infrared spectrum was identical with that of Eastman Kodak Co. spectral grade isoöctane, $n^{25}\mathrm{D}$ 1.3380.

2,2,3,3-Tetramethylbutane which solidified in the distilling head during the distillation of the reaction mixture, was recrystallized once from methanol, m.p. 100–101°, reported[34] m.p. 100.6°. The infrared spectrum was identical with that of 2,2,3,3-tetramethylbutane reported by the American Petroleum Institute Project 44 (Spectrum 444).

2,4,4-Trimethyl-1-pentene occurred in a mixture containing the other C_8-hydrocarbon as well as ethanol. It could not be separated from the 2,2,3,3-tetramethylbutane, even by gas chromatographic techniques. Therefore, 11 ml. of the distillate in which the 2,4,4-trimethyl-1-pentene was present was diluted with 30 ml. of ether, washed 7 times with 25-ml. portions of water (to remove the ethanol), and twice with saturated salt solution. The ether layer was dried over sodium sulfate and the ether then slowly evaporated. To the residue, in 25 ml. of glacial acetic acid, was added 1.06 g. of benzyl mercaptan (0.0086 mole), 10 mg. of hydroquinone and finally 50 drops of 18 M sulfuric acid. After standing 16 hours at room temperature, the reaction mixture was diluted with an equal volume of water and extracted with two 35-ml. portions of CCl_4. After drying the extract over sodium sulfate, the CCl_4, as well as anything else volatile at 100° (10 mm.), was removed by distillation. The oily residue, which was void of any mercaptan odor, was oxidized with 10 ml. of peracetic acid. The addition of water to this oxidation mixture resulted in a white precipitate, 0.425 g., m.p. 120.3–121.0°, after 3 recrystallizations from 30% ethanol. This was identified as benzyl 1,1,3,3-tetramethylbutyl sulfone, since it did not depress the melting point of known material (see above).

Thermal Reaction of DTBP with Triethyl Phosphite—DTBP (31.6 g., 0.216 mole) and 121 g. of triethyl phosphite (0.73 mole) were heated below a reflux condenser for 42 hours at 120°. Nitrogen was bubbled through the reaction mixture continuously, and the gaseous stream passed through a trap at −80°. Gas chromatographic examination of the contents of the trap revealed a mixture of low (C_4) and high (C_8) boiling hydrocarbons, very similar to the mixture obtained in the photolysis of DTBP in triethyl phosphite, with the exception that apparently no 2,4,4-trimethyl-1-pentene formed, but instead a peak corresponding to authentic 2,2,4-trimethyl-2-pentene. A white crystalline solid, 0.53 g., whose infrared spectrum was identical with that of 2,2,3,3-tetramethylbutane, except for medium sized peaks at 9.7 and 10.9 μ (where triethyl phosphite has very strong bands) was found at the inlet to the trap. After 2 sublimations (atmospheric pressure, 50°) a product, m.p. 93–97°, was obtained. The infrared spectrum was again identical with that of 2,2,3,3-tetramethylbutane; however, the peaks at 9.7 and 10.9 μ were still present, although greatly reduced in relative size. Fractional distillation of the reaction mixture revealed 86.4 g. of triethyl phosphate (110% based on oxygen available from the peroxide), b.p. 126° (40 mm.), $n^{25}\mathrm{D}$ 1.4048; 16 g. of material boiling above the triethyl phosphate was found, but not identified.

Reaction of *t*-Butyl Hydroperoxide with Triethyl Phosphite.—*t*-Butyl hydroperoxide was added dropwise to 9.7 g. of triethyl phosphite at 0°. Reaction was instantaneous and exothermic and addition was continued until no further heat was produced. Gas chromatographic analysis of the reaction mixture revealed that only two products formed, *t*-butyl alcohol and triethyl phosphate. When the reaction was repeated in the presence of 0.100 g. of trinitrobenzene (a pink solution with triethyl phosphite), an exactly analogous instantaneous and exothermic reaction occurred.

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(34) S. W. Ferris, "Handbook of Hydrocarbons," Academic Press, Inc., New York, N. Y., 1955, pp. 25–256.

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY AND THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Conformational Analysis. VII. Reaction of Alkylcyclohexyl Bromides with Thiophenolate. The Conformational Equilibrium Constant of Bromine[1]

BY ERNEST L. ELIEL[2] AND RALPH G. HABER

RECEIVED AUGUST 26, 1958

The bimolecular substitution and elimination rates of cyclohexyl bromide (k), *cis*-4-*t*-butylcyclohexyl bromide (k_a) and *trans*-4-*t*-butylcyclohexyl bromide (k_e) with thiophenolate have been measured. The over-all rate for the (axial) *cis* isomer is about 61 times as large as that for the (equatorial) *trans* isomer, the ratio for the corresponding tosylates (ref. 8) being 36, The equilibrium constant: axial cyclohexyl bromide $\rightleftarrows$ equatorial cyclohexyl bromide, calculated by the previously presented (ref. 3) equation $K = (k_a - k)/(k - k_e)$ is 3.4, corresponding to a difference of 0.73 kcal./mole between equatorial and axial bromine. This difference, which is supported by data in the literature, is considerably smaller than the accepted difference of 1.6–1.8 kcal./mole between equatorial and axial methyl. It is suggested that the difference is due largely to London forces which, at the inter-atomic distance between axial positions in cyclohexane, are of similar order of magnitude as the repulsive van der Waals forces. Contrary to an earlier report (ref. 8), elimination occurs in the reaction of *trans*-4-*t*-butylcyclohexyl tosylate as well as *trans*-4-*t*-butylcyclohexyl bromide with thiophenolate. This observation supports the "merged mechanism" of Winstein, Darwish and Holness (ref. 36) for the thiophenolate displacement.

In a previous paper[3,4] we have proposed the relationship $K = (k_a - k)/(k_a - k_e)$ (i) where K is the conformational equilibrium constant for the atom or group X (Fig. 1), k_a and k_e are specific rates of a suitable reaction[5] for the axial and equatorial isomer, respectively, and k is the experimental rate constant of the naturally occurring equilibrium mixture of the two conformational isomers for the reaction in question. The constants k_a and k_e are measured experimentally by studying the reaction in question with 4-*t*-butylsubstituted compounds.[4] Because of the large bulk of the 4-*t*-butyl group,[4] this group will tend to occupy exclusively the equatorial position. Therefore, in *cis*-4-*t*-butylcyclohexyl-X, X will occupy the axial position[6] and the compound will react at the specific rate k_a, whereas in *trans*-4-*t*-butylcyclohexyl-X, X will occupy the equatorial position

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(1) (a) Presented, in part, before the Division of Organic Chemistry, San Francisco Meeting, Am. Chem. Soc., April 15, 1958; (b) Paper VI, *J. Org. Chem.*, in press.

(2) National Science Foundation Senior Postdoctoral Fellow 1958–1959.

(3) E. L. Eliel and C. A. Lukach, THIS JOURNAL, **79**, 5986 (1957).

(4) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955), have earlier proposed an equivalent relationship $k = N_e k_e + N_a k_a$ where N_e and N_a are the mole fractions of substrate in the equatorial and axial conformation, respectively.

(5) The nature of the reaction chosen is immaterial.

(6) Provided X is substantially smaller than *t*-butyl.

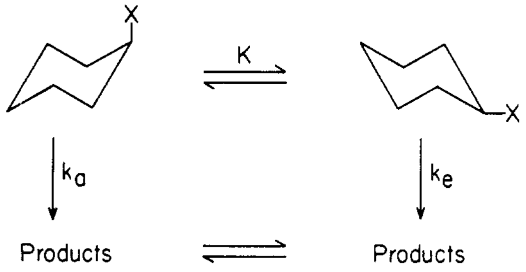


Fig. 1.

and the compound will react at the specific rate k_e.[7]

Previously, equation i has been used to calculate the conformational equilibrium constant for hydroxyl (from oxidation[4] or acetylation[3] rates) and for the tosylate group (from solvolysis rates[4] or bimolecular reaction rates with thiophenolate[8]). The present paper reports the application of the same treatment to a calculation of the conformational equilibrium constant for bromine. This seemed of interest since a previous estimate[9] of the energy difference E_{Br} between equatorial and axial bromine in cyclohexyl bromide had yielded the surprisingly small value of 0.7 kcal./mole. In comparison, the corresponding value for the methyl group is generally accepted to be 1.6–1.8 kcal./mole,[10] despite the fact that methyl and bromine are usually thought of as being similar in size.[11] Infrared studies on cyclohexyl bromide also support a low value for E_{Br}, since fairly intense bands ascribable to the axial as well as the equatorial form are found in the spectrum.[12,13] Moreover, the energy difference between the *gauche* and *trans* form of propyl bromide—which should be equal to 1/2 E_{Br}[14]—is only 0.1–0.5 kcal./mole,[15] whereas the corresponding value for *n*-butane is 0.8 kcal./mole.[14]

Results

The kinetics of the reaction of cyclohexyl bromide, *cis*- and *trans*-4-*t*-butylcyclohexyl bromide[16] and *cis*-4-methylcyclohexyl bromide[16] with sodium thiophenolate in 87% ethanol was followed essentially by the method previously described,[8] *i.e.*, the over-all rate was followed acidimetrically and the substitution rate alone was followed iodimetrically. However, since previous work had indicated that in slow runs of the type encountered in the present study (extending over several days), extensive oxidation of thiophenolate interfered with the iodimetric titrations, the present work was carried out in ampoules sealed under nitrogen. This gave steady and reproducible ratios of k_S/k_T (k_S = substitution rate, k_T = total rate, $k_E = k_T - k_S$ = elimination rate). Average rate constants for our runs are given in Table I.[17] Included in Table I are data earlier obtained for *n*-butyl bromide and *sec*-butyl bromide in stoppered flasks.[18] The individual runs are shown in Table III (Experimental) and a typical run is detailed in Table IV.

TABLE I

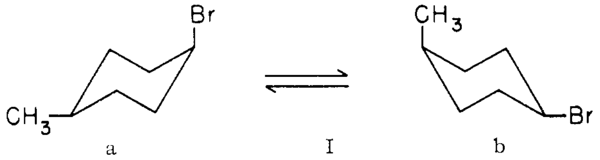
AVERAGED RATE CONSTANTS[a] FOR ALKYL BROMIDES WITH THIOPHENOLATE IN 87% ETHANOL AT 25.1°

Alkyl group	$k_T \times 10^5$	k_S/k_T	$k_S \times 10^5$	$k_E \times 10^5$
n-Butyl	1750	1[b]	1750	0
sec-Butyl	68.2	*ca.* 1[c]	*ca.* 68.2	*ca.* 0
cis-4-*t*-Butylcyclohexyl	9.44	0.51	4.81	4.63
cis-4-Methylcyclohexyl	6.40	.49	3.14	3.26
Cyclohexyl	2.28	.53	1.21	1.07
trans-4-*t*-Butylcyclohexyl	0.154	(.54)[d]	(0.083)[d]	(0.071)[d]

[a] In l. mole^{-1} sec.$^{-1}$. [b] Assumed. [c] Inferred from the fact that 1-bromoöctane gave only 2-octyl phenyl thioether (in 84% yield) with sodium thiophenolate. [d] These values are low in accuracy.

From the data in Table I, the conformational equilibrium constant K for bromine (*cf.* Fig. 1, X = Br) can be calculated by means of equation (i) using either substitution rate constants, k_S, or elimination rate constant, k_E. The value for K from substitution rates is 3.2, that from elimination rates 3.6. The two values are in satisfactory agreement. We shall use an average value of K_{Br} of 3.4. This is also the value obtained from the overall rate constants (k_T) which are apt to be more accurate than the apportioned constants k_S and k_E. The corresponding free energy difference ΔF_{Br} is −0.73 kcal./mole.

It is rather surprising that this free energy difference is so much smaller than the corresponding difference for methyl although, as mentioned above, there are a number of observations in the literature in agreement with this finding. The same point



a I b

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[7] It is assumed that the *t*-butyl group exerts no polar or steric effect across the ring. Evidence for the correctness of this assumption has been provided.[3,4]

[8] E. L. Eliel and R. S. Ro, THIS JOURNAL, **79**, 5995 (1957).

[9] E. J. Corey, *ibid.*, **75**, 2301 (1953).

[10] W. G. Dauben and K. S. Pitzer in M. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, chapter 1.

[11] L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1948, p. 189, gives the van der Waals radius of bromine as 1.95 Å. and that of the methyl group as 2.0 Å.

[12] M. Larnaudie, *Compt. rend.*, **235**, 154 (1952); P. Klaeboe, J. J. Lothe and K. Lunde, *Acta Chem. Scand.*, **10**, 1465 (1956); S. Mizushima, private communication. A contrary indication comes from molar Kerr constants—R. J. W. LeFèvre and C. G. LeFèvre, *Chemistry & Industry*, 55 (1956)—according to which cyclohexyl bromide appears to exist almost entirely in the equatorial conformation.

[13] P. Klaeboe, J. J. Lothe and K. Lunde, *Acta Chem. Scand.*, **11**, 1677 (1957), have calculated, by an admittedly crude method, N_e/N_a = 0.85/0.15 corresponding to a value of E_{Br} of 1.0 kcal./mole.

[14] Reference 10, p. 18.

[15] C. Komaki, I. Ichisima, K. Kuratani, T. Miyazawa, T. Shimanouchi and S. Mizushima, *Bull. Chem. Soc. Japan*, **28**, 330 (1955); J. Goubeau and H. Pajenkamp, *Acta Phys. Austr.*, **3**, 283 (1949); see also J. K. Brown and N. Sheppard, *Trans. Faraday Soc.*, **50**, 1164 (1954).

[16] E. L. Eliel and R. G. Haber, *J. Org. Chem.*, in press.

[17] The specific rates k_T in Table I are all somewhat smaller than the preliminary data reported by us: E. L. Eliel and R. G. Haber, *Chemistry & Industry*, 264 (1958). The reason for this is not clear, for although the preliminary rates were obtained in stoppered flasks, this should not affect k_T. Possibly a fluctuation in solvent composition is responsible, since the rates are quite solvent sensitive.[8] Both the earlier runs and those here reported were carried out with one batch of solvent for all the bromides, but the two studies used, of course, different solvent batches.

[18] Data obtained by Dr. Rolland S. Ro.

is borne out, at least qualitatively, by the rate constant for *cis*-4-methylcyclohexyl bromide (Table I). If bromine and methyl were of equal size, this compound should exist to an equal extent as the isomers with equatorial and axial bromine (Ia and b, respectively). In that case, applying the formula[4] $k = N_e k_e + N_a k_a$, since $N_e = N_a = 0.5$, k_T for *cis*-4-methylcyclohexyl bromide should be 4.8×10^{-5} l. mole^{-1} sec.$^{-1}$. That the actual value (Table I) is substantially larger means that the compound exists predominantly in the form with axial bromine (Ia) and that, therefore, bromine is smaller than methyl.[19]

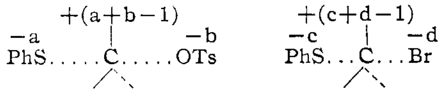
Discussion

Relative Rates.—The relative rates of substitution of various halides and tosylates[8] by thiophenolate are listed in Table II. It is of interest that the bromide rates are much more sensitive to structural changes than the tosylate rates, the extreme range (*k*-*n*-butyl-X: *k*-*trans*-4-*t*-butylcyclohexyl-X) being 713 for the tosylates and 21,100 for the bromides. In fact, as the last column in Table II indicates, whereas the secondary tosylates all react faster than the corresponding bromides, *n*-butyl bromide reacts faster than *n*-butyl tosylate. The difference between tosylates and bromides cannot be ascribed to different preferred ground-state conformations of the acyclic compounds, for since bromine and the tosylate group[8] are of about the same size,[20] the ground-state conformational equilibria should be about the same for the acyclic tosylates and bromides. Moreover, the difference between the two series persists for the *cis*- and *trans*-4-*t*-butylcyclohexyl compounds whose conformations are presumably fixed. The difference between the two series must therefore be sought in the respective transition states. We propose that because of the well-recognized greater propensity of tosylate (as compared with bromide) to depart as an anion,[21] the distance between the reaction center and the incoming thiophenoxide ion on one hand and the departing anion on the other in the transition state is greater for tosylates (IIa) than for bromides (IIb). This would also imply that the negative charges on the incoming and departing ions, and the positive charge on the central carbon atom, are greater for tosylate than for bromide, *i.e.*, $(a + b) > (c + d)$.[22] If these assumptions are granted, then, because of the greater distances, the energy of IIa should be affected less by steric effects than that of IIb. This would account for the lesser rate differences in the tosylate series. In addition, because of the larger positive charge at the central carbon atom in IIa, the energy of this transition state should be lowered by an extra methyl substituent more than that of transition state IIb. In other words, the difference in rate between a primary and secondary tosylate (5.3-fold) should be smaller than that for the corresponding bromide (26-fold) not only because of a smaller steric retardation, but also because of a larger polar acceleration. (However, as the data show, the polar acceleration does not quite compensate for the steric retardation, even in the case of the tosylates.[23]) An alternative statement of the same interpretation is to say, in the terminology of Winstein, Grunwald and Jones,[24] that although the reactions of both tosylates and bromides with thiophenolate are largely of type N (equivalent to S_N2), the tosylate reaction is somewhat more shifted toward the *Lim* side (equivalent to S_N1) of the reaction spectrum. In fact, both reactions respond to the sterochemical criterion[25a] of complete inversion and the kinetic criterion[25b] of second-order kinetics corresponding to the S_N2 reaction, but the solvent effect is that of an S_N1 reaction.[25c]

TABLE II

RELATIVE SUBSTITUTION RATE CONSTANTS FOR THE REACTION OF ALKYL BROMIDES AND ALKYL *p*-TOLUENESULFONATES WITH THIOPHENOLATE IN 87% ETHANOL AT 25.1°

Alkyl group	Relative rate Bromide	Relative rate *p*-Toluenesulfonate	k_{ROTs}/k_{RBr}
n-Butyl	364	23	0.48
sec-Butyl	14	4.3	2.3
cis-4-*t*-Butylcyclohexyl	1.0	1.0	7.5
Cyclohexyl	1/4.0	1/3.6	8.4
trans-4-*t*-Butylcyclohexyl	1/58	1/31	13



IIa IIb

Transition states

It is still hard to account for the fact that *n*-butyl bromide actually reacts *faster* with thiophenolate than *n*-butyl tosylate, rather than just at the same rate or very slightly slower. The reversal of k_{ROTs}/k_{Br} is peculiar to the thiophenolate reaction, for with ethoxide ion ethyl tosylate[26] ($k_{45} = 2.36 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$) reacts faster than ethyl bromide[27] ($k_{55} = 1.97 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$).[28] The reversal may be a result of London forces which act

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[19] The quantitative agreement is, unfortunately, not satisfactory. If ΔF_{CH_3} is -1.6 kcal./mole and ΔF_{Br} is -0.7 kcal./mole, ΔF for *cis*-4-methylcyclohexyl bromide should be $+0.9$ kcal./mole, corresponding to a K of 0.22. The calculated rate constant for $K = 0.22$ — $k = (k_eK + k_a)/(K + 1)$[8] — is 7.7×10^{-5} l. mole^{-1} sec.$^{-1}$, in poor agreement with the observed value of 6.4×10^{-5}. A similar, though even worse disagreement was observed in the case of *cis*-4-methylcyclohexyl tosylate; ref. 8.

[20] See, however, ref. 4.

[21] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 340–341 has pointed out that tosylates are more prone to react by the S_N1 (ionization) mechanism than corresponding halides.

[22] The tosylate ion is better able to carry negative charge because it distributes it over three oxygen atoms.

[23] P. B. D. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold and J. D. H. Mackie, *J. Chem. Soc.*, 3200 (1955), have postulated, on the basis of calculation, that the polar effect of the extra methyl substituent is retarding. It has been pointed out elsewhere—E. L. Eliel in M. Newman's "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 74—that there are difficulties with this interpretation. With respect to the present study, we grant, however, that instead of speaking of a greater polar acceleration for tosylate (as compared with bromide) one might postulate a lesser polar retardation, and still come out with the same result.

[24] S. Winstein, E. Grunwald and H. W. Jones, THIS JOURNAL, **73**, 2700 (1951).

[25] Ref. 21, (a) pp. 377–386; (b) pp. 313–314; (c) pp. 345–350.

[26] M. S. Morgan and L. H. Cretcher, THIS JOURNAL, **70**, 375 (1948).

[27] E. D. Hughes, C. K. Ingold, S. Masterman and B. J. McNulty *J. Chem. Soc.*, 899 (1940).

[28] Comparable results for secondary alkyl compounds are not available, since their reaction with ethoxide is largely elimination.

TABLE III

RATE CONSTANTS IN L. MOLE^{-1} MIN.$^{-1}$

Run	Compound	10^3k_T	k_S/k_T	a[a]	b[a]
1*	Cyclohexyl bromide	1.47 ± 0.14	0.60 ± 0.04	0.1266	0.1266
2		1.28 ± .07	.50 ± .02	.2860	.1416
3		1.42 ± .03	.50 ± .06	.1418	.1418
4		1.40 ± .02	[b]	.2864	.1335
5		1.28 ± .03	[b]	.1433	.2625
6	*cis*-4-*t*-Butylcyclohexyl bromide	5.97 ± .18	0.48 ± 0.01	.1063	.1063
7		5.36 ± .20	.54 ± .01	.05097	.1055
8	*trans*-4-*t*-Butylcyclohexyl bromide	0.092[c]	.54[d]	.1257	.2102
9	*cis*-4-Methylcyclohexyl bromide	3.80 ± .06	.49 ± .04	.05845	.1213
10		3.88 ± .07	.49 ± .02	.1213	.1213
11	*trans*-4-t-Butylcyclohexyl tosylate	1.07 ± .01	.60 ± .03	.06046	.1425

[a] Concentrations in mole/l., first figure, bromide, second figure, thiophenolate. [b] Ampoules not purged with nitrogen, no reliable data obtained. [c] This run showed a downward drift. [d] Single determination.

more effectively between the highly polarizable thiophenolate and the polarizable bromide than between thiophenolate and the less polarizable tosylate, and are also less important for ethoxide than for thiophenolate.[29] It is evident that these forces must become less important as the reaction shifts in mechanism from the N to the *Lim* end of the spectrum, since, in the extreme *Lim* case, the rate is independent of the nature of the nucleophile.

The Conformational Equilibrium of Bromine.—The present work, together with data in the literature, indicates that bromine in an axial position of cyclohexane is substantially less encumbered than a methyl group in the same position. This is, at first sight, surprising, since bromine in an *o*-position of a biphenyl is more hindering to rotation than methyl.[30a] Moreover, when placed next to a hindering *o*-substituent in a biphenyl, bromine has a larger buttressing effect than methyl.[30b,31]

Two causes, in our view, contribute to the inversion of the relative steric effects of bromine and methyl in the biphenyls on one hand and the cyclohexanes (*e.g.*, Ia) the interfering C–H and C–X moieties are oriented parallel. Therefore, the greater length of the C–Br bond (1.94 Å.) over C–CH_3 (1.54 Å.) makes the H–Br distance (2.67 Å.) somewhat larger than H–CH_3 (2.55 Å). Contrariwise, in the biphenyls, the interfering *o,o'*-groups pointed toward each other, and the greater length of C–Br over C–CH_3 increases rather than decreases the interference.[11,31a] Secondly, the absolute magnitude of the interference is much greater in the biphenyls than in the cyclohexanes, because the internuclear distance between the interfering groups in the biphenyls is much smaller.[32] This means that in the biphenyls the group interaction is controlled very largely by van der Waals repulsive forces, or by the bond deformation forces which take their place after the interaction energy has been minimized.[32] In the cyclohexanes, the van der Waals forces, which fall off with a very high (*ca.* 12th) power of the distance are much less important and London dispersion forces[33] of an attractive nature become of importance comparable to that of the van der Waals forces. For example, we have calculated[34] a London energy of 0.84 kcal./mole for the interaction between axial bromine and axial hydrogen (1:3) and 0.39 kcal./mole of bromine and adjacent hydrogen (1:2-e,e or 1:2-e,a). Therefore, the difference in London energy between axial and equatorial bromine is $(2 \times 0.84 + 2 \times 0.39) - 4 \times 0.39 = 0.9$ kcal./mole.[35] Although this calculation is extremely crude—because of the inherent inaccuracy of the formula and because it neglects the smaller interactions for the methylcyclohexane case—it does show that at the interatomic distances in question (2.5 to 3 Å.), London forces, which fall off with only the sixth power of the distance, are not negligible in comparison with van der Waals forces. In fact, their order of magnitude is the same as that of the over-all energy differences of many conformational isomers and that of some barriers to internal rotation.

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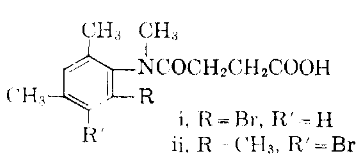
(29) J. F. Bunnett, THIS JOURNAL, **79**, 5969 (1957); J. D. Reinheimer and J. F. Bunnett, *ibid.*, **81**, in press.

(30) (a) R. L. Shriner and R. Adams in H. Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, Vol. I, p. 362. (b) p. 368.

(31) R. Adams and N. K. Sundholm, THIS JOURNAL, **70**, 2667 (1948), have shown that i racemizes three times as fast as ii. However, this case should not be taken to mean that bromine is less interfering than methyl because the situation is complicated by a resonance interaction of the amino group and bromine substituent *ortho* to it, as demonstrated by the authors. The buttressing effect of the extra bromine substituent in ii also makes the comparison of i and ii somewhat unfair.



i, R = Br, R′ = H
ii, R = CH_3, R′ = Br

(31a) A possible contributing factor may be presented here. In the methyl group, most of the van der Waals repulsion is due to the hydrogen atoms and the group is essentially spherical, *i.e.*, has the same van der Waals radius in all directions. But bromine may be thought of as being pear-shaped: the van der Waals radius is greatest on the side of the bromine pointing away from the carbon (the region involved in the *o–o'* biphenyl interaction) and smallest in the vicinity of the C–Br bond itself (the region involved in the Br–H 1,3-diaxial interaction); *cf.* ref. 11, p. 193.

(32) F. H. Westheimer, *J. Chem. Phys.*, **15**, 252 (1947), gives the *o–o'* H–Br distance in a coplanar biphenyl as 1.61 Å. before deformation and 2.31 Å. at the deformation required for minimizing the interaction energy.

(33) F. London, *Trans. Faraday Soc.*, **33**, 8 (1937); *cf.* ref. 29.

(34) Using the formula in K. S. Pitzer, "Quantum Chemistry," Prentice-Hall, Inc., New York, N. Y., 1953, p. 201; the polarizabilities given J. A. A. Ketelaar, "Chemical Constitution," Elsevier Publishing Co., Amsterdam, Holland, 1953, p. 90; the ionization potentials of ref. 11 and the interatomic distances of ref. 13. We have also calculated the induction energy between C–Br and C–H—*cf.* ref. 33—but this is less than 0.1 kcal./mole.

(35) Considering that there are two 1:3 diaxial interactions and two 1:2 axial–equatorial interactions for the axial bromine and two 1:2 diequatorial and two 1:2 equatorial–axial interactions for the equatorial bromine.

TABLE IV

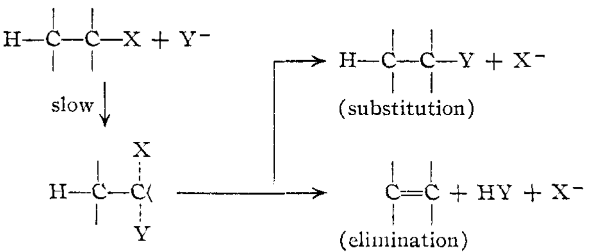
KINETIC RUN FOR REACTION OF *cis*-4-METHYLCYCLOHEXYL BROMIDE WITH SODIUM THIOPHENOLATE

Bromide, 2.149 g., 12.133 mmoles; base, 25 ml., 0.4853 *N*, 12.133 mmoles; thiophenol, 1.7 g., 15 mmoles; total volume, 100 ml.; $a = 0.1213$

Time, min.	Base,[a] ml.	Iodine,[b] ml.	Iodine consumed Ml.	Iodine consumed Meq.	Base consumed Ml.	Base consumed Meq. (x)	$a - x$,[c] ml.	$10^3 k_T$[d]	%[e]	k_S/k_T[f]
0	3.75	13.30	0	0	0	0	0.6020	...	0	..
366	4.31	[g]	..	....	0.56	0.0499	.5521	2.04[h]	8.3	..
739	5.47	11.70	1.60	0.0803	1.72	.1532	.4488	3.81	25.4	0.52
1470	6.56	10.86	2.44	.1224	2.81	.2505	.3518	3.99	41.6	.49
1881	6.95	10.53	2.77	.1390	3.20	.2850	.3170	3.94	47.3	.49
3113	7.75	9.92	3.38	.1696	4.00	.3562	.2458	3.84	59.2	.48
5251	8.55	9.32	3.98	.1997	4.80	.4274	.1746	3.84	71.0	.47
14887	9.60	8.56	4.74	.2379	5.85	.5209	.0811	3.56[h]	86.5	.46

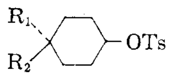
[a] 0.8905 *N* base required to back-titrate a 5-ml. aliquot quenched in 10 ml. of hydrochloric acid equivalent to 10.51 ml. of base. [b] 0.05018 *N* iodine required to titrate 5-ml. aliquot. [c] The *a*-value here used was calculated from the zero titer and refers to the number of milliequivalents of base in 5 ml. of solution. The value calculated from the original amount of base is 0.6065. [d] $x/at.\ (a - x)$. [e] Percentage reaction, $x/0.6020$. [f] Meq. iodine consumed/meq. base consumed. [g] Not determined. [h] Not taken into account in value reported in Table III.

The Merged Mechanism.—Recently Winstein, Darwish and Holness[36] have postulated a "merged mechanism" of nucleophilic substitution and elimination. According to this mechanism, a substrate reacts with a nucleophile, in a rate-determining step, to give an *intermediate* III (instead of the usual transition state) which will then, in a subsequent fast competition, give rise to either substitution or elimination product



III

The merged mechanism was originally postulated in order to explain the considerable amount of bimolecular elimination which *trans*-4-*t*-butylcyclohexyl tosylate (IV) (equatorial tosylate) undergoes with bromide ion, even though no bimolecular elimination of the equatorial tosylate occurs with the stronger base ethoxide.[4] At the time it was believed that the merged mechanism did not operate with thiophenolate as the nucleophile, since our earlier report[37] had indicated no elimination to occur with IV and thiophenoxide. Later, however, we postulated the merged mechanism to account for the fact the 4,4-dimethylcyclohexyl tosylate (V), though reacting at the same over-all rate with thiophenoxide as cyclohexyl tosylate (VI), gives almost exclusively substitution product, whereas VI gives about half substitution and half elimination product.[38] Implied in this report is the assumption



IV $R_1 = (CH_3)_3C;\ R_2 = H$
V $R_1 = R_2 = CH_3$
VI $R_1 = R_2 = H$

that thiophenolate *can* react by the merged mechanism. Because of this contradiction, we have now reëxamined the reaction of IV with thiophenoxide and found that, contrary to our earlier report,[8,37] elimination as well as substitution does occur. In fact, the sealed tube kinetic run indicated 40 ± 3% of the total reaction to be elimination, and the elimination product, 4-*t*-butylcyclohexene, also was isolated. *trans*-4-*t*-Butylcyclohexyl bromide also undergoes a substantial amount of elimination with thiophenolate, as indicated both kinetically (Table I) and by isolation.[16] We believe these bimolecular eliminations may be due to the merged mechanism.[36,37] The operation of the merged mechanism does not affect the argument given earlier regarding transition states (*cf.* IIa, IIb), since the intermediates as well as the rate-determining transition states in the merged mechanism are very similar to IIa and IIb.

Experimental

Cyclohexyl bromide was commercial material, redistilled, b.p. 60° (21 mm.). *cis*-4-Methylcyclohexyl bromide,[16] *cis*- and *trans*-4-*t*-butylcyclohexyl bromides[16] and *trans*-4-*t*-butylcyclohexyl *p*-toluenesulfonate[8] were prepared as described elsewhere. The purity of the bromides was checked by infrared analysis. The tosylate had m.p. 89.7–90.5° (lit.[8] 89–90°). Thiophenol (sample kindly donated by Pitt-Consol) was used as received. The solvent, 87% ethanol by weight, and the base were prepared as previously described.[8]

Kinetic Runs.—The appropriate amount of base was pipetted into a 50-ml. or 100-ml. volumetric flask, a *ca.* 10% excess of thiophenol added and the solution blanketed with nitrogen and placed in a thermostat at 25.1 ± 0.1°. A weighed amount of bromide (or a thermostated solution of a weighed amount of tosylate in the solvent) was transferred into the flask by means of 87% ethanol previously brought to 25.1° and ethanol was added to the mark. The solutions were mixed thoroughly and two 5-ml. aliquots were immediately withdrawn and titrated for zero-time base and thiophenol content, respectively, as previously described.[8] The remaining solution was aspirated into a 100-ml. syringe equipped with a large needle and distributed over six or seven ampoules of about 15-ml. capacity in such a way that each ampoule held at least 12 ml. (The ampoules were made by drawing out clean 25 × 150 mm. Pyrex test-tubes.) The ampoules were immediately placed in water at 25°, flushed with nitrogen for about 40 sec., sealed off and placed in the thermostat. At the appropriate time, an ampoule was withdrawn from the thermostat, opened, and two 5-ml. portions of the solutions pipetted into glacial acetic acid and standardized 0.1 *N* hydrochloric acid, respectively, and titrated with 0.05 *N* iodine and 0.1 *N* base, respectively. The over-all rate constant, k_T, was calculated from the base titers using the integrated second-order rate equations for equal or unequal concentration of the reactants, as the case might be. The ratio k_S/k_T was calculated at each point by dividing the change in iodine titer since the beginning of the reaction, converted to milliequivalents, by the corresponding change in base titer similarly converted.

[36] S. Winstein, D. Darwish and N. J. Holness, THIS JOURNAL, **78**, 2915 (1956).

[37] E. L. Eliel and R. S. Ro, *Chemistry & Industry*, 251 (1956); also ref. 8.

[38] E. L. Eliel and R. S. Ro, *Tetrahedron*, **2**, 353 (1958).

The runs are summarized in Table III and a typical run is detailed in Table IV. All runs except the first (marked with an asterisk) were followed to 73% conversion or more; one run with cyclohexyl bromide was followed to 97.5% completion without change in rate constant and one with *cis*-4-*t*-butylcyclohexyl bromide was followed to 99.1% completion with the rate constant being steady up to 86.3%. All rate constants, k_T, but one were free of drift between 25 and 75% reactions, as were, in most cases, the k_S/k_T ratios, except in two runs where the ampoules were not flushed with nitrogen and the ratio was completely erratic and too high, evidently due to oxidation difficulties. The one run less satisfactory than the rest is that for *trans*-4-*t*-butylcyclohexyl bromide which reacts extremely slowly and was followed for over a month. Because of shortage of substance, only one ratio k_S/k_T could be obtained, but this one definitely evidenced elimination, as did the isolation experiments (see below). The over-all specific rate, k_T, showed a downward drift. The constant k_T reported for *trans*-4-*t*-butylcyclohexyl bromide in Tables I and III was averaged over the first 30% of the reaction (24,000 minutes).

Controls.—In addition to the controls previously performed[8] the following points were checked: *Consumption of iodine by olefin formed:* A solution of two drops of 4-*t*-butylcyclohexene in 7.5 ml. glacial acetic acid (the amount used for quenching) turned yellow on the addition of one drop of *ca.* 0.05 *N* iodine solution. *Oxidation of thiophenol during filling of ampoules:* A solution for a kinetic run was prepared in the usual way except that no substrate was added. The base and iodine titers (*ca.* 0.1 and 0.05 *N* solutions, respectively) at the times indicated were: zero, 4.60 ml., 12.61 ml.; 1110 min., 4.45 ml., 12.51 ml; 2913 min., 4.50 ml., 12.53 ml.; 17,995 min., 4.52 ml., 12.55 ml. Evidently the fluctuations in iodine titer are no greater than those in base titer and not much greater than the limits of ordinary titration accuracy, indicating no appreciable oxidation of thiophenol during the filling of the ampoules. The same point is also emphasized by the lack of drift of the $k_S:k_T$ ratio in the kinetic runs; if there had been initial oxidation, this ratio should have drifted downward.

Isolation Experiments.—The isolation of 4-*t*-butylcyclohexene and *trans*-4-*t*-butylcyclohexyl phenyl thioether from *cis*-4-*t*-butyl-cyclohexyl bromide and of the same olefin and the epimeric *cis*-thio-ether from the corresponding *trans*-bromide have been described previously.[16] We have also isolated cyclohexene from the reaction of cyclohexyl bromide with sodium thiophenolate. The previous reaction of *trans*-4-*t*-butylcyclohexyl tosylate (IV) with thiophenolate was repeated on one-third the previous scale.[8] Since control experiments showed that 4-*t*-butylcyclohexene codistils with ethanol and is hard to recover from the distillate, the reaction mixture, after standing one month, was poured into dilute aqueous potassium hydroxide and extracted with pentane. The pentane solution was washed with aqueous potassium hydroxide, water, and then three times with 20% aqueous calcium chloride to remove ethanol. It was dried over calcium chloride, concentrated through a column and distilled. There was obtained 0.90 g. (20%) of 4-*t*-butylcyclohexene, b.p. 63° (27 mm.) (lit.[8] 55–57° (15 mm.)) and 3.4 g. (40%) of *cis*-4-*t*-butylcyclohexyl phenyl thioether, b.p. 165° (7 mm.) (lit.[8] 184–186° (13 mm.). Both products were identified by infrared spectra.[8] The thioether, this time, crystallized, m.p. 39.7–40.6° after two recrystallizations from 95% ethanol.

Reaction of 19.3 g. (0.1 mole) of 2-octyl bromide with excess sodium thiophenolate under conditions similar to the ones previously used for 2-octyl tosylate[8] (but extending the reaction time to one week) gave 13.5 g. (84%) of 2-octyl phenyl thioether, b.p. 157–159° (15 mm.) (lit.[8] 158.5–160° (15 mm.)) as the only product isolated. The infrared spectrum of this thioether was identical with that of material obtained from the tosylate.[8]

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NOTRE DAME, IND.

COMMUNICATIONS TO THE EDITOR

ISOPENTENOL PYROPHOSPHATE ISOMERASE

Sir:

A product of mevalonic acid metabolism recently has been isolated[1,2] to which the structure of Δ^3-isopentenol pyrophosphate (IsPP) has been assigned tentatively.[3] Concurrent investigations with authentic IsPP have established it as well as farnesol pyrophosphate (FaPP) as intermediate compounds in the biosynthesis of squalene.[4] More recently, studies have been directed to the sequence leading from IsPP to FaPP. A preparation derived from baker's yeast has been found to catalyze the migration of the unsaturated bond of IsPP to yield γ,γ-dimethylallyl pyrophosphate (DmalPP).

Chemically prepared[4] IsPP-1-C^{14} was incubated with the yeast enzyme. Although the product could be distinguished from IsPP by virtue of its extreme acid lability, paper electrophoresis under alkaline conditions failed to separate the product from IsPP. Studies with IsPP^{32} indicated that pyrophosphate was released on acidification of the product. It was anticipated that acid cleavage would occur at the –C–O– linkage and that if the original product were DmalPP, it would to some extent undergo allylic rearrangement[5] to form dimethylvinylcarbinol in addition to dimethylallyl alcohol. Cleavage with phosphatase, which acts at the –O–P– linkage should yield only dimethylallyl alcohol. Products of both such hydrolyses were analyzed and the results were in accord with that expected from the cleavage of DmalPP (Table I).

Preliminary data indicate that DmalPP is incorporated into FaPP and that IsPP-isomerase is the only iodoacetamide-sensitive[4] step in the enzymatic sequence between mevalonic acid and squalene. A special role is suggested for the sulfhydryl group in the isomerization such as the

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(1) F. Lynen, in Ciba Foundation Symposium on Biosynthesis of Terpenes and Sterols, J. and A. Churchill Ltd., London, in press.

(2) K. Bloch, *ibid.*

(3) S. Chaykin, J. Law, A. H. Phillips, T. T. Tchen and K. Bloch, *Proc. Nat. Acad. Sci. U. S.*, **44**, 998 (1958).

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(5) R. H. DeWolfe and W. G. Young, *Chem. Revs.*, **56**, 753 (1956).