ACID CATALYZED HYDROLYSIS OF CYCLIC BENZOPHENONE ACETALS. EFFECTS OF RING SIZE AND RING SUBSTITUENT

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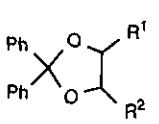
Abstract—Rates of acid-catalyzed hydrolysis of 5- to 8-membered ring benzophenone acetals (**1-4**) in 80% dioxane-water(v/v) were dependent upon the ring size and the ring-substituted methyl group as well as the condensed-rings. These kinetic results are interpreted in terms of the ring strain, the stereoelectronic effects, and the hydrophobicity.

There have been numerous investigations on the acid catalyzed hydrolysis of a wide variety of cyclic and acyclic acetals.[1] However, very little is known about the cyclic benzophenone acetals, especially with six membered and larger ring size,[2] probably because of difficulties in the synthesis by the standard methods owing to the increasing ring strain.[3]

Recently, we found that the reaction of diphenyldiazomethane with 2,3-dichloro-5,6-dicyanobenzoquinone(DDQ) in the presence of alcohols gave the corresponding benzophenone acetals in good yields together with the reduced 2,3-dichloro-5,6-dicyanohydroquinone.[4] Application of this redox reaction to α,ω-diols provided 5- to 8-membered ring benzophenone acetals.[5] These situations prompted us to investigate the hydrolysis of these medium ring sized acetals.

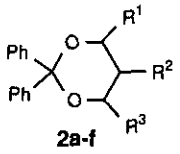
In this paper, we report the hydrolysis of 5- to 8-membered ring benzophenone

acetals(**1-4**) and discuss the effects of the ring size, the ring-substituents, and the condensed rings on the hydrolysis from the structural and electronical point of view.



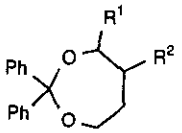
1a-f

a; R^1=R^2=H
b; R^1=Me, R^2=H
c; R^1=R^2=Me (cis)
d; R^1=R^2=Me (trans)
e; R^1,R^2=$(CH_2)_4$ (cis)
f; R^1,R^2=$(CH_2)_4$ (trans)



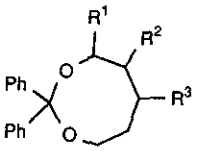
2a-f

a; R^1=R^2=R^3=H
b; R^1=Me, R^2=R^3=H
c; R^1=R^3=H,R^2=Me
d; R^1=R^3=Me (cis), R^2=H
e; R^1=R^3=Me (trans), R^2=H
f; R^1, R^3=$(CH_2)_3$ (cis), R^2=H



3a-c

a; R^1=R^2=H
b; R^1=Me, R^2=H
c; R^1=H, R^2=Me



4a-d

a; R^1=R^2=R^3=H
b; R^1=Me, R^2=R^3=H
c; R^1=R^3=H, R^2=Me
d; R^1=R^2=H, R^3=Me

RESULTS AND DISCUSSION

A. EFFECTS OF RING SIZE

The rate constants and the activation parameters were collected for the HCl-catalyzed hydrolysis of unsubstituted, variously methyl-substituted, and ring-condensed 5- to 8-membered ring benzophenone acetals (**1-4**) at 30 °C in 80% dioxane-water(Table 1).

It was found that the rate constants(k) of unsubstituted (**1-4**)**a** increase with increasing ring size; 8-membered **4a** hydrolyzed 35 times faster than 5-membered **1a**. This rate dependency on the ring size can be explained on the basis of the combination of the ring strain and the stereoelectronic effects. The strain energies of 5- to 8-membered ring cycloalkanes are estimated to be in the order of cyclohexane(0.0 kcal/mol; as a hypothetical strainless model) < cyclopentane(6.2) < cycloheptane(6.3) < cyclooctane(9.7).[6] By analogy, ring strain of the present acetals seems to be in the same order and hence to achieve the slowest hydrolysis rate for the 6-membered **2a**. However, **2a** hydrolyzed *ca.* 5 times faster than the strained 5-membered **1a**, though larger ring-sized homologs (**3a**) and (**4a**) suffered an expected acceleration due to the increased ring strain. According to the generally accepted A-1 mechanism for hydrolysis of acetals, the rate-determining step is an unimolecular

decomposition of the conjugated acid(SH^+), which is given by a pre-equilibrium protonation of the substrate(S), to a oxocarbenium ion(C^+), as formulated in below.[1]

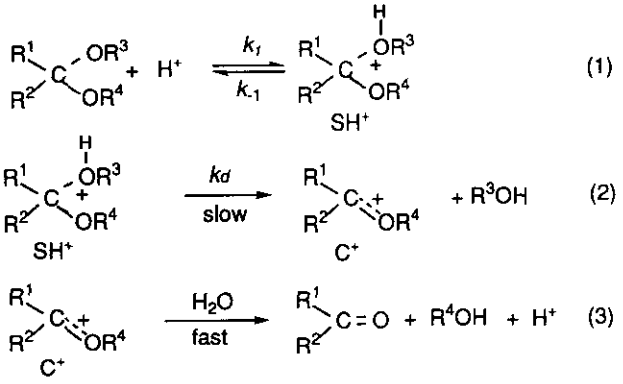
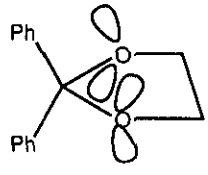


Table 1. Rate Constants(k) and Activation Parameters for HCl-catalyzed Hydrolysis of Cyclic Benzophenone Acetals(**1-4**) at 30 °C in 80% Dioxane-Water(v/v)

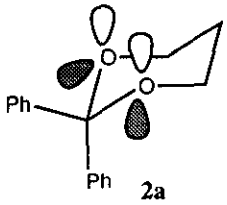
Acetal	10^3k,dm^3/mol·s	$\Delta H^{\ddagger}$, kJ/mol	$\Delta S^{\ddagger}$, J/mol·K
1 a	9.69[a)]	89.9	12.9
1 b	1.11		
1 c	0.250		
1 d	0.0412		
1 e	1.02		
1 f	118		
2 a	47.4[a)]	95.4	44.2
2 b	6.26		
2 c	15.5		
2 d	0.154		
2 e	14.2		
2 f	1170		
3 a	136[a)]	79.9	1.96
3 b	41.6		
3 c	38.6		
4 a	338[a)]	69.6	-24.6
4 b	427		
4 c	235		
4 d	210		

a) The k (x 10^3) values at different temperature were 3.00(20 °C) and 33.5(40 °C) for **1a**, 13.1(20 °C) and 170(40 °C) for **2a**, 395(40 °C) and 1030(50 °C) for **3a**, and 880(40 °C) and 1980(50 °C) for **4a**.

Therefore, the reverse hydrolytic order between 5-membered **1a** and 6-membered **2a** can be ascribed to the stereoelectronic effects[7] by which the antiperiplanar sp^3 hybrid lone pair electrons(shaded lobes) of the acetal oxygens in the chair-formed **2a** will promote the bond-breaking of the protonated C-O bond in the transition state(TS). For **1a**, such electron-donating participation will be considerably reduced on account of rather planar envelope structure unfavorable for the antiperiplanar interaction.



1a



2a

Activation parameters in Table 1 show that the values of $\Delta S^{\neq}$ are nearly of the magnitude generally found for unimolecular A-1 reactions, and a compensation between $\Delta H^{\neq}$ and $\Delta S^{\neq}$ is roughly operative. From the slope(=0.73) of the regression equation, $T\Delta S^{\neq} = 0.73\Delta H^{\neq} - 58.4$ (T=303.15K, r=0.96), it was found that the change of the ring size is more effective on the enthalpy term than on the entropy one. Moreover, a plot of $\Delta H^{\neq}$ against the ring size is suggestive of the ring strain of these acetals mainly responsible for the change of $\Delta H^{\neq}$, i.e., the most strainless 6-membered **2a** must go up to the largest activation energy(Figure 1). However, the profile of $\Delta S^{\neq}$ implies that the small enthalpy changes especially for the

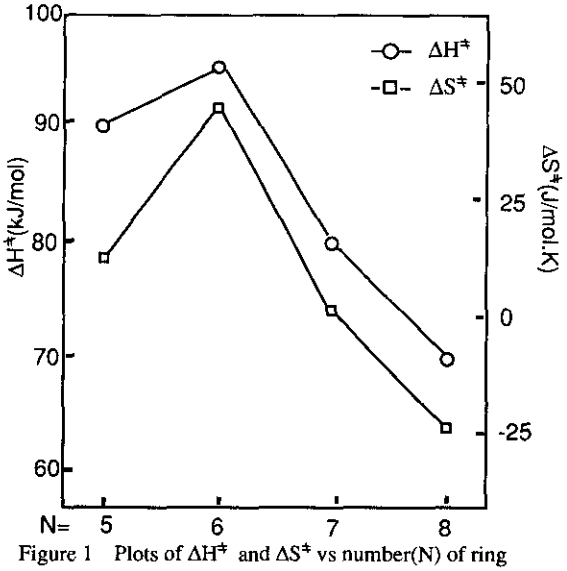


Figure 1 Plots of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ vs number(N) of ring atoms for hydrolysis of cyclic benzophenone acetals(**1-4**)a

strained acetals (**3a**) and (**4a**) are compensated by the unfavorable entropy changes, probably because of restriction of bond rotation for the antiperiplanar conformation in the transition state.

B. EFFECTS OF RING SUBSTITUENT

a) MONOSUBSTITUTED ACETALS

The introduction of methyl groups to the various positions of acetal rings more or less supressed the hydrolysis rates only except α-substituted 8-membered ring (**4b**) as found in the plots of log *k* against the position of the substitution(Figure 2). The rate-retarding effects by α-substituted methyl group were most intensified for 5-membered **1b**, gradually weakened for 6- and 7-membered **2b** and **3b**, and finally reversed for 8-membered **4b** as shown in the rate profile(Figure 2).

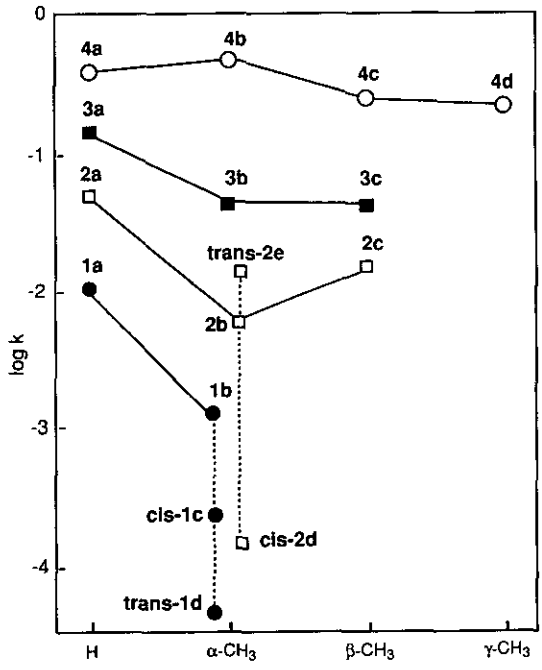


Figure 2 Plots of log k for hydrolysis of variously methylated cyclic benzophenone acetals

This phenomenon may be interpreted as the result of the cooperation of the increased hydrophobicity and the additional ring strain as well as the inductive effects by methyl group. The hydrophobic effects mainly disturb the pre-equilibrium protonation of acetal, providing smaller equilibrium constant, $K_S(=k_1/k_{-1})$, in eq. 1. Since the overall rate constant(k) of acid catalyzed hydrolysis of acetals is given by the eq. 4, introduction

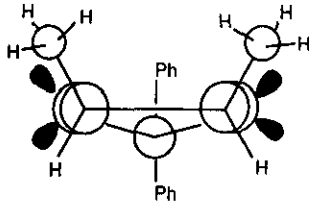
$$k=K_S \times k_d \quad (k_d/k_{-1}<<1) \qquad (4)$$

of α-methyl group will lead to the rate-retardation, where k_d is the rate constant for the rate-determining step (eq. 2). However, the additional ring strain, which should

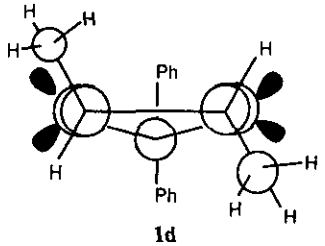
be more strengthened in the intrinsically strained system, is expected to facilitate the bond-breaking of the conjugated acid(SH^+). Thus, the small hump for 8-membered **4b** is due to the acceleration of the rate-determining step. Methyl substitution at the β-position produced a complicated feature in the rate profiles. For 6-membered acetal, β-substituted **2c** is 2.5 times more reactive than α-substituted **2b**. The reason is probably that the one methylene-unit spacing considerably reduces the hydrophobicity around the acetal linkage, although the transition state will be inductively less stabilized by β-methyl group. In contrast to the case of strainless 6-membered acetal, 7- and 8-membered acetals showed decrescent rate profiles in going from α, β, to γ-substitution in spite of a possible decrease in hydrophobicity near acetal functions. Both of these ring systems possess appreciable strain energies and the values will be much more dependent on the substituents and the substituted positions. Thus, the detailed analysis of the monotonous hydrolytic behaviors requires the exact estimate of strain energies in the present reaction medium.

b) DISUBSTITUTED ACETALS

The α,α'-dimethyl-substituted acetals (**1c**, **1d**, **2d**, and **2e**) exhibited a noticeable hydrolytic behavior depending on the cis- and trans-substitution. For 5-membered acetals, both the cis- and trans-**1c** and **1d** hydrolyzed only 1/4 and 1/27 as fast as mono-substituted **1b** (Table 1 and Figure 2). This rate-detardation can mainly be ascribed to the enhanced hydrophobicity of dimethyl-substituted 1,3-dioxolane ring. The six times higher reactivity of cis-isomer comparable to trans-one apparently reflects the steric repulsion between the vicinal methyl groups as depicted in Newman projection of **1c**. Trans-form (**1d**) is completely free from the repulsive

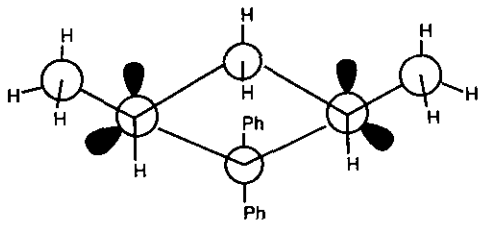


1c

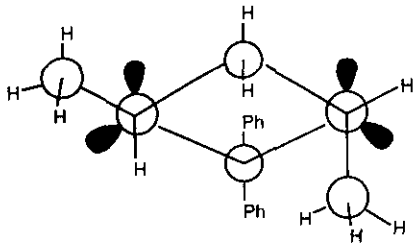


1d

interaction of the two methyl groups. However, in the case of 6-membered acetals, hydrolysis rate of trans-α,α'-disubstituted **2e** is 92 times larger than that of cis-substituted **2d**. According to the conformational analysis of these acetals,[8] the high reactivity of trans-form is interpreted by considering a diaxial interaction of a pair of phenyl and methyl group in 1,3-dioxane ring structure. Such appreciable steric repulsion appears to be also responsible for rather higher lability of **2e** than monomethyl-substituted **2b**, overcoming the unfavorable hydrophobicity. The cis-substituted **2d** can locate the two methyl groups in equatorial positions to avoid the enormous steric repulsion encountered in **2e**.



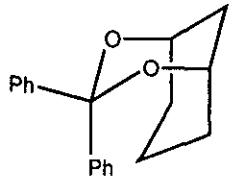
2d



2e

c) BICYCLIC ACETALS

It is also noted that bicyclic structure brought about a remarkable rate-acceleration compared with the corresponding α,α'-dimethyl-substituted monocyclic acetals(Table 1). Thus, cis-fused five-membered **1e** hydrolyzed *ca.* 4 times faster than the relevant dimethyl cis-substituted **1c** and trans-fused **1f** hydrolyzed approximately 3000 times as fast as dimethyl trans-substituted **1d**. The high reactivity of **1f** can be rationalized on account of the significant torsional strain caused by trans-fusion of 6-membered ring. Of much interest is the large acceleration of trimethylene-bridged 6-membered **2f**. This acetal exhibited *ca.* 7600 times increase in hydrolysis rate compared with the corresponding dimethyl cis-substituted **2d**. The high reactivity is arising from the crowding around the axial phenyl and the inward flipped trimethylene bridge.



2f

EXPERIMENTAL

Kinetic Measurements. The rates of hydrolysis of acetals were measured spectrophotometrically by following the absorption of generated benzophenone in 80% dioxane-water(v/v). Detail was described in our previous papers.[9]

Materials. Dioxane was dried over sodium and fractionated. Water was deionized through an ion exchange resin. New cyclic benzophenone acetals (**1b-f**, **2b-f**, **3b-c**, **4b-d**) were prepared according to the previously reported procedure[5] and were identified by ir, nmr, mass spectra, and elemental analyses. The ir, nmr, and mass spectra were taken on a Perkin-Elmer 983G, a Varian EM390, and a Hitachi RMU 6E spectrometer, respectively. The analytical data for (**1-4**)**a** were reported in our previous paper.[5]

4-Methyl-2,2-diphenyl-1,3-dioxolane(1b): 74% yield; mp 68-69 °C, colorless prisms(from ether); ir(KBr) 2892, 1451, 1208, 1103, 1009, 694 cm^{-1}; nmr($CDCl_3$) δ 1.34(d, J=5.7Hz, 3H, CH_3), 3.57(m, 1H, CH), 4.0-4.5(m, 2H, CH_2), 7.1-7.7(m, 10H, 2xPh); mass m/z 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-4,5-Dimethyl-2,2-diphenyl-1,3-dioxolane(1c): 55% yield; mp 141-142 °C, colorless prisms(from benzene-pentane); ir(KBr) 2879, 1448, 1221, 1087, 701 cm^{-1}; nmr($CDCl_3$) δ 1.22(d, J=6.3Hz, 6H, 2xCH_3), 4.1-4.4(m, 2H, 2xCH), 7.1-7.6(m, 10H, 2xPh); mass m/z 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-4,5-Dimethyl-2,2-diphenyl-1,3-dioxolane(1d): 44% yield; mp 120-122 °C, colorless prisms(from ether); ir(KBr) 2868, 1449, 1225, 1093, 1002, 695 cm^{-1}; nmr($CDCl_3$) δ 1.2-1.5(m, 6H, 2xCH_3), 3.6-4.0(m, 2H, 2xCH), 7.1-7.7(m, 10H, 2xPh); mass m/z 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, colorless prisms(from benzene-pentane); ir(KBr) 2949, 1453, 1223, 1078, 997, 697 cm^{-1}; nmr($CDCl_3$) δ 0.8-2.2(m, 8H, $(CH_2)_4$), 3.8-4.4(m, 2H, 2xCH), 6.8-7.8(m, 10H,

2xPh); mass m/z 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, colorless prisms(from benzene-pentane); ir(KBr) 2946, 2885, 1453, 1234, 1067, 701 cm^{-1}; nmr($CDCl_3$) δ 0.8-2.5(m, 8H, $(CH_2)_4$), 3.1-3.5(m, 2H, 2xCH), 6.8-7.7(m, 10H, 2xPh); mass m/z 280(M^+). Anal. Calcd for $C_{19}H_{20}O_2$: C,81.39; H,7.19. Found: C, 81.50; H, 7.23.

4-Methyl-2,2-diphenyl-1,3-dioxane(2b): 78% yield; mp 91-91.5 °C, colorless prisms(from ether); ir(KBr) 2953, 1449, 1238, 1187, 1087, 1015, 698 cm^{-1}; nmr($CDCl_3$) δ 1.25(d, J=6.3Hz, 3H, CH_3), 1.4-2.2(m, 2H, CH_2), 3.8-4.2(m, 3H, OCH_2+CH), 7.1-7.6(m, 10H, 2xPh); mass m/z 254(M^+). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.24; H, 7.13.

5-Methyl-2,2-diphenyl-1,3-dioxane(2c): 40% yield; mp 111-113 °C, colorless prisms (from ether); ir(KBr) 2949, 1452, 1238, 1097, 1020, 701 cm^{-1}; nmr($CDCl_3$) δ 0.79(d, J=8.4Hz, 3H, CH_3), 1.9-2.4(m, 1H, CH), 3.5-3.6 and 3.8-4.2(m, 4H, 2xOCH_2), 7.1-7.7(m, 10H, 2xPh); mass m/z 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-4,6-Dimethyl-2,2-diphenyl-1,3-dioxane(2d): 74% yield; mp 124-126 °C, colorless prisms(from ether); ir(KBr) 2973, 1452, 1189, 1121, 1043, 702 cm^{-1}; nmr($CDCl_3$) δ 1.30(d, J=6.3Hz, 6H, 2xCH_3), 1.5-1.6(m, 2H, CH_2), 3.7-4.2(m, 2H, 2xCH), 7.0-7.6(m, 10H, 2xPh); mass m/z 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-4,6-Dimethyl-2,2-diphenyl-1,3-dioxane(2e): 74% yield; mp 133-134° C, colorless prisms(from ether); ir(KBr) 2972, 1449, 1221, 1079, 702 cm^{-1}; nmr($CDCl_3$) δ 1.27(d, J=6.3Hz, 6H, 2xCH_3), 1.5-1.6(m, 2H, CH_2), 3.6-4.1(m, 2H, 2xCH), 7.0-7.7(m, 10H, 2xPh); mass m/z 268(M^+). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.36; H, 7.51.

cis-3,3-Diphenyl-2,4-dioxabicyclo[3.3.1]nonane(2f): 62% yield; mp 138-139 °C, colorless prisms(from benzene-pentane); ir(KBr) 2945, 1465, 1249, 1208, 1137,

1021, 710 cm^{-1}; nmr($CDCl_3$) δ 1.0-2.7(m, 8H, $(CH_2)_3$+CH_2), 4.3-4.6(m, 2H, 2xCH), 7.0-7.7(m, 10H, 2xPh); mass m/z 280(M^+). Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.17; H, 7.26.

4-Methyl-2,2-diphenyl-1,3-dioxacycloheptane(3b): 59% yield; mp 72-74 °C, colorless prisms(from ether); ir(KBr) 2947, 1452, 1223, 1095, 1006, 710 cm^{-1}; nmr($CDCl_3$) δ 1.22(d, J=8.1Hz, 3H, CH_3), 1.4-1.9(m, 4H, $(CH_2)_2$), 3.4-4.0(m, 3H, OCH_2+CH), 7.0-7.8(m, 10H, 2xPh); mass m/z 268(M^+). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.27; H, 7.51.

5-Methyl-2,2-diphenyl-1,3-dioxacycloheptane(3c): 62% yield; mp 130-131 °C(from ether); ir(KBr) 2948, 1452, 1208, 1085, 1031, 699 cm^{-1}; nmr($CDCl_3$) δ 0.83(d, J=6.6Hz, 3H, CH_3), 1.1-1.2(m, 3H, CH_2+CH), 3.2-3.9(m, 4H, 2xOCH_2), 6.9-7.8(m, 10H, 2xPh); mass m/z 268(M^+). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.50; H, 7.55.

4-Methyl-2,2-diphenyl-1,3-dioxacyclooctane(4b): 29% yield; mp 41-43 °C, colorless prisms(from ether); ir(KBr) 2931, 1443, 1203, 1108, 1038, 712 cm^{-1}; NMR($CDCl_3$) δ 0.99(d, J=6.5Hz, 3H, CH_3), 1.2-2.0(m, 6H, $(CH_2)_3$), 3.2-4.0(m, 3H, OCH_2+CH), 6.9-7.8(m, 10H, 2xPh); mass m/z 282(M^+). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.74; H, 7.89.

5-Methyl-2,2-diphenyl-1,3-dioxacyclooctane(4c): 30% yield; colorless oil; ir(neat) 2939, 1452, 1208, 1110, 1067, 701 cm^{-1}; nmr($CDCl_3$) δ 0.81(d, J=7.1Hz, 3H, CH_3), 1.1-1.2(m, 5H, $(CH_2)_2$+CH), 3.0-3.7(m, 4H, 2xOCH_2), 7.0-7.7(m, 10H, 2xPh); mass m/z 282(M^+). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.99; H, 7.92.

6-Methyl-2,2-diphenyl-1,3-dioxacyclooctane(4d): 33% yield; mp 42-44 °C, colorless prisms(from ether); ir(KBr) 2928, 1439, 1232, 1110, 698 cm^{-1}; nmr($CDCl_3$) δ 0.98(d, J=6.9Hz, 3H, CH_3), 1.2-2.1(m, 5H, 2xCH_2+CH), 3.3-3.9(m, 4H, 2xOCH_2), 7.0-7.8(m,10H,2xPh); mass m/z 282(M^+). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.89; H, 7.87.

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8. Conformational analysis was made by Dreiding model. It is apparent that cis-substituted **2d** predominates in the chair-form, since the boat-form must suffer the 1,4-diaxial interaction between the phenyl group and the hydrogen atom as well as the intrinsically unfavorable conformation. With respect to trans-substituted **2e**, chair-form is also put forward on the basis of a comparison of its nmr spectrum with that of cis-**2d**. Both of acetals revealed the methylene multiplet at the same region(1.5-1.6 ppm), strongly supporting the same chair-conformation. In boat-form, one of the axial methyleme protons would resonate in more higher field owing to the shielding effects of the axial phenyl nucleus.
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