Conformational Analysis. LXXV. The Methylation Rates of *cis*- and *trans*-4-*tert*-Butyl-*N*,*N*-dimethylcyclohexylamines[1,2]

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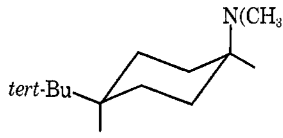
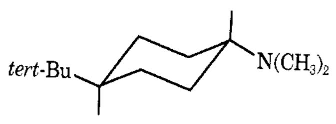
The rates of methylation of *cis*- and *trans*-4-*tert*-butyl-*N*,*N*-dimethylaminocyclohexane have been measured as functions of temperature, and the trans reacts about 50 times faster. The activation enthalpies are similar (10.1 kcal/mol for trans and 9.2 for cis), but the activation entropies differ considerably (−29.6 eu for trans and −40.3 for cis). The data suggest that the structures of the stereoisomeric 4-methyl-*N*,*N*-dimethylaminocyclohexanes were incorrectly assigned and that the *cis*-4-*tert*-butyl-*N*,*N*-dimethylaminocyclohexane reacts through a chair conformation and not a boat as previously suggested.

Although there are many literature references regarding rates of saponification and esterification at groups exocyclic to cyclohexane rings,[4] prior to the beginning of this investigation there was no available information regarding the rates of alkylation of simple, conformationally stable exocyclic amines.[5,6] In this work, the rates of methylation of *cis*- and *trans*-4-*tert*-butyl-*N*,*N*-dimethylcyclohexylamines (I and II) in acetonitrile were determined at various temperatures.

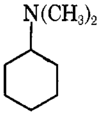


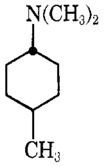
I

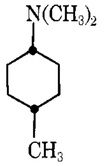


II

Peeling and Stone,[7] in a short communication, reported the second-order rate constants for the methylation of the isomeric methyl-*N*,*N*-dimethylcyclohexylamines with iodomethane at 40°. The following data are reproduced from their publication.

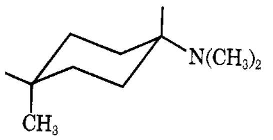




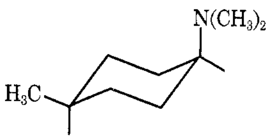


	III	IV	V
k_2 (mol^{-1} min^{-1}) at 40°	3.11	2.4	3.2

From a consideration of some of the principles of conformational analysis,[1] these data are quite surprising. It is now clear[4] that the cis isomer V is not conformationally rigid as was assumed by these authors, and it will exist as a mixture of two conformers V$_e$ and V$_a$, one in which the amine group is equatorial and one in which the amine group is axial. Sicher and coworkers[8] have determined from pK_a measurements a conformational free energy of 2.1 kcal/mol for the dimethylamino group. Using this value, together with the average value reported for the conformational free energy of the methyl group in solution (1.7 kcal/mol[9]), one calculates that the equilibrium mixture at 0° will contain 65% V$_e$ and 35% V$_a$. Since it may be assumed that V exists to an appreciable extent as conformer V$_a$, where the dimethylamine group is axial, and since it is known experimentally that axial groups undergo reactions at reduced rates when compared to equatorial groups in cases in which the congestion increases in the product (and hence transition state) relative to the starting material,[10-13] V would be expected to undergo methylation at a slower rate than the trans isomer IV. The implication, then, is that in this particular reaction the axial amine alkylates more rapidly than the equatorial. Alternatively, Peeling and Stone may have assigned the configurations of the amines incorrectly (no details given), assuming their work is otherwise valid.



V$_e$



V$_a$

In the present work, we have studied the conformationally well-defined 4-*tert*-butyl-*N*,*N*-dimethylcyclohexylamines to see if the unexpected implication of the work of Peeling and Stone can be verified. Winstein and Holness[14] have established that the 4-*tert*-butyl-substituted cyclohexane ring is conformationally biased to the extent that it is ordinarily conformationally pure. By utilizing the 4-*tert*-butyl-substituted isomers, rates of reactions can be measured on the separate equatorial and axial substituents. Kinetic data gathered in this manner are valid for interpreting the data on the unsubstituted compound only if the 4-*tert*-butyl group does not change the reactivity of the compound relative to the cyclohexyl system by either steric or electronic interaction. Evidence which indicates that this assumption is a good approximation has been gathered by a

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[1] Paper LXXIV: N. L. Allinger, J. J. Maul, and M. J. Hickey, *J. Org. Chem.*, in press.

[2] This work was supported in part by Grant GP 15263 from the National Science Foundation.

[3] Correspondence concerning this work should be directed to this author at the University of Georgia.

[4] For leading references, see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965.

[5] After this work was completed, a paper by Sicher and coworkers[6] was published on the same subject.

[6] J. Sicher, M. Tichý, J. Závada, and J. Krupička, *Collect. Czech. Chem. Commun.*, **33**, 1438 (1968).

[7] E. R. A. Peeling and B. D. Stone, *Chem. Ind. (London)*, 1625 (1959).

[8] J. Sicher, J. Jonáš, and M. Tichý, *Tetrahedron Lett.*, 825 (1963).

[9] J. A. Hirsch in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967, p 204.

[10] Reference 4, p 72 ff.

[11] E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Amer. Chem. Soc.*, **83**, 2351 (1961).

[12] N. B. Chapman, R. E. Parker, and P. J. A. Smith, *J. Chem. Soc.*, 3634 (1960).

[13] J. L. Mateos, C. Perez, and H. Kwart, *Chem. Commun.*, 125 (1967).

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

number of investigators;[15] however, some recent work has been critical of this approach.[16,17]

In the present work, the known *cis*- and *trans*-4-*tert*-butyl-*N*,*N*-dimethylcyclohexylamines (I and II) have been prepared. The pseudo-first-order rate constants for methylation in acetonitrile when the system was flooded with methyl iodide have been measured by means of a conductimetric bridge. The validity of this method has been previously established in amine systems.[18,19] The mathematics used is that applied by Shamma and Moss.[18,20]

Results

The results of the methylation of *cis*- and *trans*-4-*tert*-butyl-*N*,*N*-dimethylcyclohexylamines (I and II) are reproduced in part in Table I (complete data are given in Table II).

First it may be noted that the trans isomer reacts some 50 times as rapidly as the cis at the same temperature. This is as one would suppose, and it casts grave doubt on the work of Peeling and Stone. The rates independently determined by Sicher[6] are in good agreement with ours. Sicher found rates of 1.52 and 78.30 (10^{-3} mol^{-1} sec^{-1}) at 20° for *cis*-I and *trans*-II, and our corresponding numbers, extrapolated and interpolated to 20°, are 1.41 and 78.77, respectively. Sicher measured rates at only one temperature and hence could determine the free energy of activation ($\Delta G^{\ddagger}$) but not the corresponding enthalpy ($\Delta H^{\ddagger}$) or entropy ($\Delta S^{\ddagger}$) for the reactions.[6] He discussed the possibility of the cis isomer proceeding through a transition state in which the ring was in a boat conformation but had no evidence on the point. Since we measured the rates as a function of temperature, we were able to draw further conclusions in this regard.

The free energy of activation ($\Delta G^{\ddagger}$) was calculated according to the following equations

$$\Delta G^{\ddagger} = -RT \ln K^{\ddagger}$$

$$K^{\ddagger} = k_2 h / k_b T$$

where k_2 is the second-order rate constant as found in Table I, h is Planck's constant equal to 6.625×10^{-27} erg sec, k_b is the Boltzmann constant equal to 1.38×10^{-16} erg/°K, and T is the absolute temperature. The enthalpy ($\Delta H^{\ddagger}$) and the entropy ($\Delta S^{\ddagger}$) were calculated from the following

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

and since $\Delta G^{\ddagger} = -RT \ln K^{\ddagger}$, $-\ln K^{\ddagger} = +\Delta H^{\ddagger}/RT - \Delta S^{\ddagger}/R$. The least-squares line was fitted to the variation of $-\ln K^{\ddagger}$ with $1/T$, and the slope and intercept gave respectively $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. For the trans and cis isomers, respectively, the enthalpies ($\Delta H^{\ddagger}$) were calculated to be 10.11 ± 0.7 kcal/mol and 9.20 ± 0.3 kcal/mol, and the entropies ($\Delta S^{\ddagger}$) were calculated to be −29.6 ± 2.4 eu and −40.3 ± 0.8 eu.

TABLE I

SUMMARY OF SECOND-ORDER RATES OF METHYLATION OF *cis*-(I) AND *trans*-4-*tert*-BUTYL-*N*,*N*-DIMETHYLCYCLOHEXYLAMINE (II) IN ACETONITRILE

	Temp, °K	k_2 (10^3 mol^{-1} sec^{-1})[a]	ln $K^{\ddagger}$	$\Delta G^{\ddagger}$, kcal/mol
Trans	273.6	23.7	−33.1209	18.009
	263.1	9.53	−33.9919	17.774
	245.1	2.38	−35.3078	17.199
Cis	296.1	1.61	−35.8863	21.117
	283.1	0.809*	−36.5315	20.553
	273.6	0.427*	−37.1382	20.193
	263.1	0.206*	−37.8271	19.779

[a] Obtained by dividing the average pseudo-first-order rate constants in Table II by the CH_3I concentration, which was 1.6 *M* or 0.80 *M* (*).

TABLE II

PSEUDO-FIRST-ORDER RATES OF METHYLATION FOR *cis*- and *trans*-4-*tert*-BUTYL-*N*,*N*-DIMETHYLCYCLOHEXYLAMINES (I AND II) IN ACETONITRILE

	Run no.	Temp, °C	k_1 (10^3 sec^{-1})	Av k_1 (10^3 sec^{-1})
Trans	1	0.5	39.3	
	2		34.5	
	3		39.8	
	4		38.0	37.9
	5	−10	16.4	
	6		15.2	
	7		15.5	
	8		14.0	15.2
	9	−28	4.63	
	10		3.88	
	11		3.62	
	12		3.11	3.81
Cis	13	23	2.58	
	14		2.54	
	15		2.63	2.58
	16	10	0.677	
	17		0.580	
	18		0.688	
	19		0.646	0.648
	20	0.5	0.324	
	21		0.352	
	22		0.358	
	23		0.331	0.341
	24	−10	0.163	
	25		0.167	0.165

Conclusions

It is found that the entropy of activation is more negative for the cis isomer than for the trans. This is what one would predict if the cis isomer is in the chair form, since the system becomes more congested and presumably more restricted in the transition state than does the trans isomer. On the other hand, if the cis isomer went over to a boat form in the transition state, since the entropy of a boat form is higher than that of a chair, other things being equal,[21] the entropy of activation should become more positive than that of the trans isomer, which it does not. There is no reason to think the cis isomer has a boat conformation in the starting material, and, in fact, there is good reason to think otherwise.[22] Compounds in which an axial *tert*-butyl would be required on a cyclohexane ring in a chair

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[15] For a review, see E. L. Eliel, *J. Chem. Educ.*, 126 (1960).

[16] (a) J. L. Mateos, C. Perez, and H. Kwart, *Chem. Commun.*, 125 (1967); (b) F. R. Jensen and B. H. Beck, *J. Amer. Chem. Soc.*, **90**, 3251 (1968).

[17] R. Brettle, D. R. Brown, J. McKenna, and J. M. McKenna, *Chem. Commun.*, 696 (1969).

[18] M. Shamma and J. B. Moss, *J. Amer. Chem. Soc.*, **83**, 5038 (1961).

[19] J. L. Imbach, A. R. Katritzky, and R. A. Kolinski, *J. Chem. Soc. B*, 556 (1966).

[20] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961.

[21] N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **82**, 2393 (1960); N. L. Allinger and H. M. Blatter, *ibid.*, **83**, 994 (1961).

[22] Reference 9, p 216.

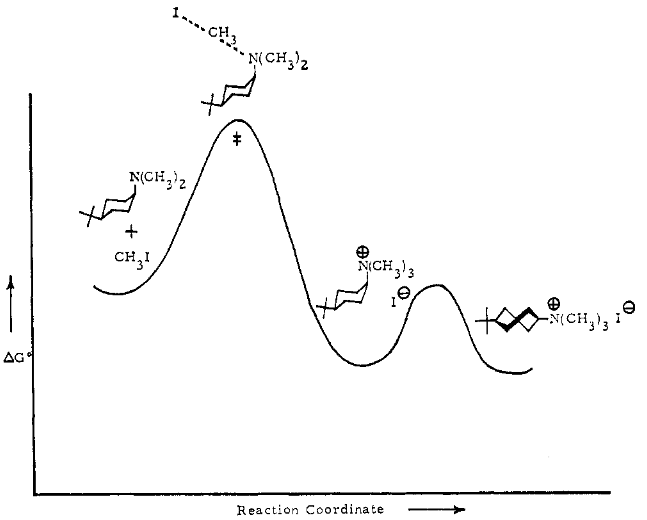

Figure 1.

form, such as *trans*-1,3-di-*tert*-butylcyclohexane, are found to have the ring largely in the boat conformation[21] and the methiodide of I should be also, although definite evidence on that point seems lacking.[23] The conclusions seem to be that the transition state is still chair, and near to starting material, and the reaction coordinate diagram must look approximately as summarized in Figure 1.

Experimental Section

***cis*-4-*tert*-Butylcyclohexanecarboxylic Acid.**—This compound was prepared according to a known procedure.[24] Chromatography of the ethyl ester (8 ft, 15% SE-30 Chromosorb W at 175° and 60 cc/min.) showed the ester to be at least 98% cis.

***cis*-4-*tert*-Butylcyclohexylamine.**—This compound was prepared from the acid according to the Schmidt method;[23] distillation yielded the amine, bp 91–92° (15 mm) [reported[23] 90° (15 mm)].

***cis*-4-*tert*-Butyl-*N*,*N*-dimethylcyclohexylamine (I).**—This compound was prepared essentially according to the method of Curtin,[23,25] bp 105–106° (25 mm). Chromatographic analysis (*vide supra*, 145° and 100 cc/min.) showed the amine to be at least 97.5% cis and the remainder an impurity which was not the trans isomer. *Anal.* Calcd for $C_{12}H_{25}N$: C, 78.62; H, 13.75. Found: C, 78.58; H, 13.66.

***trans*-4-*tert*-Butylcyclohexanecarboxylic Acid.**—The acid was prepared by known methods[11,23] and recrystallized from hexane, mp 172–174° (reported[24] 174–175°). Chromatography of the ethyl ester (*vide supra*) showed the acid to contain 98.4% of the trans isomer.

***trans*-4-*tert*-Butylcyclohexylamine.**—This compound was prepared from the acid by the same method as used for the cis amine, bp 92–93° (17 mm).[23,26]

***trans*-4-*tert*-Butyl-*N*,*N*-dimethylcyclohexylamine (II).**—This compound was prepared by a method identical with that used to prepare the cis amine I, bp 112–113° (28 mm). Chromatography (*vide supra*) showed that the amine was at least 99% trans. *Anal.* Calcd for $C_{12}H_{25}N$: C, 78.62; H, 13.75. Found: C, 78.86; H, 13.93.

Kinetic Measurements.—A solution of 100 mg ± 3.4 mg of amine was dissolved in 100 ml of acetonitrile (Matheson Coleman and Bell, AX 149, purified by distillation from magnesium sulfate under nitrogen) and stored under nitrogen. Resistance measurements were made on 10-ml aliquots of the standard amine solution to which was added 1.0 ml or 0.5 ml of methyl iodide (Matheson Coleman and Bell reagent grade IX 195) using an Industrial Instruments, Inc., conductivity bridge, Model No. RC16B2. The solution was kept under nitrogen during each kinetic run in a special cell designed to bubble nitrogen constantly through the solution.

Registry No.—I, 2523-69-5; II, 2523-68-4.

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[23] D. Y. Curtin, R. D. Stolow, and W. Maya, *J. Amer. Chem. Soc.*, **81**, 3330 (1959), have interpreted the reactions of the methiodide of I in terms of a chair form, and it seems that there must be at least a substantial amount of chair in equilibrium with the boat.

[24] H. H. Lau and H. Hart, *ibid.*, **81**, 4897 (1959).

[25] S. H. Pine, *J. Chem. Educ.*, 118 (1968).

[26] A value of 142–145° (17 mm) has been reported by D. V. Nightingale, J. D. Kerr, J. A. Gallagher, and M. Maienthal, *J. Org. Chem.*, **17**, 1017 (1952), but it appears that this value is incorrect.

Crystalline Complexes of Macrocyclic Polyethers with Thiourea and Related Compounds

C. J. PEDERSEN

Contribution No. 215 from the Elastomer Chemicals Department, Experimental Station, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware 19898

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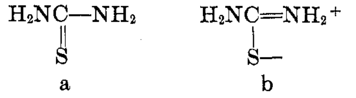
Crystalline complexes of macrocyclic polyethers with thiourea and with compounds related to thiourea have been prepared. Their stoichiometry lies between one molecule of polyether to one to six molecules of the other component, but no obvious rule for fixing the ratios has been discovered. The sizes of the molecules and the stoichiometry appear to eliminate the possibility that these are inclusion compounds and the exact nature of these complexes has yet to be determined.

The preparation and properties of a number of macrocyclic polyethers derived from aromatic vicinal diols have been previously reported.[1] It was shown that dibenzo-18-crown-6,[2] one of the polyethers, forms complexes with ammonium and monosubstituted ammonium salts which contain separate anions. It was considered possible that thiourea (a) will assume the tautomeric



$$\underset{\mathrm{a}}{\mathrm{H_2N}\underset{\mathrm{S}}{\underset{\|}{\mathrm{C}}}\text{—}\mathrm{NH_2}} \qquad \underset{\mathrm{b}}{\mathrm{H_2N}\underset{\mathrm{S}\text{—}}{\underset{|}{\mathrm{C}}}{=}\mathrm{NH_2}^+}$$

zwitterion form (b) and complex with the cyclic polyether. There also was the possibility, however remote, for the formation of inclusion compounds of cyclic polyethers and their salt complexes when they are exposed to thiourea under suitable conditions. If such inclusion compounds did form, they would be, in the case of the salt complexes, doubly wrapped salts, first surrounded by the polyether and then by thiourea. A short study, therefore, was undertaken to test these intriguing possibilities. When thiourea was actually found to form complexes with several macrocyclic polyethers, the action of some compounds related to thiourea was also investigated.

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[1] C. J. Pedersen, *J. Amer. Chem. Soc.*, **89**, 7017 (1967).

[2] The abbreviated nomenclature for the cyclic polyethers is described in the first reference and will be used here without further explanation.