Table VI. Equilibrium Constants for Acyl Transfer Reactions[a]

Reaction	R = H		R = CH_3	
	K[b]	ΔG[c]	K[b]	ΔG[c]
$RCOOH + HN(CH_3)_2 \rightleftarrows RCON(CH_3)_2 + H_2O$	6.4×10^{8}[d]	−9.29[e]	1.8×10^{4}[d]	−5.8[f]
$RCOOCH_3 + HN(CH_3)_2 \rightleftarrows RCON(CH_3)_2 + HOCH_3$	5.8×10^{9}	−11.29[g]	9.6×10^{4}	−6.8[g]
$RCOOH + H_2N^+(CH_3)_2 \rightleftarrows RCON(CH_3)_2 + H_3O^+$	1.3×10^{-4}	+5.3[h]	3.6×10^{-7}	+8.8[h]
$RCOO^- + HN(CH_3)_2 \rightleftarrows RCON(CH_3)_2 + HO^-$	3.5×10^{-4}	+4.72[h]	8.8×10^{-6}	+6.9[h]

[a] In aqueous solution at 25°; standard state for water is the pure liquid at unit activity; standard state for solutes is 1 M aqueous solution with an infinitely dilute reference state. [b] Dimensionless unless otherwise noted. [c] kcal mol^{-1}. [d] M^{-1}. [e] Reference 19. [f] See text. [g] Calculated from $\Delta G_f°$(aq) values in Table II. [h] Calculated from $\Delta G°$ for the neutral molecules and pK_a values from Table IV as well as $K_w = 10^{-14}\ M^2$.

including those evaluated here, are contained in Table II. Heats of formation, vaporization, and solution of dimethylformamide and dimethylacetamide have been published, so the $\Delta H_f°$(aq) values needed for the thermochemical calculations were easily obtained. The equilibrium constant for the reaction of dimethylamine with formic acid to form dimethylformamide is known,[34] so $\Delta G_f°$(aq) for dimethylformamide is calculable from other values in the table. The equilibrium constant for formation of dimethylacetamide from dimethylamine and acetic acid was assumed to be the same as for the analogous reaction of propionic acid;[35] amide forming reactions are normally insensitive to substituent effects in the acid, but there does appear to be a steric effect on going from dimethylformamide to dimethylamides of higher fatty acids, since the measured value for dimethylpropionamide[35] is smaller than that predicted by a linear free energy relationship for primary or secondary amides.[34]

Heats of vaporization of the dimethylamide dimethyl acetals were calculated from the Wadsö equation;[36] standard entropies of the gaseous compounds were estimated from the entropies of the corresponding hydrocarbons using correction factors proposed by Stull, *et al.*[4b]

In Table VI are listed equilibrium constants for the acyl transfer reactions considered in this work; they were calculated from the thermochemical data in Table II and the pK_a values in Table IV.

Acknowledgment. I thank the National Research Council of Canada for financial support of this work.

(34) A. R. Fersht and Y. Requenna, *J. Amer. Chem. Soc.*, **93**, 3499 (1971).

(35) H. Morawetz and P. S. Otaki, *J. Amer. Chem. Soc.*, **85**, 463 (1963).

(36) I. Wadsö, *Acta Chem. Scand.*, **20**, 544 (1960).

Pentacyclodecane Chemistry. X. The Synthesis and Acetolysis of *syn*- and *anti*-6-Methylpentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]dec-6-yl *p*-Toluenesulfonate. Further Evidence Concerning Bridging in Secondary 1,3-Bishomocubyl Systems[1,2]

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Contribution from Chemicals Research, Dow Interdiscipline Group, The Dow Chemical Company, Midland, Michigan 48640. *Received July 26, 1973*

Abstract: Irradiation of 3-methyl-*endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-*syn*-3-ol (**14**) in acetone gave 6-methylpentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]decan-*syn*-6-ol (**15**). Peracid oxidation of 6-methylenepentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]-decane (**19**) gave the corresponding isomeric epoxides **20** and **21** which were reduced with lithium aluminum hydride to give a 56:44 mixture of 6-methylpentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]decan-*anti*-6-ol (**22**) and **15**. Acetolysis of the tertiary syn and anti tosylates **16** and **23** of the alcohols **15** and **22**, respectively, and the acid-catalyzed addition of acetic acid to the olefin **19** at 45° gave the corresponding syn and anti acetates **17** and **24** in 63:37, 75:25, and 69:31 ratios, respectively. These product distributions indicate that no inherent steric or strain effect, which could account for the high degree of stereospecificity observed in the solvolysis of the corresponding secondary tosylates, is present in the 1,3-bishomocubyl system. The acetolysis rates of **16** and **23** at 34.5° are nearly equal. The addition of methylmagnesium iodide and methyllithium to pentacyclo[5.3.0.$0^{2,5}$.$0^{3,9}$.$0^{4,8}$]decan-6-one (**18**) gave the alcohols **15** and **22** in 82:18 and 78:22 ratios, respectively. Acid-catalyzed equilibration of **15** and **22** at ~25° gave a 48 ± 4:52 ± 4 ratio, respectively.

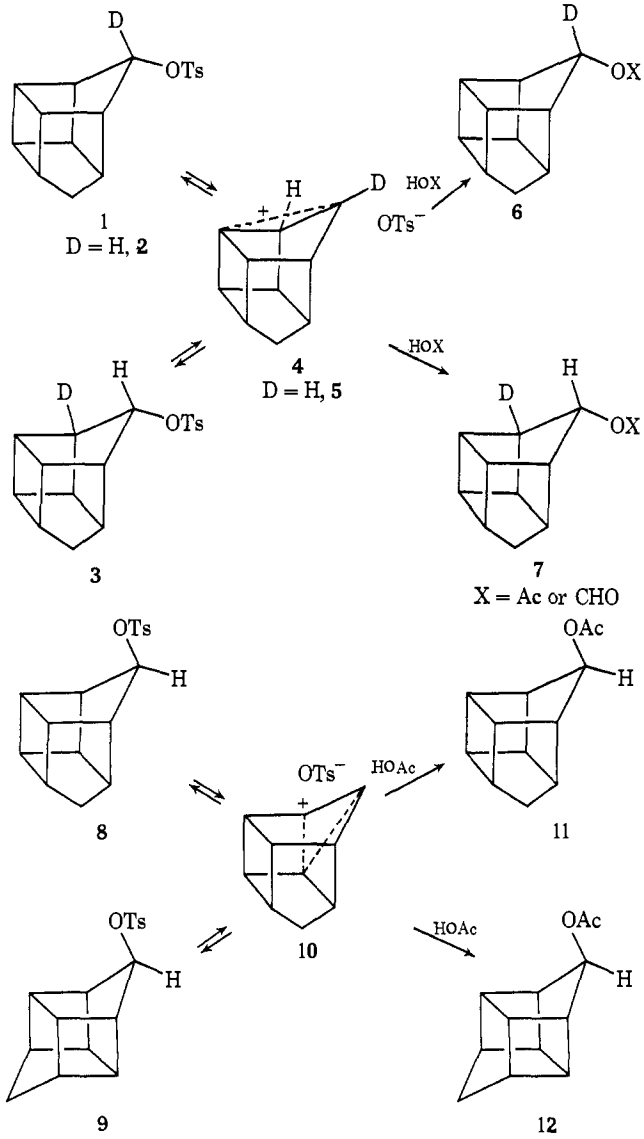
Stereochemical,[1,3] isotopic labeling,[1,3c] and kinetic[3a,b] studies are consistent with the postulate that the solvolyses of the *syn*-**1** (and **2**) and *anti*-**8** 1,3-bishomocubyl tosylates involve the σ-bridged ions **4** (and **5**) and

(1) Part IX: W. L. Dilling, R. A. Plepys, and R. D. Kroening, *J. Amer. Chem. Soc.*, **94**, 8133 (1972).

(2) A preliminary account of part of this work was reported in part VII: W. L. Dilling and J. A. Alford, *Tetrahedron Lett.*, 761 (1971).

(3) (a) W. L. Dilling and C. E. Reineke, *Tetrahedron Lett.*, 2547 (1967); (b) W. L. Dilling, C. E. Reineke, and R. A. Plepys, *J. Org. Chem.*, **34**, 2605 (1969); **37**, 3753 (1972); (c) W. L. Dilling, R. A. Plepys, and R. D. Kroening, *J. Amer. Chem. Soc.*, **91**, 3404 (1969); **92**, 3522 (1970); (d) S. F. Brown, Senior Thesis, Princeton University, 1967.

Scheme I



10, respectively (Scheme I).[4] An alternate explanation involves equilibrating ions pairs and front-side solvent capture.[1,3b] The pertinent results on which the above statements are based are the following. (1) The syn tosylates **1** and **2** solvolyzed to give equal amounts of esters **6** and **7** with the formation of no more than 3–4% each of isomers **11** and **12**.[1,3a–c] (2) The tosylates **8** and **9** solvolyzed to give 85–87% of acetate **12**, 12–15% of acetate **11**, and ~1% of acetate **6** (D = H, X = Ac).[3a,b,d] (3) The 1,3-bishomocubyl tosylates solvolyzed 10^3–10^4 times faster than predicted for unassisted solvolyses.[3a,b]

The possibility that a steric or strain effect is responsible for the *ca.* 90% retention of configuration observed in the solvolyses of the related 7-norbornyl esters[5,6] has been advanced[5] as an alternate explanation to σ bridging.[6,7] The same reason could account for the predominant retention of configuration in the 1,3-bishomocubyl system, **1** and **8**, which contains the 7-norbornyl nucleus. The solvolyses of some syn and anti tertiary 1,3-bishomocubyl esters thus were undertaken as a test of these theories on the grounds that a steric or strain effect should still manifest itself or even be more pronounced in the tertiary systems, while σ bridging should be of less importance than in the secondary systems. It is generally accepted by both proponents of classical and nonclassical ions that the more stable the cationic center the less stabilization the center will require from σ bridging.[8] The point of contention is whether or not participation is completely eliminated in tertiary cations.[8o,q] The stable long-lived secondary 2-norbornyl cation in fluorosulfonic acid–antimony pentafluoride and related solvents is proposed to be completely σ delocalized,[9] the 2-methyl- or 2-ethyl-2-norbornyl cation to be partially σ delocalized,[9c,10] and the 2-phenyl-2-norbornyl cation to be essentially devoid of σ delocalization.[9c,10a,11]

In recent years, there have been reports that the high exo–endo rate ratios and product distributions observed in the extensively studied secondary 2-norbornyl systems,[12] which were supposedly characteristic of bridged cations, were also observed in tertiary 2-norbornyl systems.[8f,h,k,13] Thus, since the presumably nonbridged tertiary cations showed exo–endo rate ratios and product distributions similar to those of the previously studied secondary systems, there was no need to postulate a special (nonclassical bridging) effect for the secondary systems. Steric and related effects have been suggested as the factors responsible for the behavior of these systems.[14]

Results

Syntheses. The syn alcohol **15** and its esters were

(4) Although the structural formulas in this paper show only one enantiomer, all the compounds capable of existing as optical isomers were actually racemic mixtures.

(5) (a) F. B. Miles, *J. Amer. Chem. Soc.*, **89**, 2488 (1967); (b) F. B. Miles, *ibid.*, **90**, 1265 (1968).

(6) (a) P. G. Gassman and J. M. Hornback, *J. Amer. Chem. Soc.*, **89**, 2487 (1967); (b) P. G. Gassman, J. M. Hornback, and J. L. Marshall, *ibid.*, **90**, 6238 (1968).

(7) B. Funke and S. Winstein, *Tetrahedron Lett.*, 1477 (1971).

(8) (a) S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Amer. Chem. Soc.*, **74**, 1113 (1952); (b) P. v. R. Schleyer, D. C. Kleinfelter, and H. G. Richey, Jr., *ibid.*, **85**, 479 (1963); (c) H. C. Brown and F. J. Chloupek, *ibid.*, **85**, 2322 (1963); (d) C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon Atom," Elsevier Publishing Co., New York, N. Y., 1963, p 63; (e) P. Beltramé, C. A. Bunton, A. Dunlop, and D. Whittaker, *J. Chem. Soc.*, 658 (1964); (f) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Amer. Chem. Soc.*, **86**, 1246 (1964); (g) *ibid.*, **86**, 1247 (1964); (h) *ibid.*, **86**, 1248 (1964); (i) H. C. Brown and H. M. Bell, *ibid.*, **86**, 5003 (1964); (j) H. C. Brown and M.-H. Rei, *ibid.*, **86**, 5004 (1964); (k) H. C. Brown and H. M. Bell, *ibid.*, **86**, 5006 (1964); (l) H. M. Bell and H. C. Brown, *ibid.*, **86**, 5007 (1964); (m) H. C. Brown and M.-H. Rei, *ibid.*, **86**, 5008 (1964); (n) P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, New York, N. Y., 1965, p 77; (o) S. Winstein, *J. Amer. Chem. Soc.*, **87**, 381 (1965); (p) H. C. Brown and G. L. Tritle, *ibid.*, **88**, 1320 (1966); (q) G. D. Sargent, *Quart. Rev., Chem. Soc.*, **20**, 301 (1966).

(9) (a) G. A. Olah, A. Commeyras, and C. Y. Lui, *J. Amer. Chem. Soc.*, **90**, 3882 (1968); (b) G. A. Olah and A. M. White, *ibid.*, **91**, 3956, 7789 (1969); (c) G. A. Olah, A. M. White, J. R. DeMember, A. Commeyras, and C. Y. Lui, *ibid.*, **92**, 4627 (1970).

(10) (a) G. A. Olah, J. R. DeMember, C. Y. Lui, and A. M. White, *J. Amer. Chem. Soc.*, **91**, 3958 (1969); (b) G. A. Olah, J. R. DeMember, C. Y. Lui, and R. D. Porter, *ibid.*, **93**, 1442 (1971).

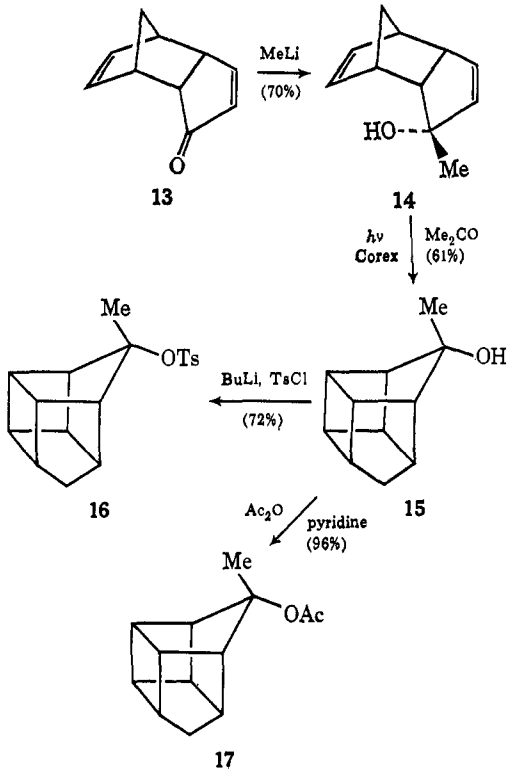
(11) D. G. Farnum and G. Mehta, *J. Amer. Chem. Soc.*, **91**, 3256 (1969).

(12) (a) S. Winstein and D. S. Trifan, *J. Amer. Chem. Soc.*, **71**, 2953 (1949); (b) S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan, and H. Marshall, *ibid.*, **74**, 1127 (1952); (c) S. Winstein and D. Trifan, *ibid.*, **74** 1147 (1952); (d) *ibid.*, **74**, 1154 (1952); (e) S. Winstein, E. Vogelfanger, K. C. Pande, and H. F. Ebel, *ibid.*, **84**, 4993 (1962); (f) S. Winstein, E. Clippinger, R. Howe, and E. Vogelfanger, *ibid.*, **87**, 376 (1965); (g) A. Colter, E. C. Friedrich, N. J. Holness, and S. Winstein, *ibid.*, **87**, 378 (1965); (h) H. L. Goering and C. B. Schewene, *ibid.*, **87**, 3516 (1965).

(13) (a) G. D. Sargent, "Carbonium Ions," Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1972, p 1099; (b) E. N. Peters and H. C. Brown, *J. Amer. Chem. Soc.*, **95**, 2397 (1973).

(14) H. C. Brown, *Chem. Britain*, 199 (1966).

Scheme II



prepared in a stereospecific manner as shown in Scheme II. The nmr spectrum of the dienol **14** showed only a single methyl resonance, indicating that none of the epimer was formed in the reaction of methyllithium with the dienone **13**.[15] Likewise the syn alcohol **15**, formed by photochemical ring closure,[17] showed only a single methyl resonance in agreement with the conclusion that the dienol **13** was a single isomer. Thus only anti (exo) attack by methyllithium on the carbonyl group of **13** occurred, as expected due to the considerable steric hindrance to endo attack in this system. The esters **16** and **17** were prepared by conventional methods. *p*-Toluenesulfonyl chloride in pyridine did not react with the tertiary alcohol **15**.

The derivatives of the anti series were synthesized according to the procedures outlined in Scheme III. Although a stereospecific route to the anti alcohol **22** could not be found, material of 97% purity was obtained in 25% yield from mixtures of the epimers **22** and **15** by fractional crystallization. Isomer distributions of the alcohols **15** and **22** were determined by the relative intensities of the C-6 methyl resonances in the nmr spectra. In addition to the Wittig reaction[18] shown in Scheme III, the olefin **19** also was prepared by treatment of the alcohols **15** and **22** with phosphorous oxychloride. The isomer distribution of the epoxides **20** and **21** is assumed to be the same (56:44) as that of the alcohols **22** and **15** since the lithium aluminum hydride reduction was essentially quantitative.

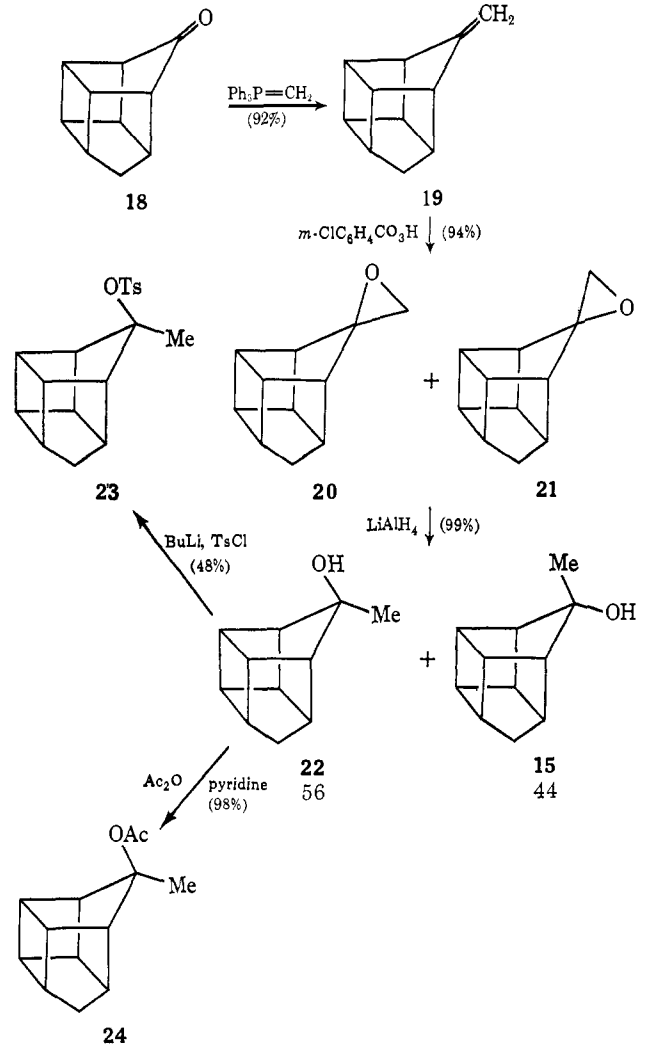
(15) Rosenblum[16] reported the reaction of the dienone **13** with methylmagnesium iodide gave the tertiary alcohol of undefined stereochemistry. The reported melting point was within 3° of that which we found for the alcohol **14** and therefore probably was the same isomer. No other data were reported by which further comparisons could be made.

(16) M. Rosenblum, *J. Amer. Chem. Soc.*, 79, 3179 (1957).

(17) For a review of this type of reaction, see W. L. Dilling, *Chem. Rev.*, 66, 373 (1966).

(18) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, 28, 1128 (1963).

Scheme III



Reaction of the ketone **18** with either methylmagnesium iodide or methyllithium gave a 4:1 ratio of the *syn*- and *anti*-alcohols **15** and **22**, respectively. Equilibration of the alcohols **15** and **22** with 50% sulfuric acid in tetrahydrofuran gave a 48 ± 4:52 ± 4 (**15**:**22**) distribution. Equilibration was not achieved by 10 or 20% sulfuric acid.

Solvolytic Studies. Preparative acetolysis of both tertiary tosylates **16** and **23** in either buffered or unbuffered acetic acid at 45° gave the *syn*-acetate **17** as the major product along with smaller amounts of the *anti*-acetate **24** (Table I). Analyses were carried out by integration of the acetoxy methyl resonances in the nmr spectrum (**17**, 2.01 ppm; **24**, 1.88 ppm; $CDCl_3$ solution) and are accurate to *ca.* ±1%. Both acetates **17** and **24** were completely stable when they were subjected to the acetolysis conditions which included the presence of 1 equiv of *p*-toluenesulfonic acid. In addition, when the reaction was followed by nmr there was no change in the product distribution as the reaction progressed. The same experiment demonstrated that no equilibration (internal return) occurred between the tosylates **16** and **23**. Internal return could have been detected easily due to the differences in chemical shift of the C-6 methyl resonances of **16** and **23**. No evidence (nmr, infrared, gc) for any olefinic or rearranged products was detected in the acetolysis of either tosylate. The kinetics of the acetolyses in un-

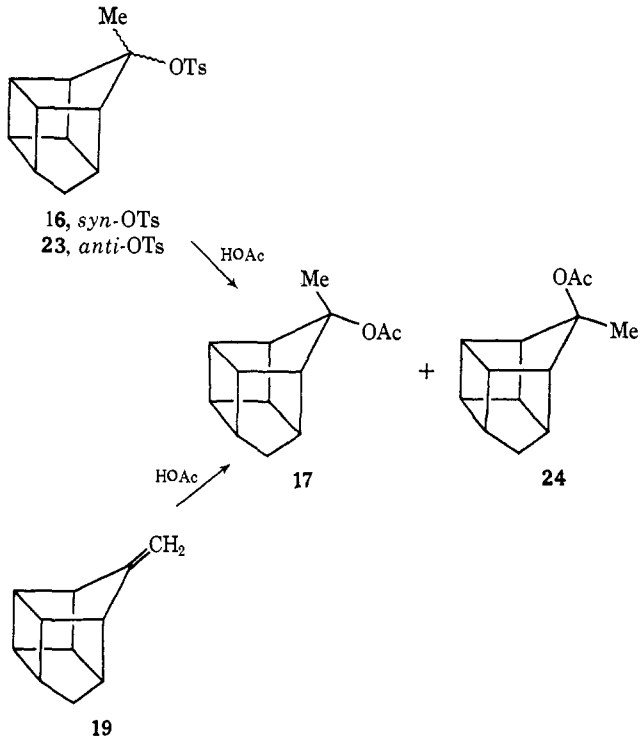


Table I. Product Distributions from Acetolysis of Tertiary 1,3-Bishomocubyl Tosylates and Acetic Acid Addition to Methylenepentacyclodecane

Starting material	Additive	Temp, °C[a]	Time, hr	Product dist, %[b] *syn*-**17**	*anti*-**24**	Total acetate yield, %[c]
syn-**16**		45	1	63	37	98
16	NaOAc	45	1	63	37	90
anti-**23**		45	1	75	25	100
Olefin **19**	TsOH	45	4	69	31	77
19	TsOH	~25[d]	3	68	32	93
19		45	48			0[e]
19		100	168	63	37	76[f]

[a] All temperatures ±1°. [b] All percentages ±1%. [c] All conversions of tosylates **16** and **23** and olefin **19** are ~100% unless specified otherwise. [d] Room temperature; no temperature control. [e] Less than 0.4% conversion of olefin **19** to acetates **17** and **24** by gc analysis. [f] Conversion 83% by gc.

buffered perdeuterioacetic acid at 34.5° were determined by nmr spectroscopy. Both tosylates react at about the same rate, $k = 4.0 \pm 0.2 \times 10^{-4}$ sec^{-1} for *syn*-**16** and $4.3 \pm 0.4 \times 10^{-4}$ sec^{-1} for *anti*-**23**.

The *p*-toluenesulfonic acid catalyzed addition of acetic acid to the olefin **19** gave an acetate mixture which had a composition intermediate between those obtained in the solvolyses (Table I). The uncatalyzed addition of acetic acid was much slower, but the product distribution was similar (Table I).

Discussion

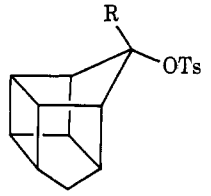
The nearly equal acetate distributions from the isomeric tosylates **16** and **23** indicate that no inherent steric or strain effect is present in the 1,3-bishomocubyl system which could account for the high degree of stereospecificity observed in the secondary system.[1,3a-c] The intermediacy of the bridged ions **4** and **10** would appear to be a reasonable alternate explanation.

The ratio of the rate constants for the solvolysis of the secondary tosylates **2** and **8** to those of the tertiary tosylates **17** and **24** is *ca.* 10^4–10^5 (Table II). These rate differences are approximately the same as those observed for many representative isopropyl and *tert*-butyl systems (*t*-BuX/*i*-PrX = 5.5×10^4 at 25°) and are much larger than those for benzylic systems ($PhCMe_2X$/PhCHMeX = 1.8×10^3).[19] The much greater demand made on the methyl group of the 7-methylnorborn-7-yl cation is evident from the *ca.* 10^8 rate acceleration over the nonmethyl derivative (Table II). The data in Table II also demonstrate the great rate leveling effect of the methyl substituent. The rates for the secondary systems differ by a factor of 300,000 while those for the tertiary systems differ by only a factor of 30.

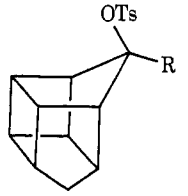
Schleyer and coworkers have presented evidence that 2-adamantyl tosylate or bromide solvolyzes with essentially no nucleophilic solvent participation and no anchimeric assistance from σ bridging.[20,21] Since the same is true of simple tertiary systems, these authors have proposed that the α-Me/H rate ratio (2-methyl-2-adamantyl bromide/2-adamantyl bromide in 80% aqueous ethanol or acetic acid) of *ca.* 10^8 is near the limit.[22] Thus any system which has an α-Me/H rate ratio less than 10^8 is interpreted as one in which the secondary compound is accelerated either by nucleophilic solvent displacement or nonclassical σ bridging.[22] The low α-Me/H rate ratio of *ca.* 10^4 for the *tert*-butyl bromide/isopropyl bromide system was attributed to acceleration of the isopropyl compound by nucleophilic solvent participation (the stereochemistry is virtually all inversion[20a]), while the value of *ca.* $10^{4.5}$ for the *exo*-2-norbornyl system was interpreted as due to anchimeric assistance (σ bridging) in the secondary system.[22] The α-Me/H rate ratios of 3.1×10^4 for the syn (**16**/**2**) and 1.1×10^5 for the anti (**23**/**8**) 1,3-bishomocubyl tosylates at 34.5° indicate an acceleration of *ca.* 10^3 for the secondary tosylates **2** and **8**. Since the stereochemistry of the acetolysis is predominantly (>95%) retention, we attribute the rate accelerations to anchimeric assistance (σ bridging). The high α-Me/H rate ratio for the 7-norbornyl system (5.1×10^7 at 50°,[19] 3.2×10^8 at 34.5°) was considered to be exceptional due to the "enormous demand on substituents for further stabilization"[19] made by this unusually unstable, strained cation.[22] The 2-adamantyl system was supposedly free from this defect; the bond angles are normal.[22] This "enormous demand" in the 7-norbornyl system is reflected in the large negative ρ value (−5.64) for the hydrolysis of 7-aryl-7-norbornyl chlorides.[23] There probably is some bond angle strain in 1,3-bishomocubyl systems also.[3b] This would have the effect of raising the observed α-Me/H rate ratio from what it would otherwise be. Thus there may be more acceleration in the 1,3-bishomocubyl systems than the α-Me/H rate ratios imply.

(19) H. Tanida, Y. Hata, S. Ikegami, and H. Ishitobi, *J. Amer. Chem. Soc.*, **89**, 2928 (1967).
(20) (a) J. L. Fry, C. J. Lancelot, L. K. M. Lam, J. M. Harris, R. C. Bingham, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2538 (1970); (b) J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *ibid.*, **94**, 4628 (1972); (c) D. J. Raber and J. M. Harris, *J. Chem. Educ.*, **49**, 60 (1972).
(21) However, see J. A. Bone and M. C. Whiting, *Chem. Commun.*, 115 (1970).
(22) J. L. Fry, J. M. Harris, R. C. Bingham, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2540 (1970).
(23) H. Tanida and T. Tsushima, *J. Amer. Chem. Soc.*, **92**, 3397 (1970).

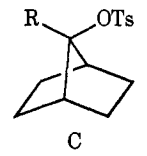
Table II. Relative Rates of Acetolysis of Secondary and Tertiary Tosylates at 34.5°



A



B



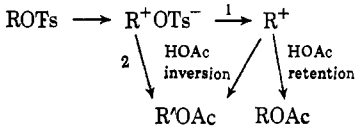
C

	R = H			R = CH_3			
Compd	Rate constant, sec^{-1}	Relative rate	E_a, kcal/mol	Rate constant, sec^{-1}	Relative rate	E_a, kcal/mol	Rate ratio R = CH_3/R = H
A	1.3×10^{-8} [a,b]	3.0×10^{6}	28.1[b]	4.0×10^{-4}	29		3.1×10^{4}
B	4.0×10^{-9} [a,b]	9.3×10^{4}	26.6[b]	4.3×10^{-4}	31		1.1×10^{5}
C	4.3×10^{-14} [a,c]	1	36.7[c]	1.4×10^{-5} [a,d]	1	27.1[d]	3.2×10^{8} [e]

[a] Calculated from data at higher temperature. [b] Data from ref 3b. [c] Data from S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Amer. Chem. Soc.*, 77, 4183 (1955). [d] Data from ref 19. [e] 4×10^{8} in 2,2,2-trifluoroethanol (D. E. Sunko, I. Szele, and M. Tomić, *Tetrahedron Lett.*, 1827 (1972)), temperature not specified.

The product distributions suggest that the acetolysis reactions of the tertiary tosylates **16** and **23** proceed mainly through a common intermediate(s). The small difference in product distributions probably arises due to a small amount of backside displacement by solvent on the initially formed intimate ion pair. Thus, the solvolyses occur by two pathways: (1) primarily by generation of a (solvent separated or symmetrically solvated dissociated) carbonium ion and (2) by backside displacement on an intimate ion pair (Scheme IV).[24] The 68:32 distribution of acetates **17** and **24**

Scheme IV



which was obtained from the addition of acetic acid to the olefin **19** at 45° probably is characteristic of the cationic intermediate(s) in the absence of the perturbing effect of the tosylate anion. This acid-catalyzed addition should produce a symmetrically solvated carbonium ion free of leaving group effects. The uncatalyzed addition at 100° gave a similar product distribution; the difference probably was due to a temperature effect. Once formed, the symmetrically solvated carbonium ion should collapse to product in both the syn and anti directions only as a result of the nature of the carbonium ion. Knowing the product distributions from each tosylate **16** and **23** one can calculate that 93% of the acetates from the *syn*-tosylate **16** and 79% of the acetates from the *anti*-tosylate **23** are formed *via* the solvent separated or dissociated carbonium ion, path 1. The remaining inverted acetates, 7% from **16** and 21% from **23**, were thus formed by direct solvent attack on the intimate ion pair, path 2. The steric effect of the leaving tosylate anion apparently predominates over that of the entering solvent molecule in controlling the relative amount of reaction *via* the intimate ion pair, path 1, based on the observation that there is less direct displacement on the *syn*-tosylate **16** ion pair and the fact that the syn side of the methylene bridge (C-6) is slightly more hindered.[3b]

An unexpected result in the acetolysis of the tertiary tosylates **16** and **23** and in the addition of acetic acid to the olefin **19** is that in all cases the predominant product was the syn acetate **17** which arose from syn attack on an intermediate cation. These results are unexpected since the ketone **18** undergoes reaction primarily by anti attack. Sodium borohydride, lithium aluminum hydride, and lithium tri-*tert*-butoxyaluminum hydride gave 76–80% anti attack.[3b] Methyllithium and methylmagnesium iodide gave 78 and 82% anti attack, respectively. A slight preference for anti attack on the 1,3-bishomocubyl system also was indicated in the epoxidation noted above. The decreased preference for anti attack in this case, 56:44, probably is due to the fact that the addition of the oxygen atom does not occur directly on the nonterminal sp^2 carbon atom,[25] and therefore less of the variability of steric effects on the syn and anti sides of the cage skeleton are felt.

The reason for the predominance of the *syn*-acetate **17** in the solvolysis and acetic acid addition reactions is not known. If the *syn*-tosylate **16** and acetate **17** were each of lower energy than their respective anti epimers **23** and **24**, examination of the appropriate Goering-Schewene diagram[26] would provide an explanation. However, the *syn*-**15** and *anti*-**22** alcohols are of nearly the same energy. Another conceivable explanation for the predominance of the *syn*-acetate **17** would involve weak σ bridging in the intermediate carbonium ion.

Experimental Section

General. Melting points were taken in capillary tubes and were uncorrected. Boiling points were uncorrected. Infrared spectra were obtained by Mr. F. L. Beman and coworkers with a Perkin-Elmer 337 grating infrared spectrophotometer. Nmr spectra were obtained by Mr. Beman and coworkers with a Varian A-60 analytical spectrometer operating at 60 MHz. All chemical shifts (δ) are relative to internal tetramethylsilane (positive when downfield from the reference). Mass spectral analyses were carried out by Dr. L. A. Shadoff and coworkers with a magnetically scanning 90° sector spectrometer, an electron ionizing voltage of 75 eV, and a sample inlet temperature of 200°. High-resolution mass spectra were obtained with a CEC 21-110B spectrometer that had a variable temperature direct probe sample introduction system. Gas chroma-

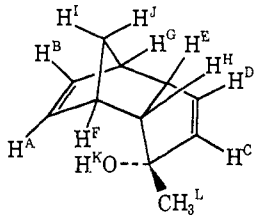
(24) See R. A. Sneen, *Accounts Chem. Res.*, 6, 46 (1973), for a recent discussion of various types of ion pairs and the stereochemistry of their reactions with solvent. It seems conceivable that inversion as well as retention could occur at the solvent-separated ion pair stage.

(25) See P. D. Bartlett, *Record Chem. Progr.*, 11, 47 (1950).

(26) See H. C. Brown, *Accounts Chem. Res.*, 6, 377 (1973), and references cited therein.

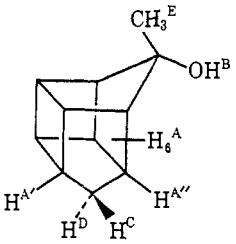
tographic analyses were carried out with a F and M 500 temperature programmed gas chromatograph. Elemental analyses were determined by Mr. R. B. Nunemaker and coworkers.

3-Methyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-*syn*-3-ol (14). Methyllithium was prepared by adding a solution of methyl iodide (28.4 g, 0.20 mol) in 50 ml of ether to a suspension of lithium wire (2.76 g, 0.40 g-atom) in 100 ml of refluxing ether under nitrogen. The solution was heated at reflux for an additional hour, and a solution of the dienone **13**[27] (16.05 g, 0.11 mol), in 100 ml of ether, was added over a period of 20 min. The mixture was heated at reflux for 2 hr. Shorter reaction times resulted in incomplete conversion of the dienone to product. The solution was cooled and poured into a solution of 20% aqueous ammonium chloride. The ether layer was separated, washed with water, and dried (Na_2SO_4). The ether was removed under vacuum to give a volatile white solid. Sublimation at 75° gave 12.4 g (70%) of fine white needles: mp 52–53° (lit.[16] mp 49–49.5°, stereochemistry not assigned); $\nu_{max}^{CCl_4}$ 3615 (m, OH), 3055 (m, =CH), 2970 (s), 2935 (m), and 2870 (m) (CH), 1625 (w, cyclopentenyl C=C), 1580 (w, norbornenyl C=C), 1375 (s, CH_3), 1345 cm^{-1} (s); $\nu_{max}^{CS_2}$ 1050 (s), 765 cm^{-1} (s); nmr spectrum ($CDCl_3$) an unsymmetrical doublet of doublets centered at 6.21 (1.2 H, H^A or H^B, J_{AB} = 5.8 Hz, $J_{AF\text{ or }BG}$ = 2.8 Hz), an unsymmetrical doublet of doublets centered at 5.86 (1.0 H, H$^{B\text{ or }A}$, J_{AB} = 5.8 Hz, $J_{BG\text{ or }AB}$ = 3.0 Hz), a singlet at 5.47 (1.8 H, H^C, H^D), an unsymmetrical doublet of doublets centered at 3.35 (1.1 H, H^E, J_{EH} = 7.7 Hz, J_{EG} = 4.7 Hz), a multiplet at 3.1–2.8 centered at 2.95 (1.9 H, H^F, H^G), an unsymmetrical doublet of doublets centered at 2.59 (1.0 H, H^H, J_{EH} = 7.8 H, J_{FH} = 3.9 Hz), a singlet at 1.47, which disappeared after the solution was shaken with D_2O (H^K), overlapping two unsymmetrical doublets of triplets centered at 1.61 (H$^{I\text{ or }J}$, J_{IJ} = 8.0 Hz, $J_{FI,GI\text{ or }FJ,GJ}$ = 1.9 Hz) and 1.41 (H$^{J\text{ or }I}$, $J_{FJ,GJ\text{ or }FI,GI}$ = 1.9 Hz, high field branch obscured) (3.2 H total), and a singlet at 1.33 ppm (2.8 H, H^L); mass spectrum, *m/e* 66 ($C_5H_6^+$), 78 ($C_6H_6^+$), 95 ($C_6H_7O^+$), 96 ($C_6H_8O^+$), 129 ($M^+ - H_2O$, CH_3^+), 144.0935 ($M^+ - H_2O$, calcd for $C_{11}H_{12}$, 144.0939), 162 (M^+, too weak for high resolution measurement).



14

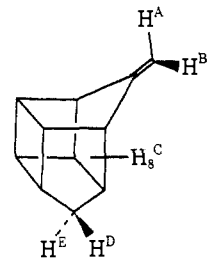
6-Methylpentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-*syn*-6-ol (15). A solution of the dienol **14** (9.0 g, 55 mmol) in 150 ml of reagent grade acetone was purged for 1.5 hr with purified nitrogen and irradiated with a 450-W Hanovia medium pressure mercury arc lamp. The lamp in a water-cooled quartz well with a Corex filter was immersed in the solution. The reaction was followed by gc analyses (10 ft × 0.25 in. Apiezon L column, 175°, He flow rate 80 ml/min, **14** t_R 10.5 min, **15** t_R 20.6 min). The reaction was complete after 3.0 hr. The acetone was removed under vacuum to give 8.7 g of white waxy solid. Sublimation at 75–80° (10 mm) gave 5.5 g (61%) of product as white crystals, mp 66–69°. Two recrystallizations from pentane gave an analytical sample: mp 80–81.5°; $\nu_{max}^{CCl_4}$ 3625 (m, free OH), 3370 (m, br, bonded OH), 2975 (s) and 2860 (m) (CH), 1455 (m) and 1380 cm^{-1} (m) (CH_3); $\nu_{max}^{CS_2}$ 1280 (m), 1162 (m), 1137 (m), 938 cm^{-1} (m); nmr spectrum ($CDCl_3$) a broad singlet at 3.25–2.96 with maximum intensity at 3.99 (1.0 H, one of H^A protons) incompletely resolved from a multiplet at 2.96 to 2.45 (five of H^A protons) with an overlapping singlet at 2.64 (H^B) (5.9 H total) which disappeared after the solution was shaken with D_2O (total relative area reduced to 4.9 H), incompletely resolved from a multiplet at 2.45–2.21 with maximum intensity at 2.35 (1.0 H, one of H^A protons) incompletely resolved from a multiplet at 2.21–1.91 with maximum intensity at 2.08 (1.1 H, one of H^A protons), an unsymmetrical doublet of triplets centered at 1.63 (1.1 H, H^C, J_{CD} = 11.3 Hz, $J_{A'C,A''C}$ = 1.4 Hz), an unsymmetrical doublet of triplets centered at 1.35 (1.0 H, H^D, J_{CD} = 11.2 Hz, $J_{A'D,A''D}$ = ~1.2 Hz), and a singlet at 1.08 ppm (2.8 H, H^E); mass spectrum, *m/e* 43 ($C_2H_3O^+$), 66 ($C_5H_6^+$), 96 ($C_5H_8O^+$), 104 ($C_8H_8^+$), 119 ($C_9H_{11}^+$), 129 ($M^+ - CH_3$, H_2O), 144 ($M^+ - H_2O$), 147 ($M^+ - CH_3$), 162 (M^+).



15

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44, H, 8.70; nuclidic mass, 162.1045. Found: C, 81.5; H, 8.67; nuclidic mass, 162.1044.

6-Methylenepentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (19). (a) By Wittig Reaction. Sodium hydride (4.8 g, 0.2 mol as a 50% dispersion in mineral oil) was washed three times with *n*-pentane to remove the mineral oil. The residual pentane was removed under vacuum; the system was flushed with nitrogen, and 100 ml of dry dimethyl sulfoxide was added. The mixture was stirred and heated (65–67°) until hydrogen evolution ceased (1 hr). The resulting solution of methylsulfinyl carbanion was cooled in an ice bath, and methyltriphenylphosphonium bromide (71.5 g, 0.20 mol) in 150 ml of warm dimethyl sulfoxide was added. The dark red solution of the ylide was stirred for 15 min, and a solution of the ketone **20**[3b,28] (29.3 g, 0.20 mol) in 100 ml of dimethyl sulfoxide was added over a period of 20 min. The mixture was stirred for 2 hr at ~25°. Water (100 ml) was added, and the mixture was extracted with pentane (3 × 200 ml). The pentane extracts were washed with water (3 × 200 ml) and dried (Na_2SO_4). The pentane was removed under vacuum to give a pale yellow oil. The oil was distilled to give 26.4 g (92%) of the olefin **19** as a colorless liquid: bp 58–59° (9 mm); $\nu_{max}^{CCl_4}$ 3080 (m, =CH), 2975 (s) and 2860 (m) (CH), 1860 cm^{-1} (m, C=C); $\nu_{max}^{CS_2}$ 877 cm^{-1} (s, C=CH_2); nmr spectrum (CCl_4) two unsymmetrical doublets centered at 4.53 (H$^{A\text{ or }B}$, J_{AB} = 1.5 Hz) and 4.47 (H$^{B\text{ or }A}$ J_{AB} = 1.5 Hz) (2.0 H total), a multiplet at 2.99–2.45 with a maximum at 2.75 (7.9 H, H^C), an unsymmetrical doublet centered at 1.67 (1.0 H, H^D, J_{DE} = 10.9 Hz), and an unsymmetrical doublet centered at 1.33 ppm (1.1 H, H^E, J_{DE} = 10.9 Hz); mass spectrum, *m/e* 39 ($C_3H_3^+$), 66 ($C_5H_6^+$), 78 ($C_6H_6^+$), 115 ($M^+ - C_2H_5$), 128 ($M^+ - CH_4$), 129 ($M^+ - CH_3$), 143 ($M^+ - H$), 144 (M^+).



19

Anal. Calcd for $C_{11}H_{12}$: nuclidic mass, 144.0939. Found: nuclidic mass, 144.0931.

(b) By Dehydration. To a solution of a mixture of the alcohols **15** and **22** (12.7 g, 78.4 mmol) in 50 ml of pyridine was carefully added 15.3 g (0.1 mol) of phosphorous oxychloride. The solution was warmed on a steam bath for 50 min and cooled in an ice bath, and the excess phosphorous oxychloride was destroyed by the cautious addition of small pieces of ice. Water (100 ml) was added, and the solution was extracted with pentane (2 × 100 ml). The pentane extracts were washed with water (2 × 100 ml) and dried (Na_2SO_4). The pentane was removed under vacuum, and the resulting oil was distilled to give 8.6 g (76%) of the olefin **19**. The infrared and nmr spectra of the product were identical with those of the product obtained by method a.

6-Methylenepentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane *anti*- (20) and *syn*-Oxides (21). To a solution of the olefin **19** (5.0 g, 35 mmol) in 20 ml of methylene chloride, which was cooled in an ice bath, was added a solution of *m*-chloroperbenzoic acid (80% active, 7.5 g, 35 mmol) in 75 ml of methylene chloride at such a rate that the temperature did not rise above 15°. The mixture was stirred for an additional hr and washed with 10% sodium sulfite solution (100 ml) followed by saturated sodium bicarbonate solution (3 × 125 ml) and water (100 ml). The solution was dried (Na_2SO_4), and the solvent was removed under vacuum to give 5.2 g (94%) of a

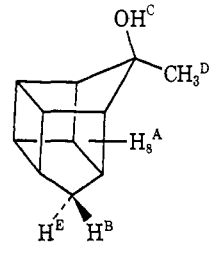
(27) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(28) R. C. Cookson, J. Hudec, and R. O. Williams, *J. Chem. Soc. C*, 1382 (1967).

mixture of the epoxides **20** and **21** as a yellow liquid: $\nu_{max}^{CCl_4}$ 3050 (m, epoxide CH_2), 2980 (s) and 2860 (m) (CH), 1255 cm^{-1} (m, epoxide ring); $\nu_{max}^{CS_2}$ 959 (m), 581 cm^{-1} (m); nmr spectrum ($CDCl_3$) a multiplet at 3.5–2.5 (7.8 H, $-CH_2O-$, six >CH protons), a multiplet at 2.47–2.15 with maximum intensity at 2.30 (1.1 H, one >CH), a multiplet at 2.15–1.84 with maximum intensity at 2.01 (0.9 H, one >CH), and four doublets centered at 1.70 (J = 11.1 Hz), 1.51 (J = 11.1 Hz), 1.44 (J = 11.2 Hz), and 1.33 ppm (J = 10.9 Hz) (2.2 H total, $-CH_2-$); mass spectrum, m/e 115 ($M^+ - C_2H_5O$), 116 ($M^+ - C_2H_4O$), 131 ($M^+ - CHO$), 145 ($M^+ - CH_3$), 160 (M^+).

Anal. Calcd for $C_{11}H_{12}O$: nuclidic mass, 160.0888. Found: nuclidic mass, 160.0868.

Lithium Aluminum Hydride Reduction of Epoxides 20 and 21. Preparation of 6-Methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-*anti*-6-ol (22). To a stirred slurry of lithium aluminum hydride (0.95 g, 25 mmol) in 50 ml of ether was added a solution of the epoxides **20** and **21** (mixture obtained in the preceding reaction) (4.0 g, 25 mmol) in 15 ml of ether at a rate sufficient to maintain a gentle reflux. The mixture was stirred for an additional hr at ~25°. Water (1 ml) was carefully added, followed by 1 ml of 15% sodium hydroxide solution and 3 ml of water. Sodium sulfate (10.0 g) was added and the mixture was stirred for 0.5 hr. The mixture was filtered, and the precipitates were washed with ether. The ether was removed under vacuum to give 4.0 g (99%) of white crystals whose nmr spectrum (methyl resonances at 1.37 and 1.08 ppm for **22** and **15**, respectively) indicated a 56:44 mixture of *anti*-**22** and *syn*-**15** alcohols, respectively. Seven recrystallizations of this mixture from hexane gave 1.0 g (25%) of the *anti*-alcohol **22** (97% **22**, 3% **15** by nmr): mp 128–128.5°; $\nu_{max}^{CCl_4}$ 3620 (m, free OH), 3270 (m, bonded OH), 2975 (s) and 2860 (m) (CH), 1455 (m) and 1380 cm^{-1} (m) (CH_3); $\nu_{max}^{CS_2}$ 1135 (m), 941 cm^{-1} (m); nmr spectrum ($CDCl_3$) a multiplet at 3.09–2.47 which consisted mainly of two broad peaks with maximum intensities at 2.87 and 2.68 (5.9 H, six of H^A protons) incompletely resolved from a broad peak at 2.47–



22

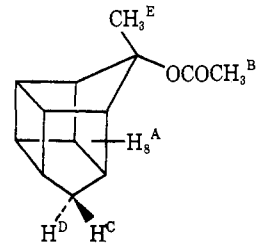
2.22 with maximum intensity at 2.35 (1.1 H, one of H^A protons) incompletely resolved from a broad peak at 2.22–1.96 with maximum intensity at 2.10 (1.1 H, one of H^A protons), an unsymmetrical doublet centered at 1.62 (1.1 H after D_2O exchange, H^B, J_{BE} = 10.5 Hz) overlapping a singlet at 1.54 (H^C) (2.0 H total) which disappeared after the solution was shaken with D_2O, a singlet at 1.37 (H^D) overlapping an unsymmetrical doublet (low-field branch obscured by methyl singlet at 1.37) centered at 1.25 ppm (H^E) (3.9 H total); mass spectrum, nearly identical with that of *syn*-alcohol **15**.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70; nuclidic mass, 162.1045. Found: C, 81.6; H, 9.20; nuclidic mass, 162.1046.

Attempts to separate the two isomers **15** and **22** by gc (10 ft × 0.25 in. columns packed with Carbowax 20M, Carbowax 4000, methylsilicone (SE-30), cyanosilicone (XE-60), Apiezon L, or 1,2,3-tri(2-cyanoethoxy)propane at temperatures ranging from 100 to 175° and flow rates of 40–80 ml/min) were unsuccessful.

Acid-Catalyzed Equilibration of *syn*-5 and *anti*-22 Alcohols. A solution of 1.0 g of an ~80:20 mixture of the *syn*-**15** and *anti*-**22** alcohols, respectively, in 10 ml of tetrahydrofuran was added to 20 ml of 50% aqueous sulfuric acid. The dark blue solution was stirred at ~25° for 24 hr and poured into 100 ml of water. The precipitate which formed was collected, dissolved in 20 ml of ether, and dried (Na_2SO_4). The ether was evaporated to give 0.5 g (50%) of a 48 ± 4:52 ± 4 mixture (nmr) of *syn*-**15** and *anti*-**22** alcohols, respectively. Similar experiments using 10 and 20% aqueous sulfuric acid failed to effect any isomerization.

6-Methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-*syn*-6-yl Acetate (17). A solution of the *syn*-alcohol **15** (0.50 g, 3.1 mmol) and 2 ml of acetic anhydride in 5 ml of pyridine was stirred for 3 days at ~25°. The reaction mixture was poured into water (30 ml) and extracted with pentane (4 × 10 ml). The pentane extracts were washed with water, 10% hydrochloric acid, and again with water. The pentane solution was dried (Na_2SO_4), and the solvent was removed under vacuum to give 0.59 g (96%) of the *syn*-acetate **17** as a colorless oil (gc analysis on a 10 ft × 0.25 in. Carbowax 4000 column at 150° with a flow rate of 80 ml/min showed <1% of a lower boiling impurity): $\nu_{max}^{CCl_4}$ 2980 (s) and 2865 (m) (CH), 1735 (s, C=O), 1455 (m) and 1380 cm^{-1} (m) (CH_3); $\nu_{max}^{CS_2}$ 1254 (s), 1240 (s, CO), 1103 cm^{-1} (m); nmr spectrum ($CDCl_3$) a multiplet at 3.00–2.53 with maxima at 2.80 and 2.71 (7.7 H, H^A), a singlet at 2.02 (3.0 H, H^B),

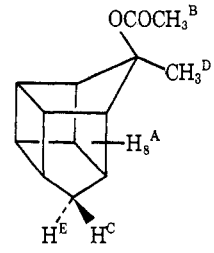


17

an unsymmetrical doublet centered at 1.64 (1.1 H, H^C), J_{CD} = 11.1 Hz), and an unsymmetrical doublet centered at 1.33 (H^D) with the weaker high-field branch obscured by an intense singlet at 1.23 ppm (H^E) (4.2 H total); mass spectrum, m/e 43 (CH_3CO^+), 66 ($C_5H_6^+$), 78 ($C_6H_6^+$), 96 ($M^+ - C_5H_6$, C_2H_2O), 129 ($M^+ - CH_3CO_2H$, CH_3), 138 ($M^+ - C_5H_6$), 144 ($M^+ - CH_3CO_2H$), 162 ($M^+ - C_2H_2O$), 204 (M^+).

Anal. Calcd for $C_{13}H_{16}O_2$: nuclidic mass, 204.1150. Found: nuclidic mass, 204.1152.

6-Methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-*anti*-6-yl Acetate (24). As described in the preceding experiment, 0.50 g of the *anti*-alcohol **22** was converted to 0.60 g (98%) of the *anti*-acetate **24** as a colorless oil (<1% of a lower boiling impurity by gc analysis as described in the preceding experiment): $\nu_{max}^{CCl_4}$ 2980 (s) and 2865 (m) (CH), 1735 (s, C=O), 1455 (m) and 1380 cm^{-1} (m); $\nu_{max}^{CS_2}$ 1247 (s, CO), 1226 (m), 1111 cm^{-1} (m); nmr spectrum ($CDCl_3$) a multiplet at 3.05–2.48 with maximum intensity at 2.74 (8.2 H, H^A), a singlet at

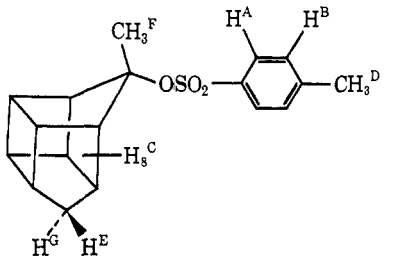


24

1.92 (2.8 H, H^B), an unsymmetrical doublet centered at 1.67 (H^C) with the stronger high-field branch obscured by an intense singlet at 1.54 (H^D) (3.9 H total), and an unsymmetrical doublet centered at 1.31 ppm (1.1 H, H^E, J_{CE} = 11.0 Hz); mass spectrum, nearly identical with that of *syn*-acetate **17**. High resolution mass spectrometry showed a molecular ion with an m/e of 204; however, it was too weak for accurate mass measurement. The fragments with m/e 162 ($M^+ - C_2H_2O$) and 144 ($M^+ - CH_3CO_2H$) were measured.

Anal. Calcd for $C_{11}H_{14}O$: 162.1045. Found: 162.1075. Calcd for $C_{11}H_{12}$: 144.0939. Found: 144.0962.

6-Methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-*syn*-6-yl *p*-Toluenesulfonate (16). According to the general procedure of Tanida and coworkers,[19] a 23% hexane solution of *n*-butyllithium (7.2 ml, ~17 mmol) was added to a stirred solution of the *syn*-alcohol **15** (2.50 g, 15.4 mmol) in 75 ml of tetrahydrofuran at 5–10° under a nitrogen atmosphere. The solution was stirred for 25 min. A solution of *p*-toluenesulfonyl chloride (3.36 g, 17.6 mmol) in 25 ml of tetrahydrofuran was added at 0–5°, and the mixture was stirred for 3 hr. The tetrahydrofuran was evaporated under vacuum. The residual yellow solid was dissolved in 225 ml of ether, washed with water, and dried over Na_2SO_4. The yellow solid obtained by evaporation of the ether was recrystallized from hexane to give 3.5 g (72%) of the *syn*-tosylate **16** as white crystals: mp 88–90° dec; $\nu_{max}^{CCl_4}$ 3075 (w, =CH), 2980 (s) and 2865 (m) (CH), 1605 (m) and 1505 (m) (C=C), 1455 (m) and 1385 (m) (CH_3), 1360 (s) and 1345 cm^{-1} (s) (S=O); $\nu_{max}^{CS_2}$ 1181 (s) and 1170 (s) (S=O), 878 cm^{-1} (s); nmr spectrum ($CDCl_3$) an unsymmetrical doublet centered at 7.81 (2.0 H, H^A, J_{AB} = 8.2 Hz), an unsymmetrical doublet centered at 7.31 (2.0 H, H^B, J_{AB} = 8.3 Hz), a multiplet at 3.11–2.20 with maxima at 2.92 and 2.59 (H^C) overlapping a singlet at 2.44 (H^D) (11.0 H total),



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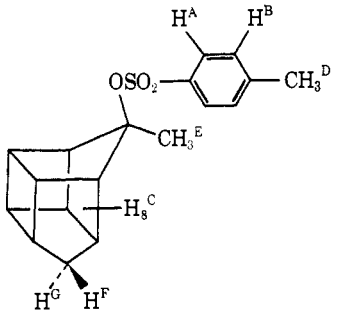
an unsymmetrical doublet centered at 1.61 (1.2 H, H^E, J_{EG} = 11.9 Hz), and a singlet at 1.37 (H^F) which obscured the more intense low-field branch of an unsymmetrical doublet centered at 1.29 ppm (H^G) (3.8 H total); mass spectrum, *m/e* 66 ($C_5H_6^+$), 78 ($C_6H_6^+$), 91 ($C_7H_7^+$), 95 ($C_6H_7O^+$), 144 ($C_{11}H_{12}^+$), 172 ($CH_3C_6H_4SO_3^+$), 250 ($M^+ - C_5H_6$), 316 (M^+).

Anal. Calcd for $C_{18}H_{20}O_3S$: C, 68.32; H, 6.37; mol wt, 316. Found: C, 68.50; H, 6.27; mol wt, 316 (mass spectrometry).

This compound decomposed after 48 hr at ~25° but could be stored for weeks at *ca.* −15°.

A solution of the *syn*-alcohol **15** (~90% **15**, ~10% **22**) (0.05 g, 0.3 mmol) and *p*-toluenesulfonyl chloride (0.07 g, 0.3 mmol) in 0.5 ml of pyridine was allowed to stand at 0° for 2 hr. Water (0.55 ml) was added dropwise over a period of 0.5 hr, and the mixture was extracted with $CHCl_3$ (3 × 0.5 ml). The combined extracts were washed successively with equal volumes of 3 *N* sulfuric acid, water, and saturated aqueous sodium bicarbonate solution. All of the above operations were carried out with the flask immersed in an ice bath. The chloroform was dried ($CaCl_2$) and evaporated under vacuum to give 0.04 g (80% recovery) of white to light yellow crystalline solid. The infrared and nmr spectra were nearly identical with that of the starting mixture of alcohols.

6-Methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-*anti*-6-yl *p*-Toluenesulfonate (23). As described in the preceding experiment, the *anti*-alcohol **22** (1.50 g, 9.25 mmol) was converted to 1.4 g (48%) of the *anti*-tosylate **23**, mp 34–36°, after recrystallization from hexane: $\nu_{max}^{CCl_4}$ 3075 (w, =CH), 2985 (s) and 2865 (m) (CH), 1605 (w) and 1505 (w) (C=C), 1455 (m) and 1385 (m) (CH_3), 1365 and 1320 cm^{-1} (s) (S=O); $\nu_{max}^{CS_2}$ 1182 (s) and 1171 (s) (S=O), 877 cm^{-1} (s); nmr spectrum ($CDCl_3$) an unsymmetrical doublet centered at 7.73 (2.0 H, H^A, J_{AB} = 8.4 Hz), an unsymmetrical doublet



23

centered at 7.27 (2.0 H, H^B, J_{AB} = 8.4 Hz), a multiplet at 2.98 to 2.30 with maximum intensity at 2.67 (8.0 H, H^C) slightly overlapping a singlet at 2.42 (3.0 H, H^D), an intense singlet at 1.69 (H^E) overlapping the weaker low-field branch of a doublet centered at 1.64 (H^F) (4.0 H total), and an unsymmetrical doublet centered at 1.27 ppm (1.0 H, H^G, J_{FG} = 11.6 Hz); mass spectrum, very similar to that of the syn isomer **16**.

Anal. Calcd for $C_{18}H_{20}O_3S$: C, 68.32; H, 6.37; mot wt, 316. Found: C, 68.01; H, 6.23; mol wt, 316 (mass spectrometry).

This compound was stored at *ca.* −15°.

Reaction of Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (18) with Methylmagnesium Iodide.[29] Methylmagnesium iodide was prepared by the addition of a solution of methyl iodide (18.2 g, 0.068 mol) in 20 ml of dry ether to 1.6 g (0.065 g-atom) of magnesium turnings covered with 50 ml of anhydrous ether. After dissolution of the magnesium was complete, a solution of the cage ketone **20**[3b,28] (4.0 g, 0.027 mol) in 20 ml of ether was slowly added over a period of 20 min. The reaction mixture was heated at reflux for 2 hr, cooled, hydrolyzed with water (10 ml), and poured into 100 ml of 20% aqueous ammonium chloride solution. The ether layer was separated, washed with water (3 × 50 ml), and dried (Na_2SO_4). The solvent was removed under vacuum to afford 3.7 g (83%) of a 82:18 mixture of *syn*-**15** and *anti*-**22** alcohols, respectively, as determined by nmr analysis.

Reaction of Ketone 18 with Methyllithium. Methyllithium was prepared by adding 7.1 g (0.05 mol) of methyl iodide in 15 ml of ether to a suspension of lithium (0.69 g, 0.10 g-atom) in 30 ml of refluxing ether under nitrogen over a period of 15 min. The mixture was refluxed for an additional 45 min, and a solution of the ketone **18** (4.28 g, 0.03 mol) in 40 ml of ether was added over a period of 15 min. The reaction mixture was heated at reflux for an additional 2 hr, cooled, and poured into 100 ml of 20% aqueous ammonium chloride solution. The ether layer was separated, washed with water (2 × 75 ml), and dried (Na_2SO_4). The solvent was removed under vacuum to give 4.7 g (97%) of a 78:22 mixture (by nmr) of *syn*-**15** and *anti*-**22** alcohols, respectively.

Preparative Acetolysis of *syn*-Tosylate 16. (a) Unbuffered. A solution of the *syn*-tosylate **16** (0.775 g, 2.45 mmol) in 20 ml of anhydrous acetic acid which contained 0.5% acetic anhydride (0.122 *M* **16**) was placed in a flask, sealed under nitrogen, and heated at 45 ± 1° for 1 hr. The deep blue solution was poured into 200 ml of ice-water and extracted with methylene chloride (5 × 25 ml). The extracts were washed with 5% aqueous sodium bicarbonate solution (3 × 50 ml), water (100 ml), and dried (Na_2SO_4). The solvent was removed under vacuum to give 0.49 g (98%) of product. Nmr analysis showed a 63:37 mixture of the *syn*-**17** and *anti*-**24** acetates, respectively, by integration of the acetoxy methyl resonances at 2.02 and 1.92 ppm, respectively. The remainder of the nmr spectrum and the infrared spectrum were also consistent with this composition. Attempts to separate the two isomers by gc using the same columns that were used above with the alcohols **15** and **22** were unsuccessful.

(b) Buffered. To a solution of 10 ml of anhydrous acetic acid which contained 300 mg (2.94 mmol) of acetic anhydride was added 260 mg (2.45 mmol) of analytical reagent grade sodium carbonate. The solution (0.490 *M* in sodium acetate) was stirred for 2 hr, and 0.356 g (1.13 mmol) of the *syn*-tosylate **16** was added (0.113 *M* **16**). The solution was heated at 45 ± 1° for 1 hr. Work-up of the reaction mixture as described afforded 0.222 g (90%) of product. Nmr analysis indicated a ratio of 63:37 for the *syn*-**17** and *anti*-**26** acetates, respectively. Both the nmr and infrared spectra were identical with those of the acetate mixture obtained in part a.

Preparative Acetolysis of *anti*-Tosylate 23. A solution of 0.745 g (2.35 mmol) of the *anti*-tosylate **23** in 15 ml of anhydrous acetic acid which contained 0.5% acetic anhydride (0.157 *M* **23**) in a sealed flask under nitrogen was heated at 45 ± 1° for 1 hr. The deep blue reaction mixture was worked up as above for the syn isomer **16** to give 0.50 g (103%) of product. Nmr analysis showed a 75:25 mixture of the *syn*-**17** and *anti*-**24** acetates respectively. The infrared spectrum was also consistent with this composition.

Stability of Acetates under Acetolysis Conditions. (a) *syn*-17. A solution 0.122 *M* in *p*-toluenesulfonic acid was prepared by dissolving 0.189 g (1.22 mmol) of *p*-toluenesulfonic acid monohydrate in 10 ml of anhydrous acetic acid and 0.125 g (1.22 mmol) of acetic anhydride. The solution was stirred at 45° for 5 days. To this solution was added 250 mg (1.22 mmol) of the *syn*-acetate **17**, and the solution was stirred at 45° for 2 hr. The solution was cooled, poured into 150 ml of water, and extracted with methylene chloride (4 × 25 ml). The extracts were washed with water (2 × 100 ml), saturated sodium bicarbonate solution (100 ml), and again with water. The solution was dried (Na_2SO_4), and the solvent was removed under vacuum to give 220 mg (89%) of acetate. The infrared and nmr spectra of the product were identical with those of the *syn*-acetate **17**. There was no evidence for the presence of any isomeric acetate **24**.

(b) *anti*-24. A solution 0.157 *M* in *p*-toluenesulfonic acid was prepared by dissolving 242 mg (1.57 mmol) of *p*-toluenesulfonic acid monohydrate in 10 ml of anhydrous acetic acid and 157 mg (1.54 mmol) of acetic anhydride. The solution was stirred at 45° for 2 days. To this solution was added 320 mg (1.57 mmol) of the *anti*-acetate **24**, and the solution was stirred at 45° for 2 hr. The reaction mixture was worked up in the same manner as in part a to give 293 mg (93%) of acetate. The infrared and nmr spectra of the product were identical with that of the starting *anti*-acetate **24**. There was no evidence for the presence of the syn isomer **17** or any other isomeric acetates.

Kinetic Acetolyses. (a) *syn*-Tosylate 16. The reaction was followed by measuring the dissappearance of the nmr signal for the C-6 methyl group in the tosylate and the appearance of the signals

(29) This reaction was first carried out by Dr. C. E. Reineke.

for the C-6 methyl groups in the product acetates. The peak area for the *p*-methyl group in the aromatic ring was used as an internal standard. A solution of 100 mg (0.316 mmol) of the tosylate **16** in 1 ml of acetic-d_4 acid (0.316 *M*) was placed in an nmr tube, and the spectrum was run (probe temperature ~35°). The tube was placed in the vapors of a refluxing ether bath (34.5°). The tube was withdrawn periodically, and the spectrum was obtained. The following results were obtained (time in seconds and per cent unreacted tosylate **16** remaining given): 0, 90.1; 2940, 46.1; 4440, 24.7; 5710, 15.0; 7080, 8.8. The rate constant, 4.0×10^{-4} sec^{-1}, and standard derivation, $\pm 0.2 \times 10^{-4}$ sec^{-1}, were calculated by the least-squares method described previously.[3b]

(b) *anti*-Tosylate 23. In a manner analogous to that described in part a, the following results were obtained for the *anti*-tosylate **23** (time in seconds and per cent unreacted tosylate **23** remaining given): 0, 89.2; 1290, 64.3; 2700, 34.2; 4240, 17.6; 5495, 9.9; 6900, 5.9. The first-order rate constant and standard derivation, calculated as in part a, were $4.3 \pm 0.4 \times 10^{-4}$ sec^{-1}.

Addition of Acetic Acid to Olefin 19. (a) *p*-Toluenesulfonic Acid Catalyzed at 45°. A solution of *p*-toluenesulfonic acid monohydrate (189.0 mg, 0.994 mmol) and acetic anhydride (102.1 mg, 1.000 mmol) in 4.0 ml of glacial acetic acid was heated at 45° for 21 hr. The solution was cooled to ~25°, and the olefin **19** (147.8 mg, 1.025 mmol) was added along with another 3.0 ml of acetic acid. The resulting solution (0.14 *M* each in olefin **19** and toluenesulfonic acid) was mixed thoroughly and heated at 45 ± 1° for 4.0 hr. After being cooled to ~25°, the dark purple solution was worked up as described above for the acetolyses to give 161.6 mg (77%) of a colorless oil. Nmr analysis indicated a composition of 69 ± 1% *syn*-acetate **17** and 31 ± 1% *anti*-acetate **24** (planimeter area measurements of the acetoxy methyl resonances on spectra run at 50 Hz sweep width). The remainder of the nmr spectrum and the infrared spectrum of the reaction mixture were consistent with this composition.

(b) *p*-Toluenesulfonic Acid Catalyzed at ~25°. A solution of 308 mg (1.62 mmol, 0.8 *M*) of *p*-toluenesulfonic acid monohydrate and 204 mg (2.0 mmol) of acetic anhydride in 2 ml of acetic acid was stirred for 4 hr. The olefin **19** (288 mg, 2.0 mmol, 1.0 *M*) was added, and the solution was stirred at ~25° for 3 hr. The reaction was greater than 95% complete (gc analysis). The dark blue solution was poured into water and extracted with ether. The ether extracts were washed with water, saturated sodium bicarbonate solution, and again with water. After the solution was dried, the solvent was removed under vacuum to give 380 mg (93%) of a 68:32 mixture of *syn*-**17** and *anti*-**24** acetates, respectively.

(c) Attempted Uncatalyzed Addition at 45°. A solution of the olefin **19** (151.7 mg, 1.052 mmol) in 7.0 ml of glacial acetic acid (0.15 *M*) was heated at 45 ± 1° for 48 hr. Gc analysis (10 ft × 0.25 in. column packed with 20% E-60 Silicone Nitrile on 60–80 mesh Gas-Chrom Z at 150°, flow rate 44 ml/min) showed no (<0.4% conversion) acetates **17** or **24** (both t_R's 30.3 min); only olefin **19** (t_R 8.2 min) was detected in addition to the solvent.

(d) Uncatalyzed Addition at 100°. The solution of unreacted olefin **19** which was obtained in the preceding section (part c) was heated at 100 ± 1° for 168 hr. Gc analysis as in part c after 48 and 168 hr indicated conversions of 39 and 83% (based only on peak areas of acetates **17** and **24** and olefin **19**, and assuming equal thermal conductivities for **17**, **19**, and **24** on a molar basis, see below), respectively, to the acetates **17** and **24**; no other products were detected. These conversions represent a first-order rate constant of 2.9×10^{-6} sec^{-1}. The amber reaction solution was worked up as in part a above to give 161.8 mg (64% conversion to acetates **17** and **24**, 16% of olefin **19** recovered, 76% yield of **17** and **24**) of pale yellow oil. Nmr analysis ($CDCl_3$) indicated a molar ratio of total acetates **17** and **24** to olefin **19** (two olefinic proton doublets centered at 4.62 and 4.56 ppm) of 80:20 and a *syn*-acetate **17** to *anti*-acetate **24** ratio of 63 ± 1:37 ± 1. The infrared spectrum was consistent with this composition.

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Semiempirical Calculations on the Electronic Structure and Preferred Conformations of Thiamine (Vitamin B_1) and Thiamine Pyrophosphate (Cocarboxylase)

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Abstract: Extended Hückel and CNDO/2 molecular orbital calculations were performed on the title compounds in their various states of ionization. The electronic structures are discussed. The charges then were used to define the regions of preferred conformations in these molecules *via* the sum of a Lennard-Jones and a Coulombic potential. The conformational energy maps for thiamine hydrochloride with unperturbed and ylide (C-2 deprotonated) thiazolium rings are fairly similar. It appears that full 360° rotation around either of the bonds connecting the two aromatic rings (C–C and C–N bond) is subject to substantial barrier of at least 15–18 kcal/mol. The energetically most favored conformational regions apparently can interconvert readily at room temperature. A suggestion is made for possible conformational changes occurring in the coenzyme upon binding of substrates and enzyme.

Thiamine or vitamin B_1 (thiamine hydrochloride, THC) is the important precursor to the coenzyme thiamine pyrophosphate (TPP). TPP has been strongly implicated in a number of enzymic processes among the most prominent of these being the α-keto acid decarboxylases and transketolases.[1]

Considerable evidence has been gathered especially concerning the mode of action of the enzyme pyruvate decarboxylase, PDC (from brewer's or baker's yeast). PDC requires TPP and Mg(II) for its action.[1] The model systems for this action strongly suggest the existence of a covalently bound pyruvate–TPP intermediate which intermediate is the actual decarboxylating specie.

The proposed mechanism involves several steps in the process.[2] First, the ylide of the coenzyme is formed by loss of a proton from C-2 of the thiazolium (THZ)

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