NOTE

The Difference in Free Energy between Equatorial and Axial Isopropyl Groups

By Nobuo Mori and Fumie Suda

(Received September 11, 1962)

The differences in free energy between equatorial and axial lower alkyl groups are the fundamental quantities on which conformational analysis is based; the values for the methyl and ethyl groups are known to be near -1.8 kcal./mol.[1-4,7,8,10] while those for the isopropyl group are in the wide range of $-2.5\sim-3.55$[3,4] kcal./mol. or are at least often taken[5] to be considerably greater those of methyl and ethyl. Further, an isopropyl group was often assumed to be almost as big as a *t*-butyl group[6].

Recently, however, Lewin and Winstein[7] have given a value of ca. -2.3 kcal./mol. for the isopropyl group from the chemical shifts in the NMR of the 1-proton in isomeric 4-isopropylcyclohexanols. Allinger and his co-workers[8] reported a lower value of -2.1 kcal./mol. from the equilibrium points for the isomerization of *cis*- and *trans*-diisopropylcyclohexanes and of isomeric 4-isopropylcyclohexanecarboxylic acid ethyl esters.

In the present work, the difference in free energy between equatorial and axial isopropyl groups has been determined in the following way. New *cis*- and *trans*-4-isopropylcyclohexylcarbinyl *p*-tosylates have been prepared and acetolyzed, and from the observed rates (k), the difference in free energy (ΔF) between the equatorial and axial isomers* have first been calculated by using the equations[3,9,10]: $K=(k_a-k)/(k-k_e)$ and $\Delta F=-RT\ln K$, where K is the equilibrium constant between equatorial and axial isomers and k_a and k_e are, respectively, the rates for *cis*- and *trans*-4-*t*-butylcyclohexylcarbinyl *p*-tosylates in the same reaction. The calculated values are shown in Table I, along with the relative rates and the mole fractions (N_a) of the axial isomers.

Therefore, the difference in free energy (ΔF_{i-Pr}) between equatorial and axial isopropyl groups may be calculated as follows: The ΔF value of $+0.32$ or 0.42 kcal./mol. for the *cis*-4-isopropyl compound may be regarded as the sum of an energy needed for moving the tosyloxymethyl group from an equatorial to an axial position (i. e., $\Delta F_{Tos}=-1.7$ at 100 and -1.8 kcal./mol. at 110°C[10]) and an energy needed for moving the isopropyl group from an axial to an equatorial position (i. e., $-\Delta F_{i-Pr}$), as illustrated by the relationship: $\Delta F=-\Delta F_{i-Pr}+\Delta F_{Tos}$; thus, the ΔF_{i-Pr} is -2.02 or -2.22 kcal./mol. The averaged value is -2.1 kcal./mol. The good agreement of this value with those obtained by Lewin and Winstein and by Allinger and his co-workers supports the conclusion[8] that the isopropyl group is essentially the same size as a methyl or ethyl group and is in quite a separate class from the *t*-butyl group.

On the basis of the above findings, the energy level of the diaxial conformation of the *trans*-4-isopropyl compound should be $2.1+1.75$ kcal./mol. higher than that of its diequatorial conformation. This corresponds to a K value of about 150 and leads to the prediction, borne out experimentally, that the acetolysis rate for *trans*-4-isopropylcyclohexylcarbinyl *p*-tosylate is identical with k_e within the range of experimental error.

Experimental

***cis*- and *trans*-4-Isopropylcyclohexylcarbinyl *p*-Tosylates** were prepared from the corresponding known carbinols[11] in the usual manner[12], by

---

[1] W. G. Dauben and K. S. Pitzer, in M. S. Newman's "Steric Effects in Organic Chemistry", John Wiley & Sons, New York (1956), p. 1.

[2] N. L. Allinger and S. Hu, *J. Am. Chem. Soc.*, **84**, 370 (1962).

[3] S. Winstein and N. J. Holness, ibid., **77**, 5562 (1955).

[4] D. S. Noyce and L. J. Dolby, *J. Org. Chem.*, **26**, 3619 (1961).

[5] A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, **1956**, 4391; W. Takagi and T. Mitsui, *J. Org. Chem.*, **25**, 1476 (1960).

[6] For example, W. Klyne, *Experientia*, **12**, 119 (1956); B. C. Lawes, *J. Am. Chem. Soc.*, **84**, 239 (1962).

[7] A. H. Lewin and S. Winstein, ibid., **84**, 2464 (1962).

[8] N. L. Allinger, L. A. Freiberg and Shih-En Hu, ibid., **84**, 2836 (1962).

* These mean those conformational isomers having, respectively, a tosyloxymethyl group in an equatorial or axial position.

[9] E. L. Eliel and C. A. Lukach, *J. Am. Chem. Soc.*, **79**, 5986 (1957).

[10] N. Mori, This Bulletin, **35**, 1755 (1962).

[11] R. G. Cooke and A. K. Macbeth, *J. Chem. Soc.*, **1936**, 1246.

[12] For example, N. Mori, This Bulletin, **34**, 1567 (1961).

TABLE I

4-Substituent	at 99.8±0.1°C				at 110.0±0.1°C			
	Relative rate	K	ΔF kcal./mol.	$N_a \times 100$	Relative rate	K	ΔF kcal./mol.	$N_a \times 100$
cis-t-Bu	4.23	0.00[a]	—	100	4.36	0.00[a]	—	100
cis-i-Pr	2.96	0.65	+0.32	60	3.12	0.58	+0.42	63
trans-i-Pr	1.00	∞	—	0.0	1.00	∞	—	0.0
trans-t-Bu	1.00	∞[a]	—	0.0	1.00	∞[a]	—	0.0

a Assumed

TABLE II. ACETOLYSIS OF *cis*-4-ISOPROPYLCYCLOHEXYLCARBINYL *p*-TOSYLATE AT 110°C

Time, sec.	Tosylate, mol./l.	k, sec^{-1}
0	9.68×10^{-3}	
7200	8.33	$(2.08) \times 10^{-1}$
12000	7.29	2.35
15600	6.68	2.38
19200	6.08	2.42
22800	5.58	2.41
26400	5.12	2.41
30120	4.56	2.41
	Mean	2.40

TABLE III. SUMMARY OF ACETOLYSIS RATES

4-Substituent	Tosylate 10^3 mol./l.	Temp., °C (±0.1°C)	10^5k, sec^{-1}
cis-i-Pr	9.68	99.8	0.860
	9.68	110.0	2.40
trans-i-Pr	9.61	99.8	0.285
	9.61	110.0	0.767
cis-t-Bu[10]	15.5	99.8	1.23
	15.5	110.0	3.35
trans-t-Bu[10]	15.5	99.8	0.290
	15.5	110.0	0.768

treating them with one equivalent proportion of *p*-toluenesulfonyl chloride in pyridine at 0∼5°C and recrystallizing from aqueous methanol. The cis-isomer was obtained as plates melting at 44.3∼44.6°C, and the trans-isomer, as prisms melting at 54∼54.5°C.

Calcd. for $C_{17}H_{26}O_3S$: C, 65.77 ; H, 8.44. Found : C, 65.69 ; H. 8.48 for the *cis*-isomer and C, 65.70 ; H, 8.32% for the trans-isomer.

All reactions and rate measurements were carried out using the same acetic acid without base and following the same procedure as has been previously reported[13] to a 30% completion at 99.8°C and to a 40% completion at 110°C. The calculated first order rate constants were steady to 3%. Table II lists the data for a typical run with *cis*-4-isopropylcyclohexylcarbinyl *p*-tosylate. The rate constants are summarized in Table III.

Tokyo College of Science
Shinjuku-ku, Tokyo

---

[13] N. Mori, ibid., 33, 1144 (1960).