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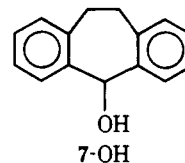
Solvolysees of Pseudo-Geminal "Equatorial" and "Axial" Systems of Tris[2.2.2]paraxylylene and Related Compounds. An Extremely Large Difference in Rates Due to Phenyl Conjugation and Transannular Interaction

Sir:

Although recent molecular orbital calculations have predicted a very large difference in energy (e.g., by 22.3 kcal/mol according to the MINDO/3 method)^{1,2} between coplanar and perpendicular conformations of benzyl cation, only a small decrease ($<10^3$ times) in the solvolysis rate due to loss of conjugation has been reported for, e.g., α -alkylbenzyl systems.³

In this paper we wish to report an extremely large reduction of the ionization rate of the pseudo-geminal "equatorial" system of tris[2.2.2]paraxylylene (**2**) compared with the 5*H*-10,11-dihydrodibenzo[*a,d*]cyclohepten-5-yl (**7**) system in connection with loss of conjugation, and also wish to describe a significant transannular effect on the rate and the reaction path in the solvolysis of the pseudo-geminal "axial" system of tris[2.2.2]paraxylylene (**3**).

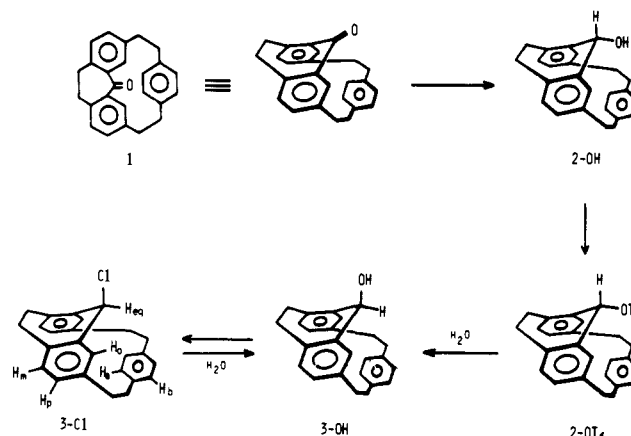
Based on spectral properties of the pseudo-geminal ketone of tris[2.2.2]paraxylylene (**1**) compared with those of 5*H*-10,11-dihydrodibenzo[*a,d*]cyclohepten-5-one (**6**), very slow ionization at the pseudo-geminal bridge position has been expected.⁴ Borohydride or alkaline zinc reduction of **1** gave the "equatorial" alcohol (**2-OH**) stereospecifically.⁵ The "axial" alcohol (**3-OH**) was obtained from hydrolysis of the "equatorial" trifluoromethanesulfonate (triflate) (**2-OTf**) again stereospecifically.⁵ In order to measure the ionization rates of **3** and **7**, pseudo-geminal "axial" chloride (**3-Cl**)^{6,7} and the *p*-nitrobenzoate of **7-OH** (**7-OPNB**)⁸ were prepared from **3-OH** and **7-OH**, respectively. On hydrolysis in 60% aqueous dioxane, all of the derivatives displayed good first-order kinetics up to 60–85% reaction. Only **3-OH**⁹ was obtained from



hydrolysis of **3-Cl**, and **7-OH** was a sole product from **7-OPNB**.

Table I summarizes the results of the kinetic investigations on **2-OTf**, **3-Cl**, and **7-OPNB**. Thus, the relative rates of **2-OTf**, **3-OTf**, and **7-OTf** are estimated to be $10^{-18.1}$, $10^{-3.4}$, and 1, respectively, using corrections for a triflate-tosylate reactivity difference of $10^{4.8,10}$ for tosylate-*p*-nitrobenzoate of $10^{9.1,11}$ and for tosylate-chloride of $10^{5.7,12}$

Scheme I



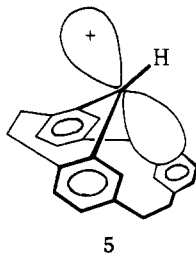
The extremely large deceleration ($10^{18.1}$ times) of the rate constant of **2-OTf** compared with **7-OTf** is mainly attributable to loss of conjugation due to lack of coplanarity between the incipient carbonium ion and the substituted phenyl rings,¹³ because based on the Dreiding model of pseudo-geminal methanotriss[2.2.2]paraxylylene (**4**) the "equatorial" C-H bond is inclined about 20° from coplanar (hence, about 40° for the "axial" C-H bond), whereas the corresponding C-H bond of 5*H*-10,11-dihydrodibenzo[*a,d*]cycloheptene (**8**) can take the perpendicular conformation easily. Angle strain about the carbonium ion center upon ionization¹⁴ of **2** should be a minor factor, for a $J(^{13}\text{C-H})$ value for the pseudo-geminal bridge carbon of **4** is 129 Hz¹⁵ and that for the corresponding carbon of **8** is 126 Hz. Steric hindrance in ionization¹⁶ by the "face" ⁵ ring or the ethano bridge in the seven-membered ring in **2** is considered also to be minor on the basis of the CPK model.

Since **3-OH** is the sole product from **2-OTf** and **3-Cl**, and both reactions obey the first-order kinetics, the reactions must proceed via the same intermediate (**5**), where the *p* orbital of the carbonium ion can transannularly interact with the π

Table I. Kinetic Data for Solvolysis in 60% (v/v) Aqueous Dioxane^a

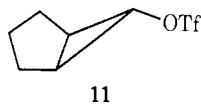
Compd	Temp, °C ^b	K_1, s^{-1}	$\Delta H^\ddagger, \text{kcal/mol}$	$\Delta S^\ddagger, \text{eu}$	K_{rel}
2-OTf	110.6	$(1.39 \pm 0.07) \times 10^{-4}$	28.0	-3.6	$10^{-18.1}$
	98.9	$(4.24 \pm 0.07) \times 10^{-5}$			
	25.0	$2.72 \times 10^{-9 \text{ c}}$			
3-Cl	40.0	$(2.45 \pm 0.00) \times 10^{-4}$	23.2	-1.2	$10^{-3.4}$
	25.0	$(3.58 \pm 0.00) \times 10^{-5}$			
3-OTf	25.0	$1.3 \times 10^6 \text{ d}$			
7-OPNB	35.0	$(1.62 \pm 0.00) \times 10^{-4}$	22.8	-2.0	1
	25.0	$(4.50 \pm 0.11) \times 10^{-5}$			
7-OTf	25.0	$3.4 \times 10^9 \text{ d}$			

^a Determined conductometrically. ^b All temperatures $\pm 0.1^\circ$ or better. ^c Extrapolated from high temperatures. ^d Estimated with the appropriate corrections for reactivities of the leaving groups; see text.



electron cloud of the "face" benzene ring. Thus water can attack the pseudo-geminal bridge carbon only from the opposite side to this ring. This explanation is also applicable to the similar attack of hydride in the reduction of **1**. As mentioned above, there is only a slight difference (about 20°) in the inclined angles of the "equatorial" and the "axial" bonds; therefore, the present significant enhancement ($10^{14.7}$ times) of the solvolysis rate of **3-OTf** relative to **2-OTf** should be attributed to the π participation^{17,18} of the "face" benzene ring with the generated carbonium ion. It is of much interest that the "face" ring locates more than 3.5 Å above the pseudo-geminal bridge carbon.

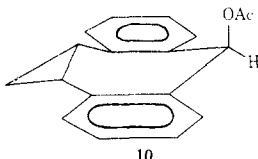
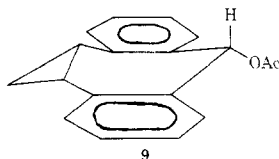
Finally, when the rate constant of **2-OTf** is compared with those of the secondary systems under the present condition, *exo*-bicyclo[3.1.0]hex-6-yl triflate (**11**), reported as the least



reactive secondary alicyclic system,^{10d} is merely 44 times less reactive than **2-OTf**. Thus, **2** is the least reactive benzhydryl system ever reported.

References and Notes

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- (7) Compound **3-Cl**: mp 204.0–206.0 °C; M^+ 358 (21) m/e 323 (100); NMR δ (CDCl_3) 2.24–3.17 (10 H, m, $-\text{CH}-$), 3.78–3.99 (2 H, m, $-\text{CH}_2-$), 5.13 (1 H, s, H_{ax}), 5.51 (2 H, m, H_β), 6.14 (2 H, d, $J = 1.7$ Hz, H_β), 6.94 (2 H, d, $J = 8.0$ Hz, H_α), 7.00 (2 H, d of d, $J = 1.7, 8.0$ Hz, H_β), 7.07 (2 H, m, H_β); ir (cm^{-1}) (KBr) 2900, 1500, 1440, 1400, 810, 740, 610.
- (8) Compound **7-OPNB**: mp 169.0–170.0 °C; NMR δ (CDCl_3) 2.9–3.8 (4 H, m, $-\text{CH}_2-$), 7.1–7.6 (8 H, m, Ph), 8.20 (4 H, s, NO_2PhCOO); ir (cm^{-1}) 1718, 1523, 1267, 1095, 720.
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- (13) The conformational environments of the seven-membered rings in 2,3:5,6-dibenzo-*cis*-4-acetoxycyclo[5.1.0]octa-2,5-diene (**9**) and the corresponding *trans*-4-acetoxy isomer (**10**) are very similar to the present



- systems. Contrary to our results, however, the *cis* ("equatorial") system (**9**) has been reported to react 240 times faster than the *trans* ("axial") system (**10**): R. F. Childs, M. A. Brown, F. A. L. Anet, and S. Winstein, *J. Am. Chem. Soc.*, **94**, 2175 (1972).
- (14) (a) P. v. R. Schleyer and R. D. Nicholas, *J. Am. Chem. Soc.*, **83**, 182 (1961); (b) C. S. Foot, *ibid.*, **86**, 1853 (1964); (c) P. v. R. Schleyer, *ibid.*, **86**, 1854 (1964).
 - (15) Since the pseudo-geminal bridge carbon is observed as a triplet in the ^{13}C NMR spectrum, both the $\text{C}-\text{H}_{\text{eq}}$ and the $\text{C}-\text{H}_{\text{ax}}$ bonds are considered to have the same hybridization.
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Cadmium-113 Fourier Transform Nuclear Magnetic Resonance of Cadmium(II) Carbonic Anhydrases and Cadmium(II) Alkaline Phosphatase

Sir:

The essential nature of the 2b metal Zn(II) in maintaining the catalytically active form of a wide variety of metalloenzymes is well established.^{1,2} Elucidation of the structure of the metal ion binding site and the functional role of the metal(s) in the mechanism of enzyme action by study of the native protein or analogs containing the chemically similar group 2b metal ions (Cd(II), Hg(II)) bound at the Zn(II) site is limited by the intrinsic properties of these ions (filled d shell) making them of little value as spectroscopic probes. Thus, despite differences in preferred coordination geometry and susceptibility to ligand-field induced structural distortions, the characteristics of the enzyme-bound metal have been largely inferred from the spectral properties of the enzymes in which transition metal ions have been substituted for the native Zn(II) ion.¹ Recent reports on the application of FT-NMR to metal nuclides in a variety of inorganic salts and small model complexes^{3,4} suggest that this technique may be suited to the direct observation of the diamagnetic analogue of the native metal bound in the microenvironment of enzymes. In this regard, the ^{113}Cd nucleus with spin $1/2$ and its higher sensitivity to NMR detection compared to ^{67}Zn is a reasonable first candidate. The large paramagnetic contribution to the shielding constant leads to large changes in the chemical shift with changes in the nature of bonding to the metal ion as reflected in a chemical shift range of >640 ppm for common compounds of cadmium.³ This fact coupled with its extreme sensitivity to substituent effects and a large dipolar contribution to the relaxation mechanism make ^{113}Cd an ideal NMR probe.

We wish to report on the observation and characteristics of the FT-NMR resonances of the ^{113}Cd (II) ion substituted for the intrinsic Zn(II) ion(s) of the metalloenzymes, bovine carbonic anhydrase B (BCAB), human carbonic anhydrase B (HCAB), and alkaline phosphatase of *E. coli* (AP).⁵

BCAB and HCAB were obtained from bovine and human erythrocytes.⁶ AP was isolated from *E. coli* CW3747.⁷ Zinc was removed from the purified enzymes either by dialysis