hexyl tosylate assists in the displacement of the tosylate through the boat-form intermediate. Allred and Winstein[6] recently reported the participation of the 5-methoxyl group in the lithium aluminum hydride reduction of 5-methoxyl-2-pentyl *p*-bromobenzene-sulfonate. In this case the oxygen atom of the methoxyl group was incorporated into the ring of 2-methyltetrahydrofuran which was formed in this reaction. Framework molecular models do not rule out the postulated reaction in the present case since they indicate that the *o*-methoxyl group of *trans*-2(2′,3′,4′-trimethoxyphenyl)cycloheptyl methanesulfonate is properly located for a backside displacement of the mesylate group. Further studies in this area are in progress.

Experimental Section

Melting points were taken using a Nalge-Axelrod melting point apparatus and are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 13-U spectrophotometer and nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer in deuterated chloroform solutions (*ca.* 10%) using tetramethylsilane as an internal standard.

1-(2′,3′,4′-Trimethoxyphenyl)cycloheptanol was prepared according to the procedure of Ginsburg and Pappo[7] as modified by Lotspeich and Karickoff[1] for the preparation of 1-(2′,3′,4′-trimethoxyphenyl)cyclohexanol.

1-(2′,3′,4′-Trimethoxyphenyl)cycloheptene.—This preparation was achieved according to the procedure of Ginsburg and Pappo.[7]

***trans*-2-(2′,3′,4′-Trimethoxyphenyl)cycloheptanol.**—The procedure which was followed in this synthesis was that of Brown and Subba Rao.[8] 1-(2′,3′,4′-Trimethoxyphenyl)cycloheptene (23.6 g) gave 21.4 g of oil, bp 135–147° (0.04 mm). This oil (3 g) was chromatograped over 108 g of neutral aluminum oxide (Merk) prepared with hexane. Successive elution with the indicated solvents gave four fractions: (1) 120 ml of pentane–25% diethyl ether, 1.26 g of mainly 1-(2′,3′,4′-trimethoxyphenyl)-cycloheptene; (2) 400 ml of pentane–80% diethyl ether, nothing; (3) 160 ml of diethyl ether, 120 mg of 1-(2′,3′,4′-trimethoxyphenyl)cycloheptanol; (4) 200 ml of pentane–10% methanol, 1.44 g of *trans*-2-(2′,3′,4′-trimethoxyphenyl)cycloheptanol. Fraction 4 was distilled: bp 142–143° (0.05 mm); $n^{23}\text{D}$ 1.5380.

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.57; H, 8.57. Found: C, 68.63; H, 8.62.

trans-2-(2′,3′,4′-Trimethoxyphenyl)cycloheptyl methanesulfonate was prepared by allowing 2.00 g (0.0071 mol) of the above alcohol to react with 0.96 g (0.0084 mol) of methanesulfonyl chloride in 5 ml of pyridine at 10° for 48 hr. The pyridine solution was worked up in the usual manner to give 1.6 g (63%) of white crystals which were recrystallized twice from methanol, mp 88–90°.

Anal. Calcd for $C_{17}H_{26}O_6S$: C, 56.98; H, 7.26. Found: C, 57.07; H, 7.22.

6H-3,4-Dimethoxybenzo[*b*]-5a,7,8,9,10,10a-hexahydrocyclohepta[*d*]furan.—*trans*-2-(2′,3′,4′-Trimethoxyphenyl)cycloheptyl methanesulfonate (5.5 g, 0.015 mol) was added to 100 ml of anhydrous methanol containing 3.00 g (0.018 mol) of potassium mercaptoacetate. The solution was heated a 55° for 60 hr and the methanol evaporated. Water (5 ml) was added and the material extracted with diethyl ether. The diethyl ether was washed with water and evaporated to yield 3.3 g of oil which solidified upon standing. The solid was crystallized from diethyl ether to yield 3.0 g of 6H-3,4-dimethoxybenzo[*b*]-5a,7,8,9,10,10a-hexahydrocyclohepta[*d*]furan, mp 70–71.5°. Attempts to reduce this compound with Raney nickel in methanol at 40 psi of hydrogen were unsuccessful. The compound also failed to react with potassium permanganate in acetone and to undergo hydroboration according to the procedure previously described. The infrared spectrum had bands at 3010, 2930, 2860, 1620, 1492, 1460, 1268, 1150, 1088, 1055, and 972 cm^{-1}. The nmr spectrum showed absorption bands at τ 3.4 (doublet, 2 H), 5.0 (broad, 1 H), 6.08 and 6.17 (6 H), 6.5 (broad, 1-H), 8.3 (10-H).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; mol wt, 248. Found: C, 72.86; H, 7.92; mol wt, 255.

The basic solution was acidified with concentrated hydrochloric acid and extracted with diethyl ether. Evaporation of the ether after washing with water yielded 1.8 g of material. Distillation of this material yielded 0.9 g of oil, bp 64–68° (0.7 mm). This material was converted into the acid chloride and treated with aniline to yield the anilide of S-methylmercaptoacetic acid, mp 77–78° (lit.[9] mp 80°). This material did not depress the melting point of an authentic sample of the anilide of S-methylmercaptoacetic acid. The residue from the distillation was taken up in chloroform and the solid removed. The chloroform was evaporated and the liquid was taken up in a small amount of diethyl ether passed over a column (22 × 150 mm) containing 18 g of silicic acid. Elution with 20% diethyl ether in hexane yielded 0.40 g of an acidic oil which had an infrared and nmr spectra identical with the acid prepared by displacement of the *cis* tosylate.

The Reaction of 6H-3,4-Dimethoxybenzo[*b*]-5a,7,8,9,10,10a-hexahydrocyclohepta[*d*]furan with Hydrogen Bromide.—Hydrogen bromide (2.4 g of 48%), 5 ml of glacial acetic acid, and 2.0 g of 6H-3,4-dimethoxybenzo[*b*]-5a,7,8,9,10,10a-hexahydrocyclohepta[*d*]furan were refluxed for 8 hr. The solution was cooled, added to water, and extracted with diethyl ether. The ether extract was washed with 5% sodium bicarbonate solution and then water. Evaporation of the ether yielded 1.5 g of oil which solidified when treated with cold petroleum ether (bp 35–37°). This material melted at 160–166° after crystallization from methylene chloride–petroleum ether (bp 35–37°) (further recrystallization did not improve the melting point): nmr, τ 3.48 (center of two doublets), 4.55 (2-H), 4.48 (1-H), 6.50 (1-H), and 8.32 (10-H); the infrared spectrum (chloroform) had bands at 3633, 2925, 1641, 1486, 1013, and 1207 cm^{-1}.

Remethylation of 6H-3,4-Dihydroxybenzo[*b*]-5a,8,9,10,10a-hexahydrocyclohepta[*d*]furan.—6H-3,4-Dihydroxybenzo[*b*]-5a,7,8,9,10,10a-hexahydrocyclohepta[*d*]furan (1.00 g, 0.0040 mol) and 0.80 g (0.020 mol) of sodium hydroxide were treated with 0.63 g (0.0050 mol) of dimethyl sulfate at 80°. After stirring for 10 min an additional 0.80 g (0.020 mol) of sodium hydroxide and 0.63 g (0.0050 mol) of dimethyl sulfate were added and the solution was refluxed for 2 hr. The resulting solution was cooled and extracted with diethyl ether. The ether extract was washed with water and the ether was evaporated to yield dark yellow crystals. These crystals were recrystallized from petroleum ether (bp 35–37°), mp 70–71.5°. They showed no depression in melting point when mixed with a sample of 6H-3,4-dimethoxybenzo[*b*]-5a,7,8,9,10-10a-hexahydrocyclohepta[*d*]furan.

Registry No.—I, 16958-54-6; free base of I, 16958-55-7; II, 16958-56-8; dipotassium mercaptoacetate, 16958-57-9.

Acknowledgments.—The author wishes to thank Dr. Charles McCarty, Chemistry Department, West Virginia University, for assistance with the proton magnetic resonance spectra. This investigation was supported by Public Health Service Research Grant (GM 09342) from the National Institutes of Health.

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[8] H. G. Brown and B. C. Subba Rao, *ibid.*, **81**, 6423 (1959).

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Conformational Analysis of 1-Methylcyclohexanol

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The free-energy difference between the two chair forms of a monosubstituted cyclohexane is generally re-

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ferred to as the conformational energy, $\Delta G^\circ(x)$, where x represents the substituent on the ring. Although conformational energies of substituents are known to be sensitive to molecular environment,[2-5] their effects have often been additive[6,7] when two or more groups are placed on the same ring. Such additivity has been found, for example, in 1,4-disubstituted cyclohexanes and to a somewhat lesser extent in the 1,3 series.[2,8] The buttressing effect of adjacent groups will preclude additivity in 1,2-disubstituted cyclohexanes; however, it may be possible to correct for this.[9] This paper deals with the question of additivity in a 1,1-disubstituted cyclohexane. The available data, Table I, for such systems generally show satisfactory agreement between calculated and experimental values. The most serious deviation occurs with methylenecyclohexane oxide and undoubtedly it results from the severe decrease in the intersubstituent angle.

TABLE I

A COMPARISON OF CALCULATED AND EXPERIMENTAL CONFORMATIONAL ENERGIES IN 1,1-DISUBSTITUTED CYCLOHEXANES

	Conformational free energies, kcal/mol		
Substituents [$\Delta G^\circ(x)$][a]	Predicted[b]	Observed	Ref
Methyl (1.7); chloro (0.4)	1.3	1.1	*c*
SR_2– (0.8); OR_2– (0.7)	0.1	*ca.* 0.0[d]	*d*
Hydroxy (0.6); ethynyl (0.2)[h]	0.4	0.6	*e*
Vinyl (1.1);[i] hydroxy (0.6)	0.5	0.64	*f*
Methyleneoxy–CH_2O (0.8 and 1.8)[j]	1.0	0.2[j]	*g*
Phenyl (3.1); $(CH_3)_2N$ (2.1)	1.0	0.5	*k*
Phenyl (3.1); $(CH_3)_2HN^+$ (2.4)	0.7	0.2	*k*
Methyl (1.7); CHO (1.35)[i]	0.35	0.14	*l*

[a] These are the conformational energies suggested by E. L. Eliel [*Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965)] for the substituents (x) in kilocalories/mole. [b] Values were obtained by subtraction of the $\Delta G^\circ(x)$ values. [c] N. L. Allinger and C. D. Liang, *J. Org. Chem.*, **32**, 2391 (1967). [d] The observed value was obtained by equilibration of the *cis–trans* isomers of 4-*t*-butylcyclohexanone trimethylene monothioketal and the dimethylene monothioketal: E. L. Eliel, E. W. Della, and M. Rogic, *J. Org. Chem.*, **30**, 855 (1965); E. L. Eliel and L. A. Pilato, *Tetrahedron Lett.*, 103 (1962). [e] R. J. Ouellette, *J. Amer. Chem. Soc.*, **86**, 3089 (1964). [f] R. J. Ouellette, K. Liptak, and G. F. Booth, *J. Org. Chem.*, **31**, 546 (1966). [g] J. J. Uebel, *Tetrahedron Lett.*, 4757 (1967). [h] No independent value is available for this group. The listed value is for C≡N. [i] No independent value is available for this group. The listed value is for CO_2CH_3. A recent value of 1.35 kcal/mol has been suggested for –CHO by G. W. Buchanan and J. B. Stothers, *Chem. Commun.*, 179 (1967). [j] These are estimated values for OR and CH_2R groups. The observed value is for methylenecyclohexane oxide. [k] S. Sicsic and Z. Welvart, *Bull. Soc. Chim. Fr.*, 575 (1967). [l] G. W. Buchanan, J. B. Stothers, and S. T. Wu, *Can. J. Chem.*, **45**, 2955 (1967).

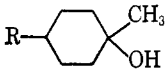
TABLE II

CHEMICAL SHIFTS OF HYDROXYL GROUPS[a]

Compound	δ (OH),[b] Hz
trans-4-*t*-Butyl-1-methylcyclohexanol (*trans* **2**)	4.8 ± 0.2
cis-4-*t*-Butyl-1-methylcyclohexanol (*cis* **2**)	27.9 ± 0.1
trans-1,4-Dimethylcyclohexanol (*trans* **3**)	4.0 ± 0.4
cis-1,4-Dimethylcyclohexanol (*cis* **3**)	25.2 ± 0.3
1-Methylcyclohexanol (**1**)	13.1 ± 0.6

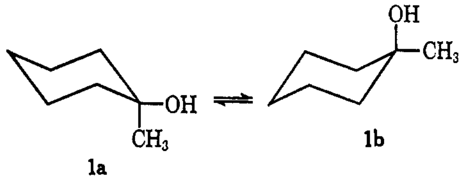
[a] The values are for 1 *M* solutions in DMSO at 35°. [b] Values are in cycles per second downfield from the low-field C-13-H satellite of DMSO. All spectra were taken at 60 MHz. The quoted errors are the average deviations of at least four independent measurements.

The conformational equilibrium of 1-methylcyclohexanol was investigated by nmr spectroscopy, using the chemical shifts of the hydroxyl protons, as a conformational probe.[10] The hydroxyl proton chemical shifts of 1-methylcyclohexanol (**1**) and the model compounds, 4-*t*-butyl-1-methylcyclohexanol (**2**) and 1,4-dimethylcyclohexanol (**3**), were measured in dimethyl sulfoxide[11] (DMSO) solution and are reported in Table II.

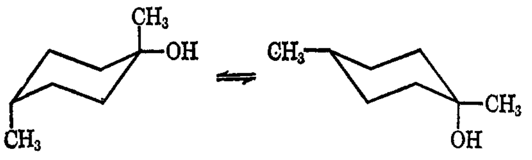


1, R = H
2, R = *t*-Bu
3, R = CH_3

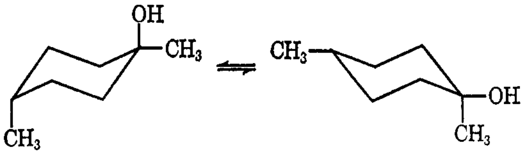
Using the chemical-shift data obtained from compounds **1**, *cis* **2**, and *trans* **2**, a free energy of −0.35 kcal/mol was calculated[12] for equilibrium 1 in DMSO at 35°. The data (Table II) obtained from *cis* **3** and *trans* **3** support this free-energy value for equilibrium 1. Thus, if the remote 4-methyl group is regarded as a unit with a conformational preference for the equatorial position of ΔG° = 1.7 kcal/mol, and the geminal CH_3/OH groups are treated as another unit with ΔG° = 0.35 kcal/mol, then *trans* **3** would be predicted[13] to exist mainly in conformation **3b** and *cis* **3** predominantly in conformation *cis* **3b**.



1a **1b** (1)



trans **3a** (3%)[13] *trans* **3b** (97%) (2)



cis **3a** (10%)[13] *cis* **3b** (90%) (3)

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(2) E. L. Eliel and T. J. Brett, *J. Amer. Chem. Soc.*, **87**, 5039 (1965).

(3) E. L. Eliel, S. H. Schroeter, T. J. Brett, F. J. Biros, and J. C. Richer, *ibid.*, **88**, 3327 (1966).

(4) R. D. Stolow, *ibid.*, **86**, 2170 (1964).

(5) D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1297 (1960).

(6) N. L. Allinger, M. A. Miller, F. A. Van Catledge, and J. A. Hirsch, *J. Amer. Chem. Soc.*, **89**, 4345 (1967).

(7) E. L. Eliel, *J. Chem. Educ.*, **37**, 126 (1960).

(8) For a discussion of the factors which give rise to this generalization, see ref 6.

(9) For examples, see J. Sicher and M. Tichy, *Collect. Czech. Chem. Commun.*, **32**, 3687 (1967), and references therein.

(10) (a) R. J. Ouellette, *J. Amer. Chem. Soc.*, **86**, 3089 (1964); (b) R. J. Ouellette, *ibid.*, **86**, 4378 (1964); (c) J. J. Uebel and H. G. Goodwin, *J. Org. Chem.*, **31**, 2040 (1966).

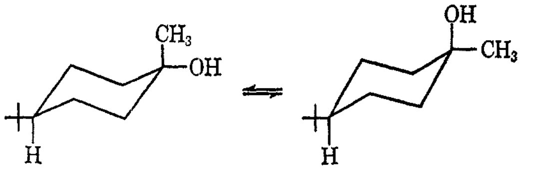
(11) In DMSO proton exchange, processes involving alcoholic hydroxyl groups are generally slow: O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964); D. E. McGreer and M. M. Mocek, *J. Chem. Educ.*, **40**, 358 (1963).

(12) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformation Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 152 ff.

(13) The percentages shown in parentheses for equilibria 2 and 3 are the expected conformational populations at 25°, assuming free-energy additivity.

As a result, the chemical shift of the hydroxyl proton of *trans* **3** (4.0 Hz) should be nearly identical with that of *trans* 2 (4.8 Hz) while that of *cis* 2 (25.2 Hz) should be close to *cis* 2 (27.9). This is indeed the case.

The experimental free energy of −0.35 kcal/mol for equilibrium 1 in DMSO is considerably smaller than the value of −1.1 kcal/mol, which would be expected assuming additivity of $\Delta G^\circ(x)$ values for the methyl (1.7 kcal/mol)[14] and hydroxyl (0.6 kcal/mol)[14,15] groups. This lack of additivity applies not only to equilibrium 1 but also to the analogous equilibrium between the isomers of 1-methyl-4-*t*-butylcyclohexanol—*cis* 2 and *trans* 2. Each isomer was separately equilibrated in aqueous acetic acid containing sulfuric acid at 25°. Analysis of the equilibrated alcohols by gas chromatography on a Carbowax 20M column showed the presence of about 58.5% *trans* 2 and 41.5% *cis* 2. This corresponds to a value of $-\Delta G^\circ = 0.2$ kcal/mol for equilibrium 4. This value is in good agreement with that obtained by nmr spectroscopy in DMSO, but is in poor agreement with the calculated value, $-\Delta G^\circ = 0.8$ kcal/mol ($-1.7 + 0.9 = -0.8$ kcal/mol). It should be noted that the calculated values for $-\Delta G^\circ$ are different for the two experiments because of the solvent change from DMSO to aqueous acid. Available data suggest that $\Delta G^\circ(\mathrm{OH})$ is greater in H-bond-donating solvents (*ca.* 0.9 kcal/mol), than in either H-bond-accepting solvents or nonbonding solvents (*ca.* 0.6 kcal/mol).[15]



(4)

cis 2 *trans* 2

The leveling effect which geminal substitution has had on the conformational preference of the CH_3 and OH groups stands in contrast to most of the available data (Table I) on 1,1-disubstituted cyclohexanes. The reasons for the lack of additivity remain obscure[16] and probably can best be uncovered through a detailed analysis of the Westheimer type.[6,17]

Experimental Section[18]

Materials.—All nmr spectra were obtained on a Varian A-60 nmr spectrometer equipped with a variable-temperature probe. The reported spectral data are the result of several independent measurements, using different batches of solvent and sample. The water concentration in the DMSO varied from about 1% to less than 0.3%. The probe temperature was 35°.

DMSO was dried by heating over calcium hydride and distilling from calcium hydride under reduced pressure (bp *ca.* 80°) as previously described.[10c]

The three 1-methylcyclohexanols (**1**, **2**, and **3**) were all obtained by addition of an ether solution of the appropriate ketone to an ether solution of methylmagnesium iodide. The procedures for preparation and separation of isomers were modeled after those described by DePuy and King.[19] Cyclohexanone gave 1-methylcyclohexanol, bp 62–64° (15 mm) [lit.[20] bp 68 (24 mm) and 56.5 (10 mm)]. 4-Methylcyclohexanone gave a mixture of *cis*- and *trans*-1,4-dimethylcyclohexanol. Chromatography on activated alumina using hexane–benzene mixtures (0–100%) for development gave first samples of the *trans* isomer, mp 70–72° (lit.[21] mp 72.5), followed by the *cis* isomer as an oil (lit.[21] mp 24°). In a similar fashion from 4-*t*-butylcyclohexanone, *cis*-4-*t*-butyl-1-methylcyclohexanol, mp 88–91 (lit.[19] mp 97.5–98°), and *trans*-4-*t*-butyl-1-methylcyclohexanol, mp 72–74° (lit.[19] mp 70.5–71°), were obtained.

Equilibration Studies.—Separate samples of *cis*- and *trans*-4-*t*-butyl-1-methylcyclohexanol (10–30 mg) were dissolved in 2–4 ml of a solution containing concentrated sulfuric acid (20 ml), glacial acetic acid (20 ml), and water (10 ml). After 4 days at 25°, the equilibrated mixtures were diluted with an equal volume of 15% sodium hydroxide solution and extracted three times with 5–10 ml of ether. The ether solutions were washed with a few milliliters of 15% sodium hydroxide solution and concentrated at atmospheric pressure. The concentrated solutions were then analyzed by vpc on a 5% Carbowax 20M column at 130–140°. The response ratio (*trans*/*cis*) for the isomers was found to be 1.02 ± 0.02 with the *cis* isomer being eluted last. Starting with the *cis* isomer, K_{eq} was found to be 1.37 and from the *trans* isomer K_{eq} was 1.43. Therefore, K_{eq} was taken to be about 1.40 and $-\Delta G^\circ\ (25^\circ) = 0.20$ kcal/mol. Control experiments demonstrated that this procedure did not fractionate known synthetic mixtures of the alcohols.

Registry No.—**1**, 590-67-0; *cis* **2**, 16980-56-6; *trans* **2**, 16980-55-5; *cis* **3**, 16980-60-2; *trans* **3**, 16980-61-3.

Acknowledgment.—We wish to thank Mr. Warren Cole for his assistance in the preparation of materials used in this work and to the National Science Foundation for a grant to purchase an nmr spectrometer.

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[14] J. A. Hirsch in "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1967, pp 199 ff.

[15] E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965).

[16] It should be pointed out that changes in the rotamer populations of substituents will occur in going from a mono- to a 1,1-disubstituted cyclohexane. The attending free-energy changes, while often small, are nevertheless not taken into account by a simple addition of free energies.

[17] J. B. Hendrickson, *ibid.*, **83**, 4537 (1961); J. B. Hendrickson, *ibid.*, **84**, 3355 (1962); J. B. Hendrickson, *ibid.*, **86**, 4854 (1964); K. B. Wiberg, *ibid.*, **87**, 1070 (1965).

[18] All melting points and boiling points are uncorrected.

[19] C. H. DePuy and R. W. King, *ibid.*, **83**, 2743 (1961).

[20] T. D. Nevitt and G. S. Hammond, *ibid.*, **76**, 4124 (1954); K. V. Anwers, R. Hintersuber, and W. Trippmann, *Ann.*, **410**, 257 (1915).

[21] G. Chiurdoglu, *Bull. Soc. Chim. Belges*, **47**, 241 (1938).

Conformational Analysis. LXIII. The 1-Methylcyclohexanol System[1,2]

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The conformational energies of simple groups on cyclohexane rings are now rather well known.[3,4] One of the questions which we are now in a position to consider concerns the degree of additivity which will result when two or more substituents are simultaneously present on the ring. If two substituents have a 1,2 relationship, their interaction is sizable.[5] If the relationship is 1,4, the interaction has long been assumed to be negligible,[6]

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[1] Paper LXII: N. L. Allinger and W. Szkrybalo, *Tetrahedron*, in press.

[2] This research was supported by Grant GP 4290 from the National Science Foundation.

[3] J. A. Hirsch in "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1967, p 199.

[4] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley and Sons, Inc., New York, N. Y., 1965, p 436.

[5] Reference 4, p 50.

[6] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).