On the Reactivity of 4-Hydroxycyclohexyl p-Tosylates

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The effect of a conformation on the reactivity in cyclohexane systems is very important*, and especially the difference in reactivity between *cis*- and *trans*-cyclohexane compounds serves generally for the study on their configurations.

The present paper describes the unexpected result that *trans*-4-hydroxy or -4-acetoxycyclohexyl *p*-tosylate was solvolyzed more rapidly than the corresponding cis isomer.

Results and Discussion

The solvolysis rates of 4-hydroxycyclohexyl *p*-tosylates were measured at 99.8°C in ethanol (98.5% by weight), and that of 4-acetoxycyclohexyl *p*-tosylates measured in acetic acid containing a slight excess of acetic anhydride. In all cases, except alkaline ethanolysis, the observed rates were of the first order and the error of the measurements was always lower than 3%. Since the mean rate constants of the acetolysis of the *cis*- and *trans*-4-acetoxylcyclohexyl *p*-tosylates were not substantially affected by addition of a small quantity of anhydrous sodium acetate, the acetolysis is probably of the unimolecular type. On the other hand, a calculated first order rate constant decreased gradually during the solvolysis of the isomeric hydroxycyclohexyl *p*-tosylates in ethanol containing sodium ethoxide in 0.02 mol./l., in agreement with the behavior of 3-methyl

* The importance was first pointed out by D. H. R. Barton (*Experientia*, **6**, 316 (1950)).

cyclohexyl *p*-tosylate described previously[1], and the mean rate constants were about 3 times of that in neutral ethanol. This fact suggests that a part of the alkaline ethanolysis consists of a bimolecular reaction based on the back-side attack of the ethoxide ion. Table I lists the data for a run with *cis*-4-acetoxycyclohexyl *p*-tosylate in acetic acid containing sodium acetate in 0.029 mol./l., while a run with *cis*-4-hydroxycyclohexyl *p*-tosylate in ethanol containing sodium ethoxide in 0.02 mol./l. is given in Table II. It is seen that in the former run a first order rate constant is satisfactorily constant and in the latter run a rate constant decreases gradually during the solvolysis.

Table I. Acetolysis of *cis*-4-acetoxycyclohexyl *p*-tosylate in acetic acid containing AcONa in 0.029 mol./l. at 99.8°C

Time, min.	Tosylate, mol./l.	$k_1\times10^3$, min^{-1}
0.0	0.0282	
30	0.0250	4.07
60	0.0220	4.14
90	0.0192	4.25
120	0.0173	4.03
150	0.0150	4.19
210	0.0122	4.03
	Mean	4.12

Table II. Ethanolysis of *cis*-4-hydroxycyclohexyl *p*-tosylate in ethanol containing EtONa in 0.02 mol./l. at 99.8°C

Time, min.	Tosylate, mol./l.	$k_1\times10^2$, min^{-1}
0.0	0.0180	
20	0.0094_5	3.68
30	0.0072	3.24
40	0.0058	3.01
50	0.0050	2.76
80	0.0031	2.30
	Mean	3.0

The rate constants and the relative rates for the isomeric tosylates are summarized in Tables III and IV, respectively.

Table III. Rate constants of solvolysis of 4-substituted cyclohexyl *p*-tosylates at 99.8°C

4-Substituent	Tosylate mol./l.	Solvent	Alkali mol./l.	$k_1\times10^2$ min^{-1}
cis-OH	0.018	a	0.020 c	3.0
	0.020	a		0.835
trans-OH	0.018	a	0.020 c	10
	0.020	a		2.97
cis-OAc	0.0282	b	0.0290 d	0.412
	0.0284	b		0.400
trans-OAc	0.0283	b	0.0292 d	1.10
	0.0284	b		1.00

a, ethanol; b, acetic acid; c, sodium ethoxide; d, sodium acetate.

Table IV. Relative rates of solvolysis of 4-substituted cyclohexyl *p*-tosylates

	4-OH		4-OAc	
Solvent	a containing c	a	b containing d	b
k_{trans}/k_{cis}	3.3	3.5	2.6	2.5

Generally, in solvolysis of rigid cyclohexane systems for example *t*-butylcyclohexyl *p*-tosylate, the compound where the departing group is axial is solvolyzed in ethanol, acetic acid or formic acid at a rate 3~4 times as fast as that of the corresponding isomer where the departing group is equatorial, and also in a mobile substituted cyclohexane system, as that shown in Fig. 1, where that two possible chair conformations are readily interconvertible, for example as 3-methoxycarbonylcyclohexyl *p*-tosylate[3] or 1, 3-di-*p*-toluenesulfoxycyclohexane[1], the solvolysis leads to an essencially similar result.

The possible conformations of 4-substituted cyclohexyl *p*-tosylates are as follows:

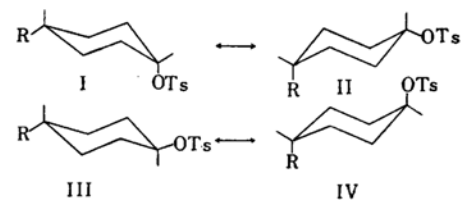

Fig. 1

where R is a substituent and Ts is the tosyl group. The conformation III of the trans form is probably more stable than the conformation IV, while the difference in stability between the conformation I and II of the cis form is probably very small or negligible, when R is not so large a group as *t*-butyl group. Thus, it is expected that the cis form is more reactive than the trans form, as described above.

However, in the present work, the *trans*-4-hydroxycyclohexyl *p*-tosylate was ethanolyzed at a rate 3.5 times as fast as that of the corresponding cis isomer, and also the *trans*-4-acetoxycyclohexyl *p*-tosylate was acetolyzed at a rate 2.5 times as fast as that of the corresponding cis isomer. These facts can not be explained on the basis of the general rule described above.

Further, the configuration of the isomeric cyclohexane-1, 4-diols, which was first established by Bayer[4], is in agreement with the chemical fact that, by direct dehydration of

1) N. Mori, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1458 (1959).
2) S. Winstein and H. J. Holmess, *J. Am. Chem. Soc.*, **77**, 5562 (1955).
3) D. S. Noyce and H. J. Weingarten, ibid., **79**, 3103 (1957).
4) A. Bayer, *Ann.*, **278**, 92 (1894).

diol over alumina, the yield of 1, 4-epoxycyclohexane from the *trans*-diol was much higher than that from the *cis*-diol[5], and it is probably right.

A further study concerning this problem will be reported shortly.

Experimental

Samples*: *cis*- and *trans*-Cyclohexane-1, 4-diol.—Quinol (25 g.) in methanol (30 cc.) in an autoclave was hydrogenated at 120°C under 80 initial atm. in the presence of Raney nickel (10 g.) for about 3 hr. until no more hydrogen was absorbed. The filtered solution was evaporated under reduced pressure and the residue was acetylated by refluxing with acetic anhydride (70 cc.) for 3 hr. and the crude diacetate crystallized from hot acetone (30 cc.), to give prisms of the *trans*-diacetate which melted at 100.5 ~102°C after one recrystallization from ligroin (b. p. 75~120°C). The yield was 13.5 g. The acetone filtrate was concentrated, diluted with benzene (5 cc.) and then ligroin, and seeded with the *trans*-diacetate in a refrigerator, to give a small amount of this material. The residual solution was concentrated and placed with occasional stirring in a refrigerator for several days until it crystallized, to give the *cis*-diacetate which melted at 34~35°C after recrystallization from a small volume of ligroin. The yield was 12 g.

A solution of the *trans*-diacetate in absolute methanol (30 cc.) treated with a very small piece of metal sodium was refluxed for 30~60 min., concentrated to a small volume under reduced pressure, dissolved in hot dry ether and cooled to 0°C, to give as prisms the *trans*-diol, m. p. 144°C.

The *cis*-diacetate was similarly treated and the residue obtained by concentration of the reaction mixture was crystallized from hot acetone, to give as needles the *cis*-diol, m. p. 110°C.

The *trans*-diol (4.9 g.) in dry pyridine (25 cc.) was treated under stirring and cooling to 0~5°C with *p*-toluenesulfonyl chloride (7.52 g.) in chloroform (25 cc.). After stirring for 3 hr. at room temperature, the mixture was poured into excess of dilute hydrochloric acid cooled with ice, the resulting chloroform solution was washed with dilute hydrochloric acid, water and then a 10% solution of sodium carbonate. dried over sodium sulfate and evaporated under reduced pressure. The residue was dissolved in hot benzene, treated with hot ligroin and cooled to room temperature, to give the *trans*-monotosylate in needles, m. p. 112.5°C after recrystallization from benzene-ligroin.

When the reaction mixture, treated with *p*-toluenesulfonyl chloride as described above, was further treated with one equivalent quantity of acetyl chloride in chloroform, it gave the *trans*-acetoxy cyclohexyl *p*-tosylate in needles, m. p. 81~81.5°C after crystallization from benzene-ligroin.

When the *cis*-diol was similarly treated and recrystallized, the *cis*-hydroxycyclohexyl tosylate (m.p. 94~95°C) and the *cis*-acetoxycyclohexyl tosylate (m. p. 105°C) were obtained.

Solvents.—*Ethanol* (98.5% by weight).—Reagent grade absolute ethanol was fractionally distilled.

Acetic Acid. — Reagent grade glacial acetic acid was crystallized twice by the freezing method, refluxed with 2% by weight of acetic anhydride and 1% by weight of anhydrous sodium acetate for 3 hr. and distilled.

Procedure.—Rates were measured by the usual ampoule technique[7]. Concentrations are given at room temperature and the reaction was followed by the titration at intervals for the sulfonic acid liberated or the base consumed during the solvolysis. Titrations in acetic acid were carried out with a 0.05 N solution of AcONa or *p*-toluenesulfonic acid in acetic acid with bromophenol blue as indicator, and in ethanol a 0.05 N solution of sodium hydroxide or hydrochloric acid in water was used for titration with phenolphthalein as indicator. Rate constants were calculated from the formula

$$k_1 = 1/t \ln a/(a-x)$$

in which a was the initial concentration of tosylate and x was the concentration of sulfonic acid liberated or base consumed at time t.

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5) R. C. Olberg, H. Pines and U. N. Ipatieff, *J. Am. Chem. Soc.*, **66**, 1096 (1944).

* All samples were prepared by the methods described in Ref. 6 with some modifications.

6) L. N. Owen and P. A. Robins, *J. Chem. Soc.*, **1959** 320.

7) N. Mori, This Bulletin, **33**, 1144 (1960).