Conformational Analysis of Isomeric 4-Substituted Cyclohexylcarbinyl p-Tosylates

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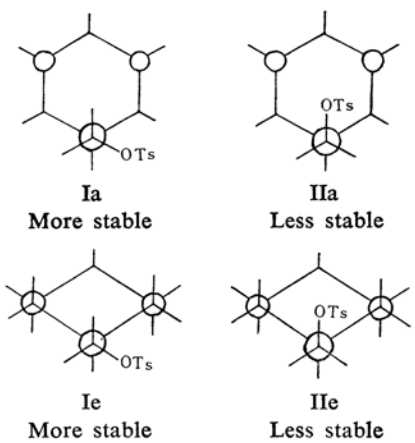
In a previous work[1] which was carried out to investigate the difference in reactivity between the axial and the equatorial *p*-toluenesulfoxymethyl group in a cyclohexane system, it was found that *cis*-4-methylcyclohexylcarbinyl *p*-tosylate was solvolyzed more rapidly in acetic acid and more slowly in ethanol than the trans-isomer. From the observed rates and the consideration for their possible conformations, it was suggested that conformation Ia rather than IIa should be favorable for the axial *p*-toluenesulfoxymethyl group and conformation Ie rather than IIe for the equatorial one.

However, the above tosylates are unsuitable to provide a precise solution for the above problem, since each of them may exist in two interconvertible chair-conformations, the conformations and their relative rates of reaction must be taken into account estimating reactivity. Consequently, it is desirable to study a pair of diastereoisomeric compounds whose chair conformations are entirely pure.



Ia More stable — IIa Less stable

Ie More stable — IIe Less stable

Fig. 1

1) N. Mori, This Bulletin, **34**, 1299 (1961).

A detailed study has now been made of solvolysis of *cis*- and *trans*-4-*t*-butylcyclohexylcarbinyl *p*-tosylate under the assumption that the *t*-butyl group is more bulky than the *p*-toluenesulfoxymethyl group so that it is entirely restricted in the equatorial orientation and exerts no direct polar or steric effect across the cyclohexane ring, as in the case of *t*-butylcyclohexyl *p*-tosylates[2,3].

The results obtained show that the *cis*-*t*-butylcyclohexyl compound with an axial toluenesulfoxymethyl group is solvolyzed more rapidly by a factor of 4 in acetic acid and more slowly by a factor of 0.5 in ethanol than the trans-form with an equatorial toluenesulfoxymethyl group and the free energy difference ($e-a$) is $-1.7\sim-1.8$ kcal./mol., which is surprisingly almost equal to $-1.6\sim-1.8$ kcal./mol.[4] for the methyl group and which supports the assumption that the *t*-butyl group is entirely restricted in the equatorial orientation.

Experimental

Samples. — *cis*- and *trans*-4-*t*-Butylcyclohexylcarbinyl *p*-tosylate were prepared from the corresponding *cis*- and *trans*-4-*t*-butylcyclohexylcarbinols according to the method[5] previously reported by the author. The former melted at 95~95.5°C and the latter at 84°C.

Acetolysis of Cyclohexylcarbinyl *p*-Tosylate.— Cyclohexylcarbinyl *p*-tosylate[1] (6 g.) and an approximately equivalent amount of anhydrous sodium acetate in acetic acid (50 cc.) in a sealed ampoule were heated at 110°C for 60 hr. The reaction mixture was neutralized with sodium carbonate and extracted with ether. After drying, the ether solution was concentrated and the residue was heated with a methanolic sodium hydroxide solution for a short period. The mixture was evaporated and extracted with ether, and the ether extract was washed with water, dried and distilled. The distillation gave only one fraction (2 g., 80% yield) boiling at 89~90°C/19 mmHg and having $n_D^{21}=1.4638$, which was identical with cyclohexylcarbinol having b. p. 91°C/18 mmHg and $n_D^{20}=1.4649$. The above methanol distilled out, on addition of a salt solution, deposited an oily product (ca. 40 mg., 1.5% yield), which absorbed bromine and was therefore probably methylenecyclohexane boiling at 103°C.

Procedure for Rate Measurements. — Solvolysis was followed in ethanol (98.5% by weight) and in acetic acid containing a slight excess of acetic anhydride to 20~50% completion at 99.8±0.1°C or to 40~60% completion at 110±0.1°C by the usual ampoule technique[6] and first order rate constants calculated were steady to ±3% in the acetolysis and to ±5% in the ethanolysis. Table I lists the data for a typical run with *cis*-4-*t*-butylcyclohexylcarbinyl *p*-tosylate at 99.8°C in acetic acid.

Table I. Acetolysis of *cis*-4-*t*-butylcyclohexylcarbinyl *p*-tosylate at 99.8°C

Time sec.	Tosylate 10^2 mol./l.	$k_1\times10^5$/sec.
0	1.550	
5400	1.450	1.23
9000	1.385	1.28
12600	1.326	1.23
16200	1.279	1.24
19800	1.219	1.21
22200	1.180	1.23
25200	1.144	1.20
28800	1.100	1.20
	Mean	1.23

Unsubstituted and 4-methyl substituted cyclohexylcarbinyl tosylates[1] previously used were also solvolyzed at 110°C. Heats and entropies of activation were calculated by means of the equation given by Eyring[7].

The rate constants obtained are summarized in Table II, along with those of some other primary alkyl *p*-tosylates for comparison.

Discussion

Behavior in Solvolysis.—Since unsubstituted and substituted cyclohexylcarbinyl *p*-tosylates are regarded as members of a β-branched primary alkyl series, a similarity of behavior in solvolysis would be expected between these *p*-tosylates and, for example, isobutyl *p*-tosylate. In fact, Table II shows that the rates and $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values of acetolysis of all cyclohexylcarbinyl *p*-tosylates used in the present work agree substantially with those of primary alkyl *p*-tosylates such as ethyl and isobutyl *p*-tosylate[8]. Further, an upward trend in rate as going from acetic acid to ethanol is not only observed for the former tosylates except *cis*-*t*-butylcyclohexycarbinyl tosylate, but also similarly for the latter tosylates, as shown in Table III. Such an upward trend in the rate attending the solvent change has not been found for secondary alkyl *p*-tosylates in general as well as cyclohexyl *p*-tosylates, while for these tosylates a downward trend in rate is observed which probably arises from the electron repelling inductive effect of α-alkyl substituents. Additionally, the absence of such α-substituents would be expected to result in lower acetolysis rates (10^{-5}/sec. at 100°C) of the primary alkyl and the cyclohexylcarbinyl *p*-tosylates, as compared

2) S. Winstein and H. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).
3) E. L. Eliel and C. A. Lukach, ibid., **79**, 5986 (1957).
4) M. Newman, "Steric Effects in Organic Chemistry", John Wiley and Sons, Inc., New York, N. Y. (1956), p. 18.
5) N. Mori, This Bulletin, **34**, 1567 (1961).
6) N. Mori, ibid., **33**, 1144 (1960).
7) S. Glasstone, K. J. Laider and H. Eyring, "The Theory of Rate Processes", McGraw-Hill Book Co., Inc., New York, N. Y. (1941), p. 196.
8) S. Winstein and H. Marshall, *J. Am. Chem. Soc.*, **74**, 1120 (1952).

TABLE II. SUMMARY OF SOLVOLYSIS RATES

4-Substituent	Solvent	Tosylate 10^2 mol./l.	Temp. °C	$k_1 \times 10^5$/sec.	$\Delta H^{\neq}$ kcal./mol.	$\Delta S^{\neq}$ e. u.
cis-t-Bu	EtOH	1.55	99.8	0.935	27.9	−7.1
	EtOH	1.30	110	2.48		
	AcOH	1.55	99.8	1.23		
	AcOH	1.55	110	3.35		
trans-t-Bu	EtOH	1.55	99.8	1.85	27.1	−12
	EtOH	1.30	110	4.45		
	AcOH	1.55	99.8	0.290		
	AcOH	1.40	110	0.768		
cis-Me	EtOH	1.79	99.8	1.28[1]	26.1	−13
	AcOH	1.78	99.8	0.723[1]		
	AcOH	1.40	110	1.85		
trans-Me	EtOH	1.79	99.8	1.83[1]	26.8	−12
	AcOH	1.81	99.8	0.298[1]		
	AcOH	1.40	110	0.782		
H	EtOH	1.60	99.8	1.40[1]	27.3	−11
	EtOH	1.64	110	2.97		
	AcOH	1.58	99.8	0.378[1]		
	AcOH	1.64	110	1.00		
EtOTs[8]	AcOH	3.8∼4.3	99.6	0.847	24.4*	−16.7
iso-BuOTs[8]	AcOH	2.5∼2.8	99.7	0.379	28.2*	−8.0

* Value at 75°C

TABLE III. RELATIVE RATES

4-Substituent	EtOH/AcOH		AcOH	EtOH	AcOH	EtOH
	99.8°C	110°C	99.8°C		110°C	
cis-t-Bu	0.76	0.74	4.23	1.00	4.36	1.00
cis-Me	1.77	—	2.49	1.37	2.41	—
H	3.7	3.0	1.30	1.50	1.30	1.20
trans-Me	6.1	—	1.03	1.95	1.02	—
trans-t-Bu	6.4	5.8	1.00	1.97	1.00	1.78
EtOTs	39*					
iso-BuOTs	6.2*					
neo-PentOTs	0.28*					

* Values at 75°C (lit. 8)

to those (10^{-3}/sec. at 100°C) of the secondary alkyl and the cyclohexyl *p*-tosylates.

In view of the result to be published in a subsequent paper that rates of acetolysis of isomeric 1, 2-bis-*p*-toluenesulfoxymethylcyclohexanes are not influenced by the presence of sodium acetate, the acetolysis of the cyclohexylcarbinyl *p*-tosylates is essentially of the unimolecular type involving a carbonium ion. Further, the acetolysis of cyclohexylcarbinyl *p*-tosylate gave predominantly one substituted product with a very small amount of olefin (see Experimental). This fact means that the acetolysis of the isomeric cyclohexylcarbinyl tosylates probably consists substantially of a substitution reaction while an elimination reaction is practically of unimportance. The ethanolysis of these compounds also may mainly consist of a substitution reaction. This expection is also supported by the fact[9] that bimolecular reaction of dimethanesulfonates of *cis*- and *trans*-1, 3-dihydroxymethylcyclohexanes with sodium iodide in acetone gives the corresponding *cis*- and *trans*-diiodide in 41 and 94% yield, respectively, and hydrolysis of the above two dimethanesulfonates in aqueous potassium hydroxide solution gives the corresponding *cis*- and *trans*-dicarbinol in a major yield (70% or more) and 4-methylenecyclohexylcarbinol in a minor yield (ca. 7%).

9) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, **1953**, 404.

Table IV. Relative rates of cis/trans

4-Substituent	99.8°C		110°C	
	EtOH	AcOH	EtOH	AcOH
t-Bu	0.51	4.2	0.55	4.3
Me	0.69	2.4	—	2.4

From Tables III and IV in which relative rates are shown, it will be seen that behavior in solvolysis of *cis-t*-butylcyclohexylcarbinyl tosylate in different solvents is essentially different from that of the trans-isomer. That is to say, the cis-form is acetolyzed more rapidly than the trans-form and on the contrary the former is ethanolyzed more slowly than the latter. The rate ratios of cis/trans in the acetolysis and in the ethanolysis are respectively 4.2 and 0.51 at 99.8°C which are almost the same as the values at 110°C, and these values agree essentially with 2.4 and 0.69 for 4-methylcyclohexylcarbinyl tosylates.

Further, the tables show that *trans*-4-*t*-butylcyclohexylcarbinyl tosylate is solvolyzed more rapidly in ethanol than in acetic acid and the ratio of EtOH/AcOH is 6.4. This value agrees substantially with 6.1 for *trans*-4-methylcyclohexylcarbinyl tosylate and also with similar values for primary alkyl tosylates, especially with a value of 6.2 for isobutyl tosylate at 75°C. This increase in rate attending the solvent change suggests that participation of the solvent, as shown in Fig. 2, which is a part of a driving force for ionization is more important in the ethanolysis of these compounds than in the acetolysis, since ethanol is of more nucleophilic nature than acetic acid.

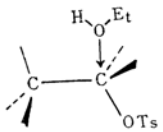
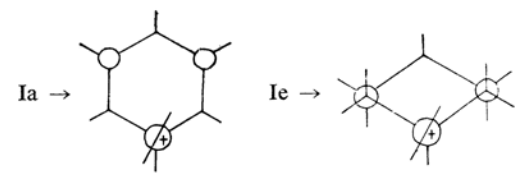


Fig. 2

On the contrary, *cis*-4-*t*-butylcyclohexylcarbinyl tosylate was solvolyzed more slowly in ethanol than in acetic acid and the rate ratio of EtOH/AcOH averages 0.75. The corresponding ratio for unsubstituted and *cis*-4-methyl substituted cyclohexylcarbinyl tosylates, however, are respectively 3.7 and 1.8 which are lower than 6.1 for *trans*-4-methylcyclohexylcarbinyl tosylate. The lowest value of 0.75 for the *cis*-4-*t*-butyl-compound would be due to the cause that the ethanolysis of this compound does not substantially involve participation of the solvent such as shown in Fig. 2 for the case of the corresponding trans-form, as will be detailed later. The relatively high ratios of EtOH/AcOH for the unsubstituted and *cis*-4-methyl substituted compounds arise from their interconvertible chair conformations.

Conformational Analysis.—In Fig. 1, the possible conformations for the axial and the equatorial toluenesulfoxymethyl group which were proposed in the previous paper[1] are projected along the C_7–C_1 axis. Conformation Ie is more stable than IIe, since the former is free from the two 1, 3-diaxial interactions which are present in the latter. On the other hand, conformation Ia is more stable than IIa, since the bulky toluenesulfoxy group in the former is separated far from the two axial hydrogens on C_3 and C_5.

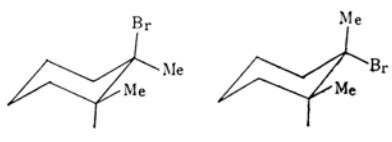
According to the consideration in the previous paper[1], in the conformation Ia there is very high crowding between the two axial hydrogens on C_3 and C_5 and the inside hydrogen on C_7. In the course of formation of the carbonium ion IIIa from the ground state Ia in Fig. 3, a large strain originally exerted on the inside hydrogen on C_7 decreases to a considerable extent. If the decrease in strain is much



IIIa IIIe

Fig. 3

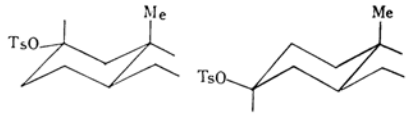
larger than that in the case of formation of the carbonium ion IIIe from the ground state Ie, that is to say, the difference in energy between Ia and IIIa is lower than that between Ie and IIIe, this would provide a convenient explanation for the high rate ratio (higher than 1) of cis/trans observed in the acetolysis of isomeric 4-*t*-butylcyclohexylcarbinyl tosylates. Such a consideration may be supported by the experimental fact[10] that *trans*- and *cis*-1, 2-dimethylcyclohexyl bromides I and II are solvolyzed at an equal rate, and therefore steric interaction affecting the axial methyl group on C_1 in the cis-form II accelerates ionization of the equatorial bromine atom, to an almost equal extent with that of the so called 1, 3-diaxial interaction-accelerate-ionization of the axial bromine atom in the trans-form.



I II

10) T. D. Nevitt and G. S. Hammond, *J. Am. Chem. Soc.*, 76, 4124 (1954).

Further, it is supported also by the fact[11] that cholestan-2α-yl tosylate (III) is solvolyzed more rapidly by a fact of 3 than cholestan-3β-yl tosylate (IV), owing to relatively high interaction between the axial hydrogen on C_2 and the methyl group in the former tosylate.



III IV

On the other hand, as described above, the ethanolysis of the 4-*t*-butylcyclohexylcarbinyl tosylate would involve a solvent participation, but in the case of the cis-isomer such a participation would not be involved. Examination of the molecular models shows that in the conformation Ia a back-side entry of nucleophilic molecules, as shown in Fig. 2, is hindered by the axial hydrogen on C_3 or C_5, but in the conformation Ie such a steric hindrance is absent. This examination can give a convenient reason for the observed lower rate ratio of of EtOH/AcOH for the cis-form containing an axial toluenesulfoxymethyl group, as compared to that for the trans-form containing an equatorial one.

Summarizing the above consideration, in the acetolysis of the compound containing a toluenesulfoxymethyl group in an axial or an equatorial position, the decrease in steric strain controls the rate. On the other hand, in the ethanolysis of the compound containing an equatorial toluenesulfoxymethyl group, a driving force for ionization consists of the decrease in strain and the high solvent participation effecting to push the toluenesulfoxy radical, where the former being less important than the latter, while in the case of the compound containing an axial toluenesulfoxymethyl group the steric hindrance results in less importance of the solvent participation and only the decrease in strain effects a substantial driving force for ionization.

Although the conformations Ia and Ie may be respectively more stable than the corresponding IIa and IIe, this does not mean that these tosylates must react only in these stable conformations, since the energy barriers for their interconversion are probably less than the activation energies involved in the solvolysis.

Further, from the above conformations, it is easily understood that steric strain for the toluenesulfoxy group and for the inside hydrogen in the respective *trans*- and *cis*-4-*t*-butylcyclohexylcarbinyl tosylates is much higher by considerable factors than in cyclohexyl tosylates in general, and such high strain would result in a high rate of solvolysis. However, α-alkyl substituents or their electron-donating inductive effect can give much higher rate-increasing effects than steric strain does, and this has been borne out by the lower acetolysis rates of the former tosylates than that of the latter tosylates.

Free Energy Difference between Axial and Equatorial Toluenesulfoxymethyl Group. — Winstein and Holness[2] proposed a very useful relationship between the specific reaction rate k for any reaction of a molecule which exists in the two interconvertible chair conformations and has a departing group directly bound to the ring, the mole fractions N_a and N_e of the two conformations at equilibrium and the respective individual rate constants k_a and k_e, as follows:

$$k = N_a \cdot k_a + N_e \cdot k_e \qquad (1)$$

On the other hand, Eliel and Lukach[3] gave an equivalent relationship, as follows:

$$k = (k_e \cdot K + k_a)/(K+1) \qquad (2)$$

where K is the equilibrium constant N_e/N_a between the two conformations. From this equation Eq. 3 may be derived.

$$K = (k_a - k)/(k - k_e) \qquad (3)$$

If the proportions of Ia and IIa and of Ie and IIe are affected by any substituent present in the tosylates, the above equations are applicable to solvolysis of the tosylates. In Table V are listed the conformational equilibrium constants derived from the rate constants in Table II by Eq. 3 in which k is the rate constant for the compound indicated, k_a is the rate constant for the purely axial isomer *cis*-4-*t*-butylcyclohexylcarbinyl tosylate and k_e is the rate constant for the purely equatorial isomer *trans*-4-*t*-butylcyclohexylcarbinyl tosylate. $\Delta F°$ in the table is the free energy difference between the chair-conformational isomers derived from the K value by Eq. 4.

$$\Delta F° = -2.3RT \log K \qquad (4)$$

The $\Delta F°$ values require comment. It must be realized that these values no more than indicate orders of magnitude, since K in Eq. 3 is obtained as a quotient of two differences, one of which is usually small and therefore affected by a large relative error. Therefore, the values for the ethanolysis, in which measurement errors have been relatively high, are unsatisfactory (not shown in the table).

The conformational equilibrium constant for cyclohexylcarbinyl tosylate in acetolysis listed in Table V indicates that about 90% of the molecules exists with the toluenesulfoxymethyl

11) S. Nishida, ibid., 82, 4290 (1960).

Table V. Summary of K and ΔF° values in acetic acid

4-Substituent	99.8°C			110°C		
	K	ΔF° kcal./mol.	N_a %	K	ΔF° kcal./mol.	N_a %
cis-t-Bu	0	—	100	0	—	100
cis-Me	1.17	−0.12	46	1.3	−0.20	44
H	9.6	−1.7	10	8.7	−1.8	9.0
trans-Me	116	−3.5	0.8	183	−5.1	0.54
trans-t-Bu	∞*	—	0.0	∞*	—	0.0

* Assumed

group equatorial in equilibrium with 10% whose toluenesulfoxymethyl group is axial. The ΔF° value of −1.7∼1.8 kcal./mol. for the cyclohexylcarbinyl tosylate seems to be reasonable for the difference $\Delta F^\circ_{\mathrm{TsOMe}}$ in free energy between the equatorial and axial toluenesulfoxymethyl group.

The conformational free energy differences $\Delta F^\circ_{\mathrm{cis}}$ and $\Delta F^\circ_{\mathrm{trans}}$ for *cis*- and *trans*-4-methylcyclohexylcarbinyl tosylates should be related to that of cyclohexylcarbinyl tosylate by the equations:

$$\Delta F^\circ_{\mathrm{cis}} = -\Delta F^\circ_{\mathrm{Me}} + \Delta F^\circ_{\mathrm{TsOMe}}$$

and

$$\Delta F^\circ_{\mathrm{trans}} = \Delta F^\circ_{\mathrm{Me}} + \Delta F^\circ_{\mathrm{TsOMe}}$$

The $\Delta F^\circ_{\mathrm{Me}}$ is the difference in free energy between an equatorial and an axial methyl group or the energy required for moving a methyl group from an equatorial to an axial position and may be taken as −1.6 kcal./mol.[4] Since the corresponding value $\Delta F^\circ_{\mathrm{TsOMe}}$ for toluenesulfoxymethyl group is −1.7 kcal./mol. at 99.8°C, the calculated free energy difference $\Delta F^\circ_{\mathrm{cis}}$ for *cis*-4-methylcyclohexylcarbinyl tosylate with an equatorial toluenesulfoxymethyl group and its conformational isomer with an axial one is 1.6−1.7 or −0.1 kcal./mol.

Similarly, from the values of −1.8 kcal./mol. at 110°C for the toluenesulfoxymethyl group, the corresponding value is −0.2 kcal./mol. The calculated values of −0.1 and −0.2 kcal./mol. are in good agreement with the observed −0.12 and −0.2 kcal./mol.

For *trans*-4-methylcyclohexylcarbinyl tosylate, the value for moving a methyl and a toluenesulfoxymethyl group from axial to equatorial positions is −1.6 −1.7 or −3.3 kcal./mol. at both temperatures, which is in good agreement with the experimental values of −5.1 and −3.5 kcal./mol.

The value of 1.7∼1.8 kcal./mol. for the difference in free energy between the conformations with a toluenesulfoxymethyl group in an equatorial and an axial position respectively is almost equal to 1.6∼1.8 kcal./mol. for the methyl group[4] and 0.7∼1.7 kcal./mol. for the toluenesulfoxy group[2,3] but lower than 2.1 kcal./mol. for the ethyl and the *n*-propyl group[2]. The relatively low value of 1.7∼1.8 kcal./mol. appears quite reasonable, however, since in view of varying experimental conditions such as difference in solvents and temperatures, complete agreement of the ΔF° values should perhaps not be expected and the value of 1.7∼1.8 kcal./mol. would not be expected to be very different, as compared to that for the other groups.

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