Conformation and Reactivity of 4-Methylcyclohexylmethyl p-Tosylates

By Nobuo Mori

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The important relation between conformation and reactivity in a cyclohexane system which contains a departing group directly bound to the cyclohexane ring and in an acyclic system has been applied in many areas of organic chemistry[1].

The present work desires to confirm the effect of conformation on the reactivity in a cyclohexane system which contains a departing group bound through a methylene group to the ring, especially by means of substituted cyclohexylmethyl *p*-tosylates. For this purpose, novel *cis*- and *trans*-4-methylcyclohexylmethyl *p*-tosylates have been prepared from the corresponding carbinols which form the basis of the *p*-tosylates, and they were solvolyzed. The *cis*- and *trans*-4-methylcyclohexylcarbinols are prepared by hydrogenolysis of the corresponding 4-methylcyclohexanecarboxylic acid esters under severe conditions, at 250°C under 200 atm. in the presence of copper-barium-chromium oxide catalyst for 10 hr.[2] The author has used advantageously lithium aluminum hydride in dry ether for conversion of the esters into the carbinols.

Experimental

Samples.—*Cyclohexylmethyl p-Tosylate.*—Benzaldehyde (20 g.) in ethanol (30 cc.) was hydrogenated under 80 initial atm. at a temperature gradually raised to 100°C in the presence of Raney nickel (10 g.) until no more hydrogen was absorbed. The filtered solution was distilled under reduced pressure to give the cyclohexylcarbinol, b. p. 74.5°C/20 mmHg. The carbinol was treated with an equimolecular amount of *p*-toluenesulfonyl chloride in pyridine at 0~5°C, to give the *p*-tosylate as needles, m. p. 30.5°C after recrystallization from aqueous methanol.

Found: C, 62.65; H, 7.51. Calcd. for $C_{14}H_{20}O_3S$: C, 62.55; H, 7.44%.

cis-4-Methylcyclohexylmethyl p-Tosylate.—A neutral solution of *p*-toluic acid (15 g.) in 10% sodium hydroxide solution in an autoclave was hydrogenated at 180~200°C under 90 initial atm. in the presence of Raney nickel (10 g.) for 2.5 hr. until no more hydrogen was absorbed. The filtered solution was worked up in the usual way, by making it acid with concentrated hydrochloric acid,

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[1] For example, see M. S. Newman, "Steric Effects in Organic Chemistry", John Wiley & Sons, Inc., New York (1956).

[2] R. G. Cooke and A. K. Macbeth, *J. Chem. Soc.*, **1939**, 1245.

extracting the separated oily product with ether, evaporating the ether and distilling the residue under reduced pressure, to give the semi-solid mass (12 g.), b. p. 129∼130°C/15 mmHg, which melted at 107∼108°C (reported 111°C[3]) after one recrystallization from aqueous methanol. The acid (1.5 g.) so obtained was esterified by refluxing it in ethanol (30 cc.) containing concentrated sulfuric acid (1 g.) for 2 hr., to give the ethyl ester (1.6 g.), b. p. 92∼93°C/28 mmHg. The ester in dry ether (5 cc.) was added stepwise into a suspension of lithium aluminum hydride (0.5 g.) in dry ether (50 cc.) at 0∼5°C. After stirring for another half an hour, the reaction mixture was treated with a small volume of dilute sulfuric acid sufficiently to make the ether layer clear, and the layer was dried over potassium carbonate and evaporated to dryness. The oily product, which consisted mainly of *cis*-4-methylcyclohexylcarbinol, was treated with *p*-toluenesulfonyl chloride (1.5 g.) in pyridine (3 cc.) and after 3 hr. poured into a mixture of concentrated hydrochloric acid and ice to separate the oily mass which solidified after a few minutes. The solid was recrystallized from aqueous methanol to give the *cis*-tosylate (1.3 g.) as plates, m. p. 44.5∼44.7°C.

Found: C, 64.00; H, 8.05. Calcd. for $C_{15}H_{22}O_3S$: C, 63.79; H, 7.85%.

trans-4-Methylcyclohexylmethyl p-Tosylate.—*p*-Toluic acid (8 g.) in glacial acetic acid (60 cc.) which had previously been treated with potassium permanganate, was hydrogenated at 70∼80°C under atmospheric pressure in the presence of Adams platinic oxide catalyst (0.5 g.)[4] for about 2 hr. without any aeration of the catalyst until no more hydrogen was absorbed. The acetic acid was removed from the filtered solution under reduced pressure and the residue was distilled to give the hexahydro-acid (5 g.), b. p. 133∼134°C/20.4 mmHg (reported 135°C/20 mmHg[3]). The acid (2 g.) was similarly converted into the *trans*-tosylate as needles, m. p. 30.5∼31.0°C and yield 1 g. after recrystallizations with slight difficulty from methanol in a dry ice-acetone bath.

TABLE I. SUMMARY OF RATE CONSTANTS AT 99.8°C

4-Substituent	Tosylate $\times 10^2$ mol./l.	Solvent	$k_1 \times 10^4$ min^{-1}
H	1.57	HAcO	2.27
	1.60	EtOH	8.42
cis-CH_3	1.78	HAcO	4.34
	1.79	EtOH	7.68
trans-CH_3	1.80	HAcO	1.79
	1.79	EtOH	11.0
Ethyl tosylate*	3.8∼4.3	HAcO	5.08
Isobutyl tosylate*	2.5∼2.8	HAcO	2.28

* Calculated from 8.47×10^{-6} sec^{-1} and 3.79×10^{-6} sec^{-1} respectively in Ref. 6.

Found: C, 63.75; H, 7.84. Calcd. for $C_{15}H_{22}O_3S$: C, 63.79; H, 7.85%.

Solvolysis rates were measured at 99.8°C in ethanol (98.5% by weight) and in acetic acid containing a slight excess of acetic anhydride by the usual ampoule technique[5]. The reactions were followed by titrating at intervals for the sulfonic acid liberated during the solvolysis to ca. 50% completion because of slow velocity. The observed kinetics were nicely first order and the precision of the measurements was usually better than 5%. The calculated first order rate constants for the tosylates and also alkyl tosylates for a comparision are summarized in Table I.

Discussion

Difference in reactivity between the two departing groups restricted respectively in axial and equatorial orientation depends on the difference in energy of the ground state, rather than the transition state; and when the departing group is axial, there is a compensating steric acceleration due to relief of crowding between this axial group and the axial hydrogen atoms in γ-position, and as a result of this the solvolysis should be quite facile for the axial group, for example as shown by the typical fact[7] that *cis*-4-*tert*-butylcyclohexyl *p*-tosylate is solvolyzed at a rate about 3 times as fast as the corresponding trans-isomer. As a matter of course, the difference disappears in the isomeric 1, 2-dimethylcyclohexyl bromides[8] which are nearly equal in the energy of their ground states, and also in the isomeric 1, 3-dimethylcyclohexyl chlorides[9].

Thus, in general, the high steric repulsion acting on the departing group as described above results in fast departure of the group, provided the transition state for solvolysis does not include at least any higher electronic effect, such as the inductive effect by substituents especially in β-position or internal participation of neighboring groups or hydrogens, as shown in the fact[10] that *tras*-2-acetoxylcyclohexyl *p*-tosylate is acetolyzed much faster than the corresponding cis-isomer. Such an electronic effect is probably not included in the transition states of the isomeric tosylates used in the present work.

Preferred Conformation and Acetolysis.—The possible chair conformations of the isomeric tosylates used in the present work are as follows:

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3) G. H. Keats, ibid., 1937, 2003.

4) This catalyst was prepared according to the method described in "Organic Synthesis", Coll. Vol. I (1948), p. 463.

5) N. Mori, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1458 (1959); This Bulletin, **33**, 1144 (1960).

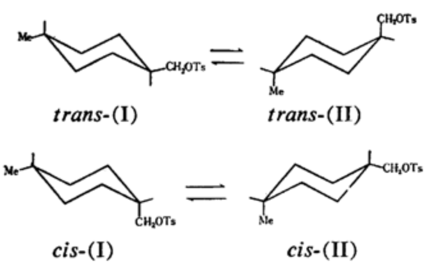
6) S. Winstein and H. Marshall, *J. Am. Chem. Soc.*, **44**, 1120 (1952).

7) S. Winstein and H. J. Holness, ibid., **77**, 5562 (1955).

8) T. D. Nevitt and G. S. Hamond, ibid., **76**, 4124 (1954).

9) H. C. Brown et al., ibid., **73**, 212 (1951).

10) S. Winstein et al., ibid., **70**, 821 (1948).

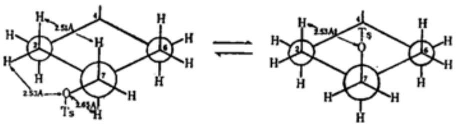


trans-(I) *trans*-(II)

cis-(I) *cis*-(II)

Fig. 1

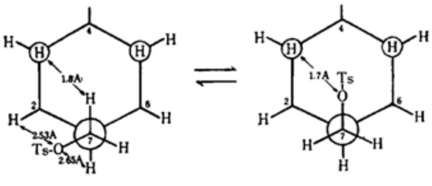
where Ts is the *p*-toluenesulfonyl group. The *trans*-(I) should be more stable than the *trans*-(II). On the other hand, the difference in stability between the *cis*-(I) and *cis*-(II) may be very small, and thus the cis-isomer is in the form of the *cis*-(I) in a considerable ground state concentration. Moreover, a favorable conformation of the *p*-toluenesulfoxymethyl group is very important, and for one in equatorial orientation it may be represented by the *e*-(III) and *e*-(IV) in Fig. 2, which are projected along the C_7 to C_1 axis and also accompanied by distances between non-bonded atoms in question,



e-(III) *e*-(IV)

Fig. 2

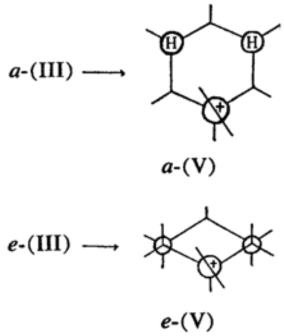
in which the conformation *e*-(III) will be more stable than *e*-(IV), because in the former only the bulky tosyl group eclipses the equatorial hydrogen on carbon atom 2 while in the latter the tosyl group eclipses the two axial hydrogens on carbon atoms 2 and 6. On the other hand, the toluenesulfoxymethyl group in axial orientation has two possible conformations which are represented respectively by the *a*-(III) and *a*-(IV) in Fig. 3, similarly projected.



a-(III) *a*-(IV)

Fig. 3

The former, in which only the bulky tosyl group and equatorial hydrogen on carbon atom 2 are opposite one another, should be of lower energy than the latter, in which the distance between the tosyl group and the two axial hydrogens on carbon atoms 3 and 5 is very short. Thus, in such preferred conformations *e*-(III) and *a*-(III), the magnitude of repulsive action on the tosyl group in the axial toluenesulfoxymethyl group may be of the same order as that in the equatorial one; and therefore it will be expected that the isomeric 4-methylcyclohexylmethyl *p*-tosylates are solvolyzed at a nearly equal rate, if only the steric repulsion in the ground states is the governing factor. However, in the present work, the solvolysis in acetic acid as a poor nucleophilic solvent gave the result that the ratio of $k_{\text{cis}}/k_{\text{trans}}$ was 2.4. The fact may be explained on the possible assumption that, if the solvolysis is a simple carbonium ion process and the solvolysis of the cis-isomer proceeds, at least in part, via the conformation *a*-(III), the difference in energy between the ground state and the consequent possible carbonium ion, such as the *a*-(V) in Fig. 4, for the cis-isomer is very low as compared to that between the ground state *e*-(III) and the carbonium ion *e*-(V) for the trans-isomer. This assumption is probably right, since the high strain on the hydrogen atom in the methylene group in the ground state can substantially disappear in the consequent transition state, though the simple carbonium ion process is not always the governing consideration.



a-(V)

e-(V)

Fig. 4

Solvent Effect and Ethanolysis.—The rate of solvolysis of a given compound is generally altered by the solvating power or nucleophilic nature of a given solvent and the solvolysis includes usually solvation of the carbonium ion intermediate and nucleophilic assistance from the solvent molecules. Primary alkyl tosylates tend to be solvolyzed more rapidly in nucleophilic solvents such as ethanol than in acetic acid, and further the relative rates of $k_{\text{EtOH}}/k_{\text{HAcO}}$ for linear lower alkyl tosylates is higher than that for β-branched alkyl tosylates. For example, the ratio⁶⁾ at 75°C is 39 for ethyl tosylate, 6.2 for isobutyl tosylate and

0.28 for neopentyl tosylate. This would be partly due to the fact that variation from primary tosylate to β-branched alkyl tosylate would decrease the amount of nucleophilic assistance from the solvent. As the tosylates used in the present work are represented as the β-branched alkyl compounds in structure, it is expected that behavior of the tosylates in various solvents is approximately in agreement with that of isobutyl tosylate.

From Table II, it is seen that the rate of solvolysis of the trans-form increases according as the solvent changes from acetic acid to ethanol, in agreement with the behavior of primary alkyl tosylates, and the rate enhancing degree, that is, the ratio of $k_{\mathrm{EtOH}}/k_{\mathrm{HAcO}}$ is 6.1. This rate increasing trend is partly due to the fact that, in the conformation *e*-(III) of the trans-form, ethanol molecules approach more easily to the reaction center atom C_7, along the C_1-C_6 axis through the two hydrogens on carbon atom 6 in a back side attack manner.

On the other hand, the rate for the cis-form increases slightly under the same solvent sequence and the ratio is 1.7. This lower ratio would be mainly due to that in the conformation *a*-(III) of cis-form the axial hydrogen on carbon atom 5 hinders a similar entrance of solvent molecules along the C_1-C_6 axis.

TABLE II. RELATIVE RATES IN DIFFERENT SOLVENTS

4-Substituent	H	*cis*-CH_3	*trans*-CH_3
$k_{\mathrm{EtOH}}/k_{\mathrm{HAcO}}$	3.7	1.77	6.1

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Department of Chemistry
Tokyo College of Science
Shinjuku-ku, Tokyo