2-Diphenyl-1,3-dioxane(2b): mp 113-115°C(from ether); IR

(KBr) 2970, 1450, 1100, 1005cm^{-1}; NMR($CDCl_3$) δ 1.7-2.0(m,CH_2, 2H), 4.03(t,OCH_2,J=6.0Hz,4H), 7.1-7.7(m,aromaticH,10H);MS *m/e* 240(M^+). Anal. Calcd for $C_{16}H_{16}O_2$:79.96;H,6.72. Found: C,79.88;H,6.65.

2,2-Diphenyl-1,3-dioxepane(2c): mp 124-126°C(from ether); IR (KBr) 2880, 1450, 1090, 700cm^{-1}; NMR($CDCl_3$) δ 1.5-1.8(m, CH_2CH_2,4H), 3.6-3.9(m,OCH_2,4H), 7.1-7.7(m,aromaticH,10H);MS *m/e* 254(M^+). Anal. Calcd for $C_{17}H_{18}O_2$:C,80.28;H,7.13. Found: C,80.19;H,7.03.

2,2-Diphenyl-1,3-dioxocane(2d): mp 41-42°C(from ether); IR (KBr) 2920, 1440, 1090, 1025cm^{-1}; NMR($CDCl_3$) δ 1.5-1.8(m, $(CH_2)_3$,6H), 3.55(t,OCH_2,J=6.3Hz,4H), 7.0-7.6(m,aromaticH,10H); MS *m/e* 268(M^+). Anal. Calcd for $C_{18}H_{20}O_2$:C,80.56,H,7.51. Found:C,80.79;H,7.49.

2,2,10,10-Tetraphenyl-1,3,9,11-tertaoxacyclohexadecane(3d): mp 217-218(from benzene); IR(KBr) 2930, 1440, 1080, 1020cm^{-1}; NMR($CDCl_3$) δ 1.2-1.9(m,$(CH_2)_3$,12H), 3.23(t,OCH_2,J=6.0Hz,8H), 7.0-7.7(m,aromaticH,20H);MS *m/e* 536(M^+). Anal. Calcd for $C_{36}H_{40}O_4$:C,80.56;H,7.51. Found:C,80.60;H,7.50.

2,2,11,11-Tetraphenyl-1,3,10,12-tetraoxacyclooctadecane(3e): mp 241-243°C(from $CHCl_3$); IR(KBr) 2930, 1445, 1090, 1020cm^{-1}; NMR($CDCl_3$) δ 1.3-1.9(m,$(CH_2)_4$,16H), 3.21(t,OCH_2,J=7.5Hz,8H), 7.1-7.6(m,aromaticH,20H);MS *m/e* 564(M^+). Anal. Calcd for $C_{38}H_{44}O_4$:C,80.81;H,7.85. Found:C,80.63;H,7.86.

2,2,12,12-Tetraphenyl-1,3,11,13-tetraoxacycloeicosane(3f): mp 181-183°C(from benzene); IR(KBr) 2930, 1445, 1090, 1025 cm^{-1}; NMR($CDCl_3$) δ 1.2-1.8(m,$(CH_2)_5$,20H), 3.21(t,OCH_2,J=6.6Hz, 8H), 7.2-7.7(m,aromaticH,20H);MS *m/e* 592(M^+). Anal. Calcd for

$C_{40}H_{48}O_4$:C,81.04;H,8.16. Found:C,81.05;H,8.14.

2,2,13,13-Tetraphenyl-1,3,12,14-tetraoxacyclodocosane(3g): mp 220-222°C(from benzene); IR(KBr) 2940, 1445, 1090, 1030 cm^{-1}; NMR($CDCl_3$) δ 1.1-1.9(m,$(CH_2)_6$,24H), 3.23(t,OCH_2,J=6.3Hz, 8H), 7.0-7.6(m,aromaticH,20H);MS *m/e* 620(M^+). Anal. Calcd for $C_{42}H_{52}O_4$:C,81.25;H,8.44. Found:C,81.43;H,8.45.

2,2,14,14-Tetraphenyl-1,3,13,15-tetraoxacyclotetracosane(3h): mp 103-104°C(from $CHCl_3$); IR(KBr) 2920, 1445, 1090, 1020cm^{-1}; NMR($CDCl_3$) δ 1.2-1.9(m,$(CH_2)_7$,28H), 3.19(t,OCH_2,J=6.8Hz,8H), 7.1-7.7(m,aromaticH,20H);MS *m/e* 648(M^+). Anal. Calcd for $C_{44}H_{56}O_4$:C,81.44;H,8.70. Found:C,81.31;H,8.71.

2,2,15,15-Tetraphenyl-1,3,14,16-tetraoxacyclohexacosane(3i): mp 171-172°C(from $CHCl_3$); IR(KBr) 2930, 1450, 1085, 1020cm^{-1}; NMR($CDCl_3$) δ 1.1-1.8(m,$(CH_2)_8$,32H), 3.20(t,OCH_2,J=6.2Hz,8H), 7.1-7.6(m,aromaticH,20H);MS *m/e* 676(M^+). Anal. Calcd for $C_{46}H_{60}O_4$:C,81.61;H,8.93. Found:C,81.79;H,8.99.

2,2,17,17-Tetraphenyl-1,3,16,18-tetraoxacyclotriacosane(3j): mp 85-86°C(from $CHCl_3$); IR(KBr) 2920, 1445, 1090, 1020cm^{-1}; NMR($CDCl_3$) δ 1.1-1.8(m,$(CH_2)_{10}$,40H), 3.20(t,OCH_2,J=6.5Hz,8H), 7.1-7.7(m,aromaticH,20H);MS *m/e* 733(M^+). Anal. Calcd for $C_{50}H_{68}O_4$:C,81.92;H,9.35. Found:C,81.62;H,9.37.

2,2,10,10,18,18-Hexaphenyl-1,3,9,11,17,19-hexaoxatetracosane (4d): mp 76-79°C(from benzene-pentane); IR(KBr) 2940, 1450, 1080, 1020cm^{-1}; NMR($CDCl_3$) δ 1.1-1.9(m,$(CH_2)_3$,18H), 2.9-3.4 (m,OCH_2,12H), 6.9-7.7(m,aromaticH,30H);MS *m/e* 804(M^+); M.W.: 834(Calcd 804). Anal.Calcd for $C_{54}H_{60}O_6$:C,80.56;H,7.51. Found: C,80.60;H,7.59.

The resinous noncyclic acetals showed the characteristic IR absorption assignable to hydroxyl groups(3350-3370cm^{-1}) and ethereal bonds(1000-1200cm^{-1}). The NMR spectra of these compounds revealed the presence of aromatic rings($CDCl_3$, δ=7.1-7.6 ppm), hydroxyl groups(2-3 ppm), and $-CH_2OH$(3.5-3.7 ppm). It is difficult to purify these resinous products so that further structural evidence was offered by the conversion into dimeric acetal when treated with excess DDM and DDQ(vide infra).

Reaction of DDM with DDQ Followed by Addition of 1,12-Dodecanediol

To a suspention of DDQ(1.18g,5.2mmol) in benzene(20ml) was added dropwise over 10 min at 20°C a benzene solution (10ml) of DDM(1.0g,5.2mmol). Introduction of equiv of powdered diol was made step by step over 1 hr, causing gradually the precipitation of $DDQH_2$. After 1 hr stirring, usual work-up of the reaction mixture provided (3j)(0.35g,18%) and (5j)(0.65g,44%).

Conversion of Noncyclic Acetals(5) into Dimeric Cyclic Acetals

This conversion was demonstrated in the case of noncyclic acetal(5g) of 1,8-octanediol by use of 2 equiv of DDM and DDQ. To a suspention of DDQ(0.59g,2.6mmol) and (5g)(0.6g,1.3mmol) in benzene(10ml) was added dropwise over 10 min at 20°C a benzene solution(5ml) of DDM(0.5g,2.6mmol). After the mixture was stirred for 2 hr, usual work-up gave (2g) in 80% yield.

The successful conversion of other noncyclic acetals also provided the corresponding dimeric acetals in over 60-80% yields.

Acid Catalyzed Hydrolysis of Dimeric Acetals(3d-i)

Kinetic measurements were made by monitoring the decrease in the respective absorption of (3d-i) at 254nm by means of HPLC with methanol as an eluent. Dimeric acetals showed the relative retention times respectively (3d,1.0), (3e,1.2), (3f,1.8), (3g,2.5), (3h,3.3), and (3i,4.8). Dilute solutions in dioxane was prepared for (3d-i) in a volumetric flask(25ml) and analyzed by HPLC in order to determine the relative calibration factors of each dimer. The concentration of dimeric acetals was in the range, 1.20 to 1.61×10^{-4} mol/dm^3. The reaction was initiated by quickly mixing this acetal solution (5ml), dioxane(4.5ml) and 0.1N hydrochloric acid(0.5ml) at 30°C in a stoppered vessel. Temperature was kept at 30°C with a Haake Model FE constant temperature circulating bath. At regular time intervals(10 min), one milliliter aliquots were nutralized with alkaline(CH_3ONa) methanol(1ml) and analyzed by HPLC. Then a known amount of (3d) in dioxane(1ml) was introduced into the stopped reaction solution as an internal standard and the mixture was again analyzed by HPLC. Combination of these two data make it possible to evaluate the net concentration of each dimer at a given time. A pseudo-first order treatment of these analytical data gave the observed rate constants(k_{obsd}) for each of (3d-i) according to eq. 3.

$$- \frac{d[3]}{dt} = k[H^+][3] = k_{obsd}[3] \qquad \text{eq. 3}$$

2-4. Summary

Macrocyclic acetals possessing a diphenylmethylene moiety were synthesized from the reaction of diphenyldiazomethane with 2,3-dichloro-5,6-dicyanobenzoquinone in the presence of α,ω-diols. The lower diols from 1,2-ethanediol to 1,4-butanediol provided only monomeric 5-7 ring acetals with 1:1 composition of diphenylmethylene/diol moiety, while 1,5-pentanediol gave monomeric, dimeric, and trimeric cyclic acetals along with noncyclic 1:2 compositional acetals. On the other hand, 1,6-hexanediol and higher homologues afforded dimeric 18-30 ring acetals together with noncyclic acetals. The product ratios of dimeric to noncyclic acetals changed alternately depending on the chain length of diols. Alternating properties were also noticed in the melting points and the rate constants of the acid catalyzed hydrolysis of dimeric acetals. These results were interpreted in terms of the ring strain of the acetals.

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Chapter 3

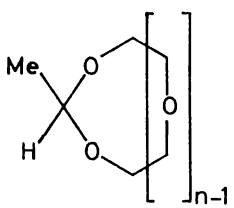
ACID CATALYZED HYDROLYSIS OF BENZOPHENONE CROWN ETHER ACETALS AND ANALOGOUS OPEN CHAIN ACETALS

3-1. Introduction

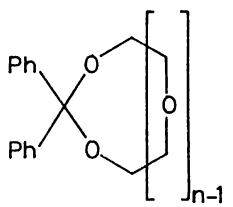
The hydrolysis of acetals was received much attention in recent years.[1,2] The generally accepted mechanism involves a fast pre-equilibrium protonation of the acetal, an unimolecular rate-determining decomposition of the conjugate acid(SH^+) to a resonance-stabilized oxocarbenium ion(C^+), and the subsequent multi step degradation into carbonyl compound and alcohol by the action of water.

One part of the experimental evidences for the above A1 mechanism is provided from the investigation of the structure reactivity relationship.[1] A great deal of information has been collected for the polar effects in the hydrolyses of cyclic or open chain acetals having the substituents on the carbonyl or alkyl moieties.[1] However, only one case is known for the hydrolysis of cyclic acetals with polyoxyethylene moiety(1), so-called crown ether acetals, probably because of the difficulty in the synthesis.[3] Recently, the author found the facile synthetic methods of benzophenone crown ether acetals(2) by means of the reaction of diphenyldiazomethane (DDM) with 2,3-dichloro-5,6-dicyanobenzoquinone(DDQ) under the influence of oligoethylene glycols.[4] This situation prompted

the author to report the results for the hydrolysis of the titled crown ether acetals and to compare the reactivities with those of the corresponding acetals of acetoaldehyde(1). Hydrolysis of the noncyclic acetals(3) was also made in the same conditions to know the effects of structural change in the oxyethylene unit moiety on the hydrolytic behavior of these acetals.

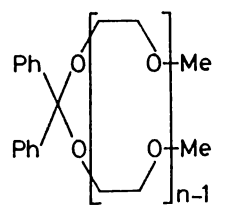


1a-f



2a-g

a ; n=1 e ; n=5
b ; n=2 f ; n=6
c ; n=3 g ; n=7
d ; n=4



3a-d

3-2. Results and Discussion

The rate constants and the activation parameters for the HCl-catalyzed hydrolysis of 2,2-diphenyl-1,3-dioxolane(2) and benzophenone crown ether acetals(2b-g) and open chain acetals (3a-d) with oxyethylene units in 80% dioxane-water are collected(Table I).

In the case of cyclic acetals of 5-23 membered rings, rate constants rise rapidly with increasing ring size, reach a maximum in 17 membered ring, and finally decrease moderately with further increasing ring size. In the open chain acetals, however, a marked effect of chain length was not observed though the number of oxyethylene units varied from 0 to 6. Similar hydrolytic behavior as observed for the benzophenone

Table I Rate Constants(k) and Activation Parameters for the Hydrolysis of 2a-g and 3a-d in 80% Dioxane-Water

acetal	number of oxygen atoms (N)	10^2k(dm^3/mol·s) 20°C	30°C	40°C	50°C	$\Delta H^{\ddagger}$(kJ/mol) a)	$\Delta S^{\ddagger}$(J/mol·K) a)
2a	2	0.30	0.97	3.36		88.9	12.9
2b	3		2.92	10.2	30.6	93.2	33.1
2c	4		14.2	45.6	146	92.3	43.1
2d	5		13.8	43.8	131	89.1	32.3
2e	6		34.0	103	277	83.0	19.7
2f	7		17.7	57.2	169	89.3	35.1
2g	8		11.6	35.6	107	88.2	28.1
3a	2		7.01	23.3	77.8	95.5	47.8
3b	4		3.50	12.0	39.8	96.6	45.7
3c	6		6.79	22.1	67.7	91.1	33.1
3d	8		7.62	23.8	71.4	88.6	25.9

a) Values at 30°C.

cyclic acetals has been given by Gold et al. for the HCl-catalyzed hydrolysis of acetoaldehyde crown acetals(1a-f) with 1-6 oxyethylene units in 60% dioxane-water.[3] As seen in the plots of log k vs number of oxygen atoms(Fig. 1), both series

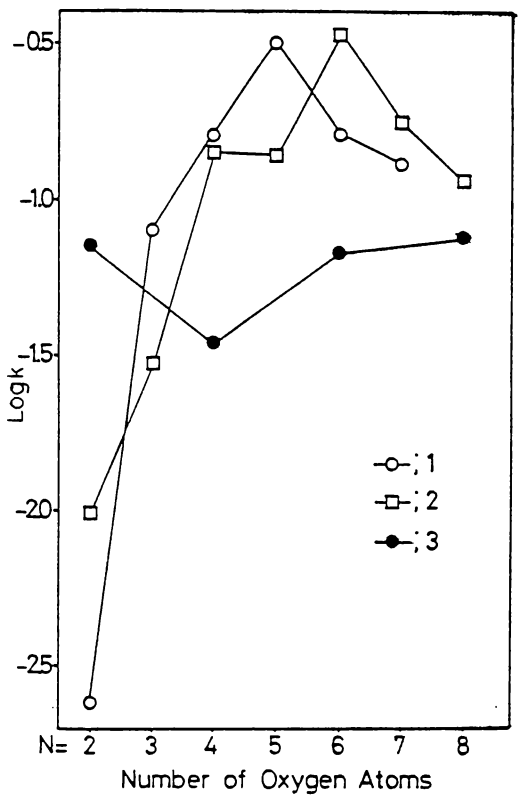


Fig. 1 Plots of log k vs number(N) of oxygen atoms for hydrolyses of crown ether acetals(1a-f and 2a-g) and open chain acetals(3a-d). Log k were calculated by using the values in 60% dioxane-water at 25°C for (1) and in 80% dioxane-water at 30°C for (2) and (3).

of these crown ether acetals exhibited very similar dependence of rates on the ring size except that the maximum rate for the acetoaldehyde series was obtained in one oxyethylene unit shorter acetal, 14 membered ring, than in the benzophenone acetals. They did not mention the reason of this rate profile

with maximum rate in 14 membered ring size. The author wants to describe the effects of the number of oxyethylene units on the hydrolysis reactivity of the benzophenone acetals by considering the contribution of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ on the rate constants.

As shown in Fig. 2, compensation relationships are generally found between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for both the crown and the open chain acetals. Interestingly, crown acetals showed sudden decrease of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in 17 membered ring, which has the maximum rate in the series, except for 5 membered one. This is the marked difference from the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ profiles for open

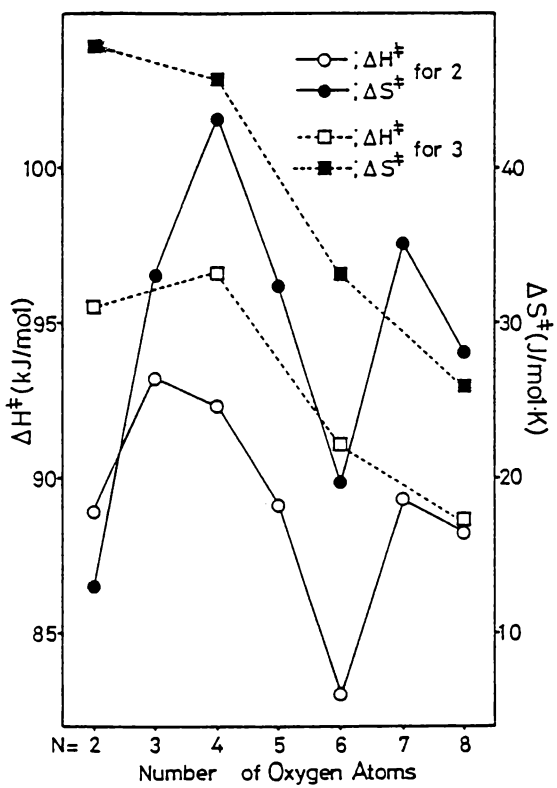
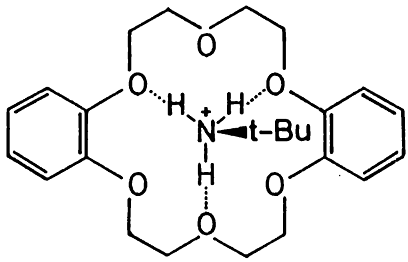


Fig. 2 Plots of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ vs number(N) of oxygen atoms for hydrolyses of (2a-g) and (3a-d) at 30°C.

chain acetals(3a-d), where these parameters substantially decreased monotonously with the increasing chain length.

Generally, in the hydrolysis of benzophenone acetals, the oxocarbenium ion intermediate(C^+) is stabilized by substantial negative inductive effects of *gem*-diphenyl group and this makes the transition state closer to the conjugate acid (SH^+) according to Hammond postulate.[1,5] This is the case of our crown ether acetals. As a characteristic property, crown acetals, especially 17 membered (2e) are expected to incorporate a H_3O^+ in the light of the fact that dibenzo-18-crown-6 forms a more stable complex with H_3O^+ than with K^+.[6] In addition, various 18-crown-6 are known to produce a stable tripod structure(4) with t-$BuNH_3^+$ as exemplified for dibenzo-18-crown-6.[7] Accordingly, it is reasonable to assume that



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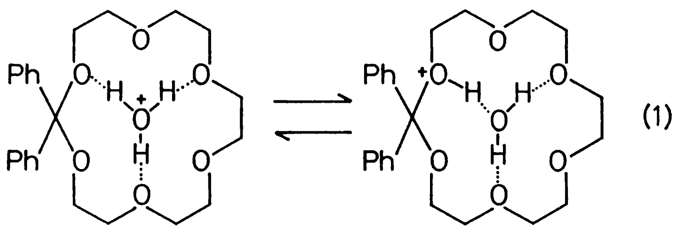
our crown acetals build up similar three hydrogen bonded structure as illustrated for (2e)(eq. 1). This hydronium ion



SH_3O^+ SH^+

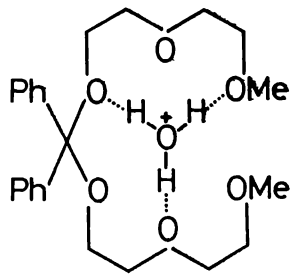
complexed acetal(SH_3O^+) may be in rapid equilibrium with the conjugate acid form(SH^+)(eq. 1). This SH_3O^+ has an ordered

structure and is to be highly stabilized. Thus, low $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for (2e) may be due to some contribution of these stable and ordered protonated structures to the conjugate acis, which is close to the transition state as mentioned above. On the other hand, the relatively low $\Delta H^{\ddagger}$ and very small $\Delta S^{\ddagger}$ for 5 membered ring(2a) may be attributed to the ring strain and the restrictive freedom in the transition state due to small ring size.

In the case of 8, 11, 14, 20, and 23 membered ring acetals, the template ability toward H_3O^+ must be reduced on account of the smaller or larger ring sizes compared to the 17 membered ring. In the case of Gold's series, the maximum rate constant is observed in just one oxyethylene unit shorter acetal(1d) compared to the benzophenone acetals. If the same explanation mentioned above could be applied to Gold's acetals, the 17 membered acetoaldehyde acetal should be most easily hydrolyzed. The author has no apparent interpretation for this discrepancy,[8] however, it may be possible that Gold's 14 membered acetal forms more stable and ordered structure with H_3O^+ because of the loss of bulky *gem*-diphenylgroup which will introduce steric hindrance and hydrophobicity in the crown ring, interfering the interaction with H_3O^+.

As for the open chain acetals, both the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, which generally decreased with the increasing chain length, contributed to the free energies in such a way that the rates were little affected by the almost equal compensation. The simple decrease of these parameters is also indicative of the same participation of a stable and ordered hydronium ion in-

corporated structure(5) in the transition states of relatively long-chained acetals as illustrated for the cyclic acetal (2e). But the lack of the bottom in (3c), which has the same 6 oxygen atoms as (2e) implies that this tripod conformation is also possible even in more long chain(3d).



5

By considering the marked drop in the complexing ability of open chain structure toward RNH_3^+ compared to the corresponding cyclic counterpart, however, it can not be excluded that the transition state is much more stabilized by the pronounced solvation of waters in going from (3a) to (3d), which leads to the smaller $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values.

3-3. Experimental Section

Materials

Cyclic and noncyclic benzophenone acetals (2a-g) and (3a-d) were prepared by means of reaction of diphenyldiazomethane and 2,3-dichloro-5,6-dicyanobenzoquinone under the influence of corresponding oligoethylene glycols, oligoethylene glycol monomethyl ethers and methanol.[4,9] General procedures were mentioned in chapter 1 and 2. The structures of newly prepared (2g) and (3b) were confirmed by IR, NMR, mass

spectrum and elemental analyses.

2,2-Diphenyl-23-crown-8(2g): colorless oil; 58% yield; IR(neat) 2870, 1450, 1210, 1100, 1020,700cm^{-1}; NMR($CDCl_3$) δ 3.3-3.8(m,OCH_2CH_2O,28H), 7.1-7.6(m,aromaticH,10H);MS *m/e* 490 (M^+). Anal. Calcd for $C_{27}H_{38}O_8$:C,66.10;H,7.81. Found:C,66.24; H,7.87.

6,6-Diphenyl-2,5,7,10-tetraoxaundecane(3b): colorless oil; 46% yield; IR(neat) 2880, 1450, 1210, 1090, 700cm^{-1}; NMR($CDCl_3$) δ 3.3-3.7(m,OCH_2CH_2O,14H), 7.1-7.6(m,aromaticH,10H); MS *m/e* 241(M-$OCH_2CH_2OCH_3$). Anal. Calcd for $C_{19}H_{24}O_4$:C,72.12; H,7.65. Found:C,71.92;H,7.42.

The analytic data of other benzophenone acetals are collected in chapter 1 and 2.

Kinetic Measurements

The rates of hydrolysis of (2b-g) and (3a-d) were measured in 80% dioxane-water(v/v) at a constant acid(HCl) concentration(4.0×10^{-3} mol/dm^3). In the case of hydrolysis of (2a) was used 2.0×10^{-1} mol/dm^3 HCl solution in the same mixed solvent. The rates were measured spectrophotometrically with a JASCO UVIDEC 505 spectrophotometer by following the increase in absorption due to the benzophenone(λ_{max}=340nm). The reactions were generally followed up to 80% completion. The pseudo-first-order rate constants(k_{obsd}) were obtained from the slopes of plots of $\ln[A_\infty-A_t]$ against time. The second-order rate constants(k) were obtained by dividing k_{obsd} with activity of H^+(a_{H^+}=0.00102 mol/dm^3 and 0.0104 mol/dm^3, respectively for the low and high HCl solutions), calculated ac-

cording to Debye-Hückel equation.[10] Constant temperature was maintained in the kinetic runs by circulating water from a Haake Model FE constant temperature circulating bath.

3-4. Summary

Kinetic studies have been made of the acid cataltzed hydrolysis of 2,2-diphenyl-1,3-dioxolane(2a) and its higher cyclic derivatives with 2-7 oxyethylene units, the crown ether acetals(2b-g), and of the benzophenone dimethyl acetal(3a) and its open chain derivatives with 2,4, and 6 oxyethylene units in 80% dioxane-water at 30, 40, and 50°C. In the crown ether acetals, rate constants generally increased with the increasing ring sizes from 5 to 17 membered ring, but gently decreased in more larger 20 and 23 membered rings, whereas the open chain acetals exhibited the rates of almost same order. The especial rate enhancement in the 17 membered ring acetal was discussed in terms of the template effect of the macrocyclic ring toward hydronium ion.

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Chapter 4

ACID CATALYZED HYDROLYSIS OF CYCLIC BENZOPHENONE ACETALS

4-1. Introduction

There have been numerous investigations on the acid catalyzed hydrolysis of acetals from a mechanistic point of view.[1,2,3] However, little is known about the cyclic benzophenone acetals, especially with six membered and higher ring sizes,[4] probably because of difficulties in a synthesis by traditional methods.[5]

In Chapter 3, the author reported the acid catalyzed hydrolysis of 8-23 membered ring benzophenone crown ether acetals and discussed the rate dependences on the ring and the number of oxygen atoms in term of the complexing abilities of these acetals toward hydronium ion. But there has been few investigations about the effects of polymethylene ring size on the hydrolysis rates of cyclic acetals.

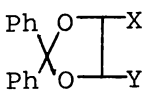
In this Chapter, the author reports the results for the hydrolysis of cyclic benzophenone acetals with polymethylene chain in the ring and discusses the effects of ring size and methyl groups substituted to methylene chain on the hydrolysis rates in terms of ring strain, stereoelectronic effect, hydrophobicity, and steric hindrance. Hydrolysis of six membered cyclic acetals of substituted benzophenones also made to obtain further information concerning the structure-reactivity

relationship.

4-2. Results and Discussion

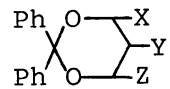
Effects of Ring Size

The rates and activation parameters for acid catalyzed hydrolysis of various 5 to 8 membered cyclic benzophenone acetals were determined in 80% dioxane-water(Table I).



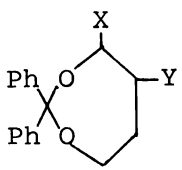
1a-d

a;X=Y=H
b;X=Me,Y=H
c;X=Y=Me(cis)
d;X=Y=Me(trans)
e;X,Y=$-(CH_2)_4-$(cis)
f;X,Y=$-(CH_2)_4-$(trans)

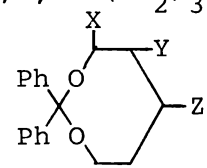


2a-g

a;X=Y=Z=H
b;X=Me,Y=Z=H
c;X=Z=H,Y=Me
d;X=Z=Me,Y=H(cis)
e;X=Z=Me,Y=H(trans)
f;X=Z=H,Y=2Me
g;X,Z=$-(CH_2)_3-$,Y=H(cis)



3a-c
a;X=Y=H
b;X=Me,Y=H
c;X=H,Y=Me



4a-d
a;X=Y=Z=H
b;X=Me,Y=Z=H
c;X=Z=H,Y=Me
d;X=Y=H,Z=Me

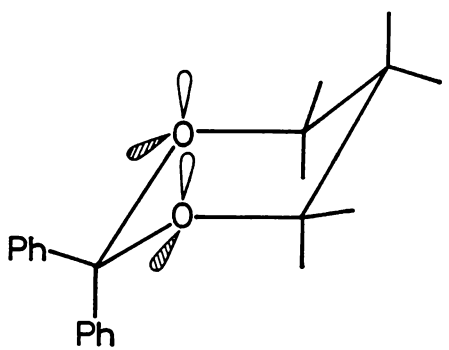
In the case of unsubstituted acetals of 5-8 membered rings, rate constants increase with increasing ring size; 8 membered ring hydrolyzed 35 times faster than 5 membered ring. This result can be explained in terms of ring strain and stereoelectronic effect.[6] A smooth hydrolysis demands antiperiplanar orientation of the C-O bond to be cleaved with the assisting lone pair of electrons of the unprotonated oxygen. In 6, 7, and 8 membered rings, the electron pair orbital on

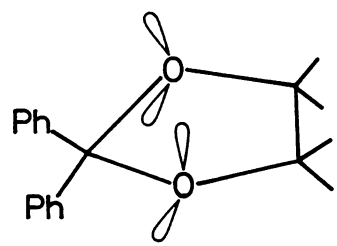
Table I Rate Constants(k) and Activation Parameters for Hydrolysis of Cyclic Benzophenone Acetals in 80% Dioxane-Water

	10^3k(dm^3/mol·s)				$\Delta H^{\neq}$(kJ/mol)[a]	$\Delta S^{\neq}$(J/mol·K)[a]
	20°C	30°C	40°C	50°C		
1a	3.00	9.69	33.5		89.9	12.9
1b		1.11	3.57	11.7	93.2	5.72
1c		0.250	0.749	2.33	88.5	-22.2
1d		0.0412	0.152	0.520	100.6	2.69
1e		1.02	3.29	8.40	83.6	-26.6
1f		118	321	792	75.0	-15.3
2a	13.1	47.4	170		95.4	44.2
2b		6.26	22.3	70.3	96.0	29.4
2c		15.5	44.8	139	87.0	7.22
2d		0.154	0.665	2.15	104.9	27.8
2e		14.2	45.7	135	89.1	13.6
2f		4.51	15.4	45.2	91.4	11.4
2g	369	1170	3460		82.5	28.5
3a		136	395	1030	79.9	1.96
3b		41.6	123	395	89.1	22.3
3c		38.6	124	394	92.1	31.7
4a		338	880	1980	69.6	-24.6
4b		427	1130	2480	69.2	-23.7
4c		235	666	1890	82.3	14.3
4d	62.0	210	635		86.3	26.6

a) Values at 30°C.

the nonleaving oxygen atom would be almost antiperiplanar with respect to the C-O bond to be cleaved. Therefore, the acceleration by such stereoelectronic effects is to the same extent in every case. On the other hand, the magnitude of ring strain increases with increasing ring sizes from 6 to 8, which results increase of rate constants. This is in harmony with the decrease in $\Delta H^{\neq}$. While in the case of 5 membered ring, which is more strained than 6 membered ring, the parallel orientation of the C-O bond with the lone pair would be impossible because of its rigid structure. Consequently, the rate of 5 membered acetal results smaller than that of 6 membered acetal.





While,6 membered 2,2-diphenyl-1,3-dioxane(2a) has maximum $\Delta H^{\neq}$ and $\Delta S^{\neq}$. As shown in Fig. 1, compensation relationships are generally found between $\Delta H^{\neq}$ and $\Delta S^{\neq}$ for these unsubstituted acetals. The maximum $\Delta H^{\neq}$ and $\Delta S^{\neq}$ of 6 membered (2a) is attributable to the mostly stabilized ground state among these 5-8 membered cyclic acetals contrary to the transition state stabilized in the similar degree.

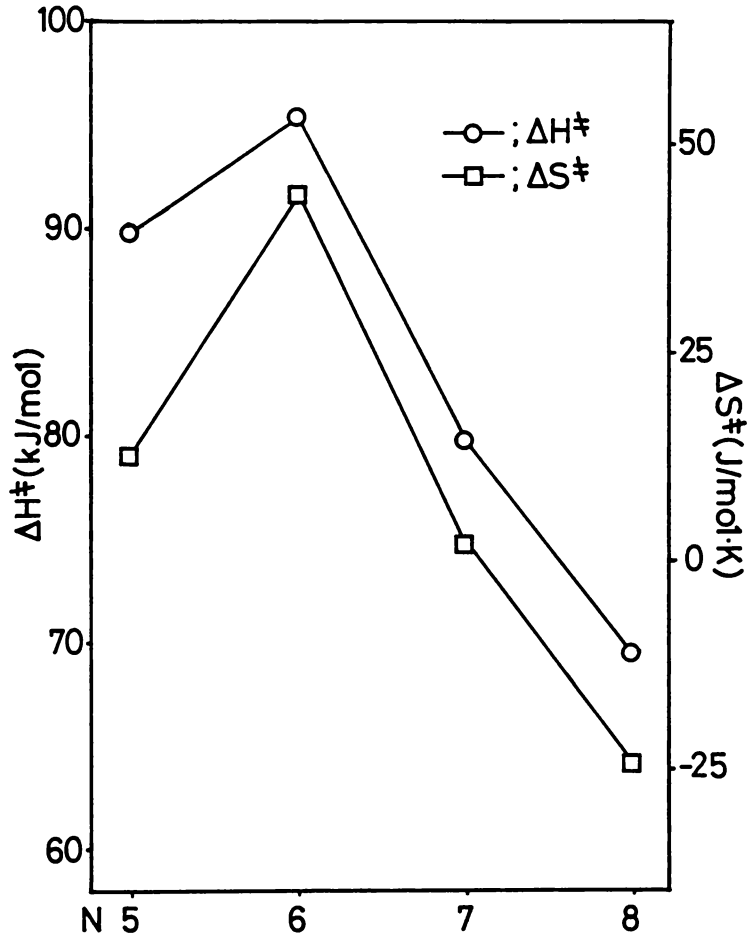


Fig. 1 Plots of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ vs number(N) of ring atoms for hydrolysis of cyclic benzophenone acetals.

Effects of Substitution of Methyl Groups to the Methylene Chain

The introduction of methyl groups to the methylene chain more or less decreased the rate except α-substituted 8 membered ring(Table I). Log k for hydrolysis of the acetals are plotted against the position of substitution in Fig. 2. This rate retardation was explained by considering the hydrophobicity and steric hindrance caused by methyl groups. These effects, both hindering the protonation, participate

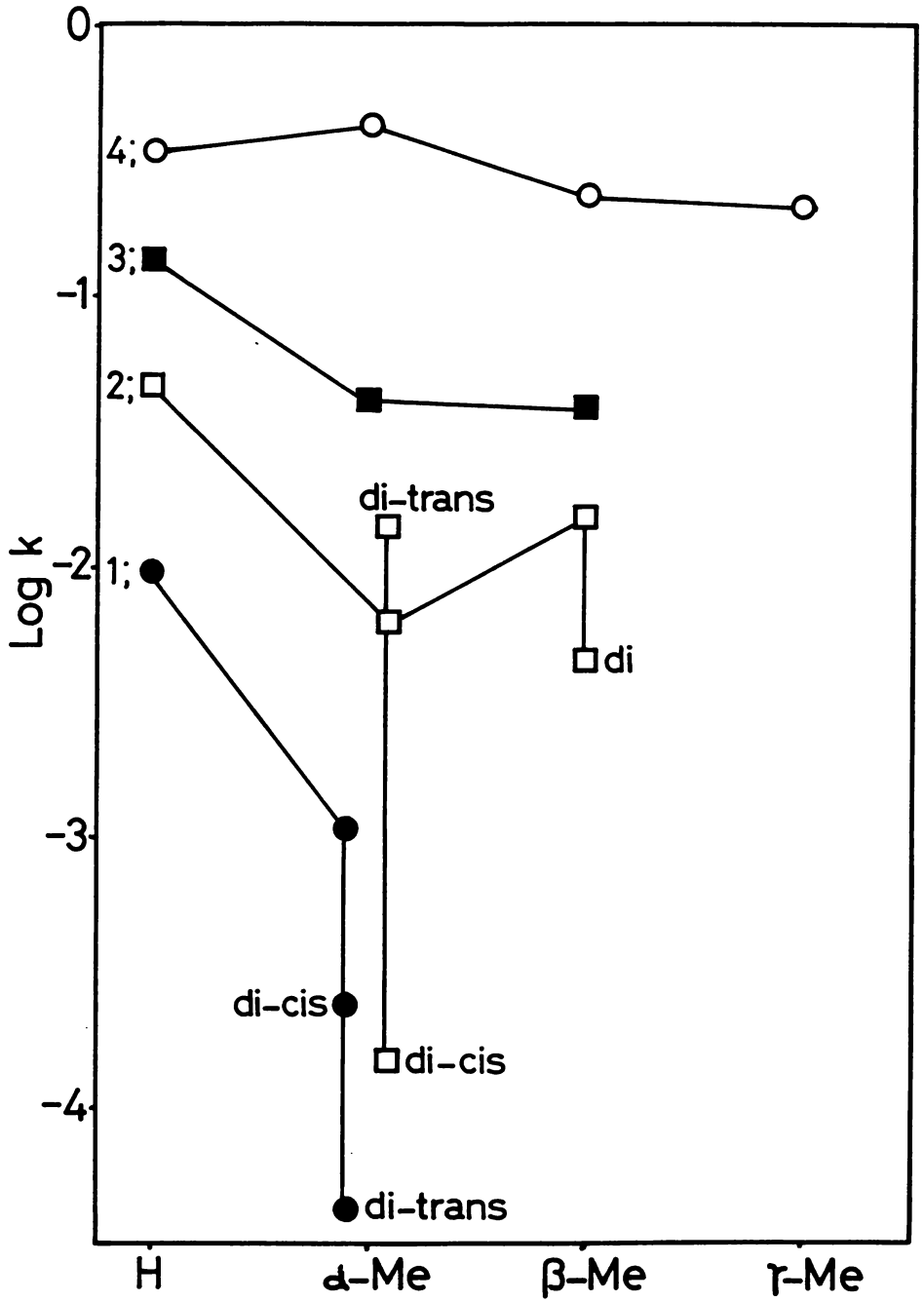
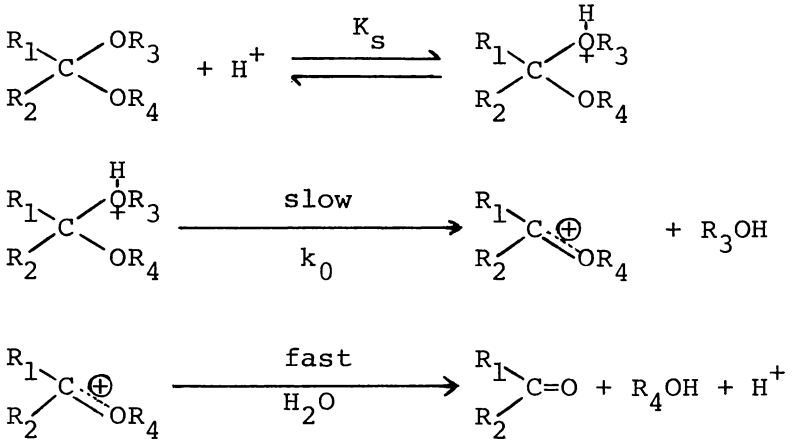


Fig. 2 Plots of log k for hydrolysis of cyclic benzophenone acetals.

in the pre-equilibrium process to result in lower K_s values mentioned in Scheme 1. Overall rate constant(k) of acid



Scheme 1

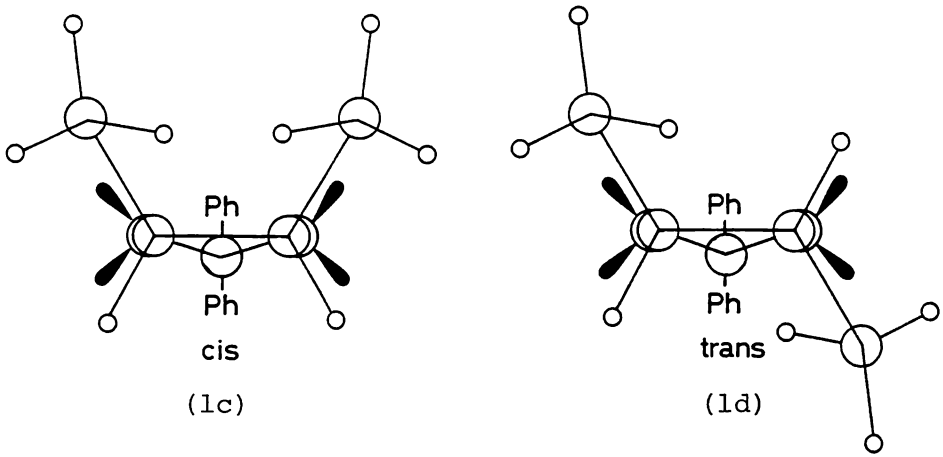
catalyzed hydrolysis of acetals is given by equation 1,

$$k = k_0 \cdot K_s \qquad (1)$$

where k_0 is the rate constant in rate determining step. Thus, steric hindrance and hydrophobicity of methyl group reduce K_s, which results in the decrease in overall rate.

The rates of α-disubstituted 5 membered acetals (1c) and (1d) are more retarded by the above mentioned effects than monosubstituted(1b). Interestingly, *cis*-form (1c) was hydrolyzed 6 times faster than *trans*-form (1d). As shown in the Newman projection(Fig. 3), one side of the ring is completely open in *cis*-form(1c), which facilitates protonation to make K_s value larger than that of *trans*-form(1d). The steric acceleration is also caused by the steric repulsion between two methyl groups which makes the k_0 value greater. While in *trans*-form (1d), methyl groups are located on both sides

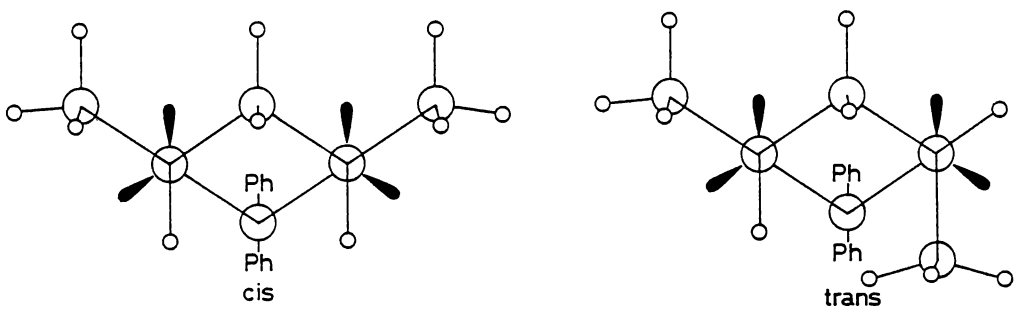
of the ring, protonation is more hindered than in *cis*-form(1c).



(1c) (1d)

Fig. 3 Newman projection of *cis*-2,2-diphenyl-4,5-dimethyl-1,3-dioxolane(1c) and *trans*-2,2-diphenyl-4,5-dimethyl-1,3-dioxolane(1d).

In contrast to the case of 5 membered acetals, as far as α-disubstituted 6 membered acetals are concerned, the hydrolysis rate of *cis*-form (2d) is 92 times smaller than that of *trans*-form (2e). According to the Newman projection of (2d) and (2e)(Fig. 4), both of the methyl groups occupied equatorial possition in (2d), while in (2e) one methyl group is in equa-



(2d) (2e)

Fig. 4 Newman projection of *cis*-2,2-diphenyl-4,6-dimethyl-1,3-dioxane(2d) and *trans*-2,2-diphenyl-4,6-dimethyl-1,3-dioxane(2e).

torial and other in axial possition. Thus, the axial methyl and the lone pair of oxygen atom are so distant that steric hindrance and hydrophobicity are not so great as in (2d). In addition, the steric repulsion between this axial methyl group and axial hydrogen atom contribute to the rate acceleration in comparison with α-monosubstituted acetal(2b) where the methyl group is in equatorial possition. On the other hand, the rate of β-monosubstituted 6 membered acetal(2c) is 2 times larger than that of (2b) because of decreased steric hindrance as well as hydrophobicity. Large rate retardation was seen in β-disubstituted (2f) on account of the *gem*-dimethyl effect which stabilizes the ring.

As for 7 and 8 membered rings, the rate constants keep the same level in α-, β-, and γ-substituted ones, this result can be explained by the fact that hydrophobic effect by a single methyl group is relatively small as the methylene chain in the ring is much longer. Rate increase found in α-substituted 8 membered ring(4b) may be due to the steric repulsion of methyl group that is in highly strained ring, increasing k_0 value.

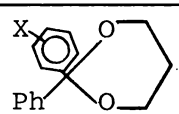
It is also noted that for the case of bicyclic acetals, *trans*-form (1f) decomposed 10^2 faster than *cis*-form (1e), because of the larger steric hindrance and hydrophobicity of the cyclohexane ring of (1e).

Bicyclic acetal (2g) exhibited the maximum rate of all acetals in this series, because notable steric repulsion between *gem*-diphenyl group and cyclohexane ring make the ring strongly destabilized.

Substituent Effects

The rates of acid catalyzed hydrolysis of eight *m*- and *p*-substituted 2,2-diaryl-1,3-dioxanes were determined in 80% dioxane-water(by volume) at 30°C(Table II). When various values of log k were correlated with the standard Hammett σ and the Brown σ^+, the σ substituent constants gave a better result(ρ= -3.10, r= 0.997) than σ^+, (ρ= -2.19. r= 0.974).

Table II Rate constants for hydrolysis of substituted 2,2-diaryl-1,3-dioxanes at 30°C.

acetal	X=	10^3k(dm^3/mol·s)
	*p*-CH_3O	491
	p-CH_3	164
	m-CH_3	66.9
	p-Ph	48.0
	H	47.4
	p-Cl	10.8
	m-Cl	2.99
	m-NO_2	0.381

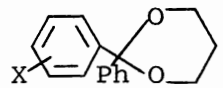
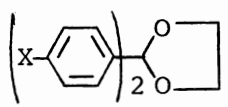
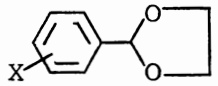
It can be corroborated, however, that the resonance substituent effects moderately contribute to the stabilization of the transition state as evaluated from the value of the resonance reaction constant(R= 0.385) in the satisfactory Yukawa-Tsuno equation.[7]

$$\log k/k_0 = -2.92(\sigma^0 + 0.385\Delta\bar{\sigma}_R^+) - 0.05$$

(n=8, r=0.999)

In Table III, the Hammett parameters have been collected for the hydrolyses of this 6 membered acetals and related 5 memebred cyclic acetals. The hydrolysis of 2,2-diaryl-1,3-dioxanes provided a larger negative ρ value, accompanied by

Table III Hammett parameters for hydrolyses of cyclic acetals.

Substrates	ρ	R	Number of substituents	Solvent	r	T(°C)	Ref.
	-2.92	0.385	8	80% dioxane	0.999	30	This work
 a)	-2.08[b]	0.240[b]	4	20% dioxane	0.998	25	8
	-3.28[b]	0.457[b]	5	50% dioxane	0.999	30	9

a) The σ^+ and σ^0 values used are the sums of the values for the two substituents.

b) Original data were treated according to Yukawa-Tsuno equation.

increased resonance effects than that of the corresponding 5 membered cyclic acetals, 2,2-diaryl-1,3-dioxolanes,[8] though a straightforward comparison is somewhat ambigous because of the change in the solvent composition. Whereas, substituted 2-aryl-1,3-dioxolanes were more subject to both polar and resonance effects than the 6 membered acetals.[9]

4-3. Experimental Section

Materials.

Cyclic benzophenone acetals were prepared by means of reaction of substituted or unsubstituted diphenyldiazomethanes and 2,3-dichloro-5,6-dicyanobenzoquinone under the influence of corresponding diols. General procedures were mentioned in Chapter 2. The structures of newly prepared acetals were confirmed by IR, NMR, mass spectrum and elemental analyses.

2,2-Diphenyl-4-methyl-1,3-dioxolane(1b): 74% yield; mp 68-69 °C(from ether); IR(KBr) 2890, 1450, 1210, 1100, 1010, 700cm^{-1}; NMR($CDCl_3$) δ 1.34(d,CH_3,J=5.7Hz,3H), 3.57(t,CH,J=7.1Hz,1H), 4.0-4.5(m,CH_2,2H), 7.1-7.7(m,aromaticH,10H);MS *m/e* 240(M^+). Anal. Calcd for $C_{16}H_{16}O_2$:C,79.96;H,6.72. Found:C,80.08;H,6.70.

cis-2,2-Diphenyl-4,5-dimethyl-1,3-dioxolane(1c): 53% yield; mp 141-142°C(from benzene-pentane); IR(KBr) 2880, 1450, 1220, 1090, 700cm^{-1}; NMR($CDCl_3$) δ 1.22(d,CH_3,J=6.3Hz,6H), 4.1-4.4 (m,CH,2H), 7.1-7.6(m,aromaticH,10H);MS *m/e* 254(M^+). Anal. Calcd for $C_{17}H_{18}O_2$:C,80.28;H,7.13. Found:C,80.33;H,7.15.

trans-2,2-Diphenyl-4,5-dimethyl-1,3-dioxolane(1d): 44% yield; mp 120°C(from ether); IR(KBr) 2870, 1450, 1225, 1090, 1000,

695cm^{-1};NMR($CDCl_3$) δ 1.2-1.5(m,CH_3,6H), 3.6-4.0(m,CH,2H), 7.1-7.7(m,aromaticH,10H);MS *m/e* 254(M^+). Anal. Calcd for $C_{17}H_{18}O_2$:C,80.28;H,7.13. Found:C,80.20;H,7.15.

cis-8,8-Diphenyl-7,9-dioxabicyclo[4,3,0]nonane(1e): 54% yield; mp 120-121°C(from benzene-pentane); IR(KBr) 2950, 1450, 1220, 1080, 1000, 700cm^{-1};NMR($CDCl_3$) δ 0.8-2.2(m,-$(CH_2)_4$-,8H), 3.8-4.4(m,CH,2H), 6.8-7.8(m,aromaticH,10H);MS *m/e* 280(M^+). Anal. Calcd for $C_{19}H_{20}O_2$:C,81.39;H,7.19. Found:C,81.35;H,7.23.

trans-8,8-Diphenyl-7,9-dioxabicyclo[4,3,0]nonane(1f): 45% yield; mp 143-144°C(from benzene-pentane); IR(KBr) 2950, 2880, 1450, 1230, 1070, 700cm^{-1};NMR($CDCl_3$) δ 0.8-2.5(m,-$(CH_2)_4$-,8H), 3.1-3.5(m,CH,2H), 6.8-7.7(m,aromaticH,10H);MS *m/e* 280(M^+). Anal. Calcd for $C_{19}H_{20}O_2$:C,81.39;H,7.19. Found:C,81.50;H,7.23.

2,2-Diphenyl-4-methyl-1,3-dioxane(2b): 78% yield; mp 91-91.5 °C(from ether); IR(KBr) 2950, 1450, 1240, 1190, 1090, 1020, 700cm^{-1};NMR($CDCl_3$) δ 1.25(d,CH_3,J=6.3Hz,3H), 1.4-2.2(m,CH_2, 2H), 3.8-4.2(m,OCH_2,CH,3H), 7.1-7.6(m,aromaticH,10H);MS *m/e* 254(M^+). Anal. Calcd for $C_{17}H_{18}O_2$:C,80.28;H,7.13. Found:C, 80.24;H,7.13.

2,2-Diphenyl-5-methyl-1,3-dioxane(2c): 40% yield; mp 111-113 °C(from ether); IR(KBr) 2950, 1450, 1240, 1100, 1020, 700cm^{-1}; NMR($CDCl_3$) δ 0.79(d,CH_3,J=8.4Hz,3H), 1.9-2.4(m,CH,1H),3.57(t, CH,J=10.4Hz,2H), 3.8-4.2(m,CH,2H), 7.1-7.7(m,aromaticH,10H); MS *m/e* 254(M^+). Anal. Calcd for $C_{17}H_{18}O_2$:C,80.28;H,7.13. Found:C,80.26;H,7.13.

cis-2,2-Diphenyl-4,6-dimethyl-1,3-dioxane(2d): 74% yield; mp 124-126°C(from ether); IR(KBr) 2970, 1450, 1190, 1120, 1040, 700cm^{-1};NMR($CDCl_3$) δ 1.30(d,CH_3,J=6.3Hz,6H),1.0-1.6(m,CH,2H),

3.7-4.2(m,CH_2,2H), 7.0-7.6(m,aromaticH,10H);MS *m/e* 268(M^+). Anal. Calcd for $C_{18}H_{20}O_2$:C,80.56;H,7.51. Found:C,80.26;H,7.55.

trans-2,2-Diphenyl-4,6-dimethyl-1,3-dioxane(2e): 74% yield; mp 133-134°C(from ether); IR(KBr) 2970, 1450, 1220, 1080, 700 cm^{-1};NMR($CDCl_3$) δ 1.27(d,CH_3,J=6.3Hz,6H), 1.64(t,CH,J=7.5Hz, 2H), 3.6-4.1(m,CH_2,2H), 7.0-7.7(m,aromaticH,10H);MS *m/e* 268 (M^+). Anal. Calcd for $C_{18}H_{20}O_2$:C,80.56;H,7.51. Found:C,80.36; H,7.51.

2,2-Diphenyl-5,5-dimethyl-1,3-dixane(2f): 55% yield; mp 81-83 °C(from ether); IR(KBr) 2940, 1450, 1200, 1100, 1020, 700cm^{-1}; NMR($CDCl_3$) δ 1.00(s,CH_3,6H), 3.60(s,CH_2,4H), 7.2-7.6(m,aromaticH,10H);MS *m/e* 268(M^+). Anal. Calcd for $C_{18}H_{20}O_2$:C,80.56; H,7.51. Found:C,80.60;H,7.54.

cis-3,3-Diphenyl-2,4-dioxabicyclo[2,2,1]nonane(2g): 62% yield; mp 138-139°C(from benzene-pentane); IR(KBr) 2950, 1460, 1250, 1210, 1140, 1020, 710cm^{-1};NMR($CDCl_3$) δ 1.0-2.7(m,-$(CH_2)_3$-,CH_2, 8H), 4.3-4.6(m,CH,2H), 7.0-7.7(m,aromaticH,10H);MS *m/e* 280(M^+). Anal. Calcd for $C_{19}H_{20}O_2$:C,81.39;H,7.19. Found:C,81.17;H,7.26.

2,2-Diphenyl-4-methyl-1,3-dioxepane(3b): 59% yield; mp 72-74 °C(from ether); IR(KBr) 2950, 1450, 1220, 1090, 1005, 710cm^{-1}; NMR($CDCl_3$) δ 1.22(d,CH_3,J=8.1Hz,3H), 1.4-1.9(m,-$(CH_2)_2$-,4H), 3.4-4.0(m,OCH_2,OCH,3H), 7.0-7.8(m,aromaticH,10H);MS *m/e* 268 (M^+). Anal. Calcd for $C_{18}H_{20}O_2$:C,80-56;H,7.51. Found:C,80.27; H,7.51.

2,2-Diphenyl-5-methyl-1,3-dioxepane(3c): 62% yield; mp 130-131°C(from ether-benzene); IR(KBr) 2950, 1450, 1210, 1090, 1030, 700cm^{-1};NMR($CDCl_3$) δ 0.83(d,CH_3,J=6.6Hz,3H), 1.1-1.2 (m,CH_2,CH,3H), 3.2-3.9(m,OCH_2,4H), 6.9-7.8(m,aromaticH,10H);

MS *m/e* 268(M^+). Anal. Calcd for $C_{18}H_{20}O_2$:C,80.56;H,7.51. Found:C,80.50;H,7.55.

2,2-Diphenyl-4-methyl-1,3-dioxocane(4b): 29% yield; mp 41-43 °C(from pentane); IR(KBr) 2930, 1440, 1200, 1110, 1040, 710 cm^{-1};NMR($CDCl_3$) δ 0.99(d,CH_3,J=6.5Hz,3H), 1.2-2.0(m,-$(CH_2)_3$-, 6H), 3.2-4.0(m,OCH,OCH_2,3H), 6.9-7.8(m,aromaticH,10H);MS *m/e* 282(M^+). Anal. Calcd for $C_{19}H_{22}O_2$:C,80.81;H,7.85. Found:C, 80.74;H,7.89.

2,2-Diphenyl-5-methyl-1,3-dioxocane(4c): 30% yield; colorless oil; IR(neat) 2940, 1450, 1210, 1110, 1070, 700cm^{-1};NMR($CDCl_3$) δ 0.81(d,CH_3,J=7.1Hz,3H), 1.1-1.2(m,-$(CH_2)_2$-,CH,5H), 3.0-3.7 (m,OCH_2,4H), 7.0-7.7(m,aromaticH,10H);MS *m/e* 282(M^+). Anal. Calcd for $C_{19}H_{22}O_2$:C,80.81;H,7.85. Found:C,80.99;H,7.92.

2,2-Diphenyl-6-methyl-1,3-dioxocane(4d): 33% yield; mp 42-44 °C(from ether); IR(KBr) 2930, 1440, 1230, 1110, 1010, 700cm^{-1}; NMR($CDCl_3$) δ 0.98(d,CH_3,J=6.9Hz,3H), 1.2-2.1(m,CH_2,CH,5H), 3.3-3.9(m,OCH_2,4H), 7.0-7.8(m,aromaticH,10H);MS *m/e* 282(M^+). Anal. Calcd for $C_{19}H_{22}O_2$:C,80.81;H,7.85. Found:C,80.89;H,7.87.

2-(*p*-Methoxyphenyl)-2-phenyl-1,3-dioxane: 62% yield; mp 52-53 °C(from benzene-pentane); IR(KBr) 2960, 1610, 1500, 1250, 1100, 1040, 700cm^{-1};NMR($CDCl_3$) δ 1.6-2.0(m,CH_2,2H), 3.76(s, OCH_3,3H), 4.00(t,CH_2O,J=5.6Hz,4H), 6.7-7.6(m,aromaticH,9H); MS *m/e* 270(M^+). Anal. Calcd for $C_{17}H_{18}O_3$:C,75.53;H,6.71. Found:C,75.69;H,6.76.

2-(*p*-Toluyl-2-phenyl-1,3-dioxane: 52% yield; mp 76-78°C(from ether); IR(KBr) 2960, 1450, 1200, 1100, 1020, 810, 700cm^{-1}; NMR($CDCl_3$) δ 1.6-1.9(m,CH_2,2H), 2.30(s,CH_3,3H), 4.00(t,OCH_2, J=5.5Hz,4H), 7.0-7.6(m,aromaticH,9H);MS *m/e* 254(M^+). Anal.

Calcd for $C_{17}H_{18}O_2$:C,80.28;H,7.13. Found:C,80.18;H,7.16.

2-(*p*-Chlorophenyl)-2-phenyl-1,3-dioxane: 55% yield; mp 60-61 °C(from pentane); IR(KBr) 2970, 1450, 1240,1100, 1020, 820, 700cm^{-1};NMR($CDCl_3$) δ 1.6-2.0(m,CH_2,2H), 4.00(t,OCH_2,J=5.6Hz, 4H), 7.1-7.6(m,aromaticH,9H);MS *m/e* 274(M^+). Anal. Calcd for $C_{16}H_{15}O_2Cl$:C,69.94;H,5.50. Found:C,70.03;H,5.53.

2-(*p*-Diphenyl-2-phenyl-1,3-dioxane: 46% yield; mp 154-156°C (from benzene-ether); IR(KBr) 2980, 1450, 1210, 1100, 1010, 695cm^{-1};NMR($CDCl_3$) δ 1.7-2.0(m,CH_2,2H), 4.08(t,OCH_2,J=5.6Hz, 4H), 7.1-7.7(m,aromaticH,14H);MS *m/e* 316(M^+). Anal. Calcd for $C_{22}H_{20}O_2$:C,83.51;H,6.37. Found:C,83.45;H,6.38.

2-(*m*-Toluyl)-2-phenyl-1,3-dioxane: 61% yield; mp 67-69°C(from pentane); IR(KBr) 2870, 1450, 1260, 1190, 1110, 1010, 710cm^{-1}; NMR($CDCl_3$) δ 1.6-1.9(m,CH_2,2H), 2.32(s,CH_3,3H), 4.00(t,CH_2O, J=5.6Hz,4H), 6.9-7.6(m,aromaticH,9H);MS *m/e* 254(M^+). Anal. Calcd for $C_{17}H_{18}O_2$:C,80.28;H,7.13. Found:C,80.19;H,7.13.

2-(*m*-Chlorophenyl)-2-phenyl-1,3-dioxane: 56% yield, mp 75-77 °C(from pentane); IR(KBr) 2950, 1570, 1460, 1240, 1190, 1100, 1010, 700cm^{-1};NMR($CDCl_3$) δ 1.5-2.0(m,CH_2,2H), 4.00(t,CH_2O,J= 5.9Hz,4H), 7.0-7.6(m,aromaticH,9H);MS *m/e* 274(M^+). Anal. Calcd for $C_{16}H_{15}O_2Cl$:C,69.94;H,5.50. Found:C,70.07;H,5.57.

2-(*m*-Nitrophenyl)-2-phenyl-1,3-dioxane: 59% yield, pale yellow oil; IR(neat) 2970, 1520, 1360, 1200, 1110, 1020, 700cm^{-1}; NMR($CDCl_3$) δ 1.4-2.2(m,CH_2,2H), 3.8-4.3(m,CH_2O,4H), 7.2-8.5 (m,aromaticH,9H);MS *m/e* 285(M^+). Anal. Calcd for $C_{16}H_{15}O_4N$: C,67.36;H,5.30;N,4.91. Found:C,67.49;H,5.38;N,4.81.

Kinetic Measurements.

The rates of hydrolysis of cyclic acetals were measured in 80% dioxane-water(by volume) at a constant acid(HCl) concentration(2.0×10^{-1} mol/dm^3). The rates were measured spectophotometrically with a JASCO UVIDEC 505 spectrophotometer by following the increase in absorption due to the substituted and unsubstituted benzophenones. The reaction were generally followed to 80% completion. The pseudo-first-order rate constants(k_{obsd}) were obtained from the slopes of plots of $\ln[A_\infty - A_t]$ against time. The second-order rate constants (k) were obtained by dividing k_{obsd} with activity of H^+(a_{H^+}), calculated according to Debye-Hückel equation. Consatnt temperature was maintained in the kinetic runs by circulating water at 30±0.05°C, from a Haake Model FE constant temperature circulating bath.

4-4. Summary

Kinetic studies have been made of the acid catalyzed hydrolysis of cyclic benzophenone acetals in 80% dioxane-water. In the unsubstituted acetals, rate constants generally increased with the increasing ring sizes from 5 to 8 membered rings. On the other hand, 6 membered 2,2-diphenyl-1,3-dioxane has maximum $\Delta S^{\neq}$ and $\Delta H^{\neq}$. The rate profile of the series was discussed in terms of the stereoelectronic effect and the strain of the rings. Seven substituents were introduced to the 6 membered 2,2-diphenyl-1,3-dioxolane and kinetic substituent effects regarding hydrolysis were studied in the same condition as unsubstituted acetals. The log k were

well correlated with the Yukawa-Tsuno equation;

$$\log k/k_0 = -2.92(\sigma^0 + 0.385\Delta\bar{\sigma}_R^+) \quad .$$

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GENERAL CONCLUSION

The following conclusion was drawn from these experimental results.

1. New compounds, monomeric and dimeric benzophenone crown ether acetals as well as noncyclic acetals were synthesized by the reaction of oligo ethylene glycols with betaine intermediate which is generated from the reaction of diphenyldiazomethane and 2,3-dichloro-5,6-dicyanobenzoquinone. Product distribution depends on the manner of addition of oligo ethylene glycols used for the reaction. With relatively small amount of oligo ethylene glycols only monomeric acetals was obtained, whole increase of relative amount of glycols resulted in production of noncyclic acetals of high yield.

2. Cyclic benzophenone acetals obtained by means of the reaction of α,ω-diols with an intermediate from the reaction of diphenyldiazomethane and 2,3-dichloro-5,6-dicyanobenzoquinone vary according to the number of methylene chain of α,ω-diols: diol with short chain length(less than 4) yielded only monomeric acetals, whereas 1,5-pentanediol produced monomeric, dimeric, and trimeric acetals together with noncyclic acetal. Dimeric and noncyclic acetal were obtained in the higher α,ω-diols Such product distribution depends on the reaction manner, ie, intramolecular or intermolecular one. The yields of dimeric acetals showed zig-zag profiles when plotted to number of ring atoms, since strain-free diamond lattice type structure is realized only in the case that number of methyl-

ene units of diols are even such as 1,6-hexanediol, 1,8-octanediol, 1,10-decanediol, and 1,12-dodecanediol. Product distribution here differs from the results obtained in the case of benzophenone crown ether acetals(Chapter 1), due to the characteristics of $-CH_2-$ and -O- within the ring.

3. Reaction rate of the 17 membered ring reached an maximum in acid catalyzed hydrolysis of benzophenone crown ether acetals where $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are reduced to a minimum. The maximum rate and the minimum activation parameters are interpreted in term of the contribution of a tripod structure of 17 membered crown ether acetal which incorporates a hydronium ion in the ring and is ordered and stabilized by the complexation.

4. With increase of ring size from 5 to 8, the reaction rate also increase in acid catalyzed hydrolysis of cyclic benzophenone acetals. The relationship between the ring size and the reaction rate is explained on the basis of the ring strain and the stereoelectronic effect. Introduction of methyl groups to the methylene units inhibits protonation due to hydrophobic property and steric hindrance of methyl group, slowing down the overall rate. On the other hand, steric repulsion generated between the methyl group and the ring strengthens the ring strain, thus accelerating the reaction rate.

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