Thermal Equilibration of Substituted *trans*-1,2-Dibromocyclohexanes

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The kinetics of the thermal equilibration of five *trans*-1,2-dibromocyclohexanes carrying substituents in the 3- or 4-position have been measured at different temperatures and the activation parameters have been determined. Values ranging between 1·64 and 2·70 for K_{eq}, 31·9 and 34·9 kcal mol^{-1} for E_a, and −1·3 and +5·3 cal K^{-1} mol^{-1} for $\Delta S^{\ddagger}$ have been found for the 3-methyl, 4-methyl, 4-t-butyl, and 4-methoxycarbonyl derivatives. The 3-t-butyl derivative deviates considerably, since it gives more than 99% of the diaxial isomer at equilibrium and has E_a 25 kcal mol^{-1} and $\Delta S^{\ddagger}$ −9·7 cal K^{-1} mol^{-1} for the diequatorial–diaxial interconversion. Possible interpretations are discussed.

THE thermal interconversion between vicinal steroid dibromides by ' 1,2-interchange '[1] has been investigated in some detail after the observation by Mauthner[2] that solutions of 5,6-dibromocholesterol exhibit mutarotation. It was later shown that this reaction involves the conversion of the 5α,6β- into the 5β,6α-dibromide,[3] a

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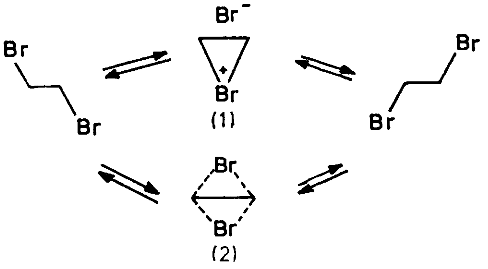
[1] D. N. Kirk and M. P. Hartshorn, ' Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 373.

[2] J. Mauthner, *Monatsh.*, 1906, **27**, 421.

[3] D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066.

reaction which takes place intramolecularly through an intermediate state; this state probably has the polar character of a bromonium–bromide intermediate (1) in polar solvents and the character of a bicyclic non-polar transition state (2) in less-polar ones.[4,5] The reaction has been reported to be subject to acidic catalysis, which, however, appears to be of a rather peculiar type since it is most pronounced with phenols, smaller with carboxylic acids,[6] and apparently absent with hydrogen bromide.[4]

Most of the work on this reaction has so far been concerned with steroid dibromides, while only little is known about its application to simpler monocyclic or acyclic dibromides. Since we had occasion in the course of our work on asymmetric brominations [7,8] to observe that the heating of substituted cyclohexane *trans*-dibromides causes equilibration between diaxial and diequatorial isomers, and that optically active vicinal dibromoalkanes and dibromocycloalkanes racemize thermally, probably through a similar mechanism,[9] we thought it worthwhile to investigate this reaction in some detail. The present paper reports data concerning a group of 3- and 4-substituted 1,2-dibromocyclohexanes.



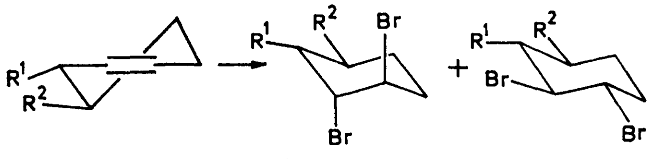
The addition of bromine to compounds (3a)–(3e) takes place exclusively in an *anti*-fashion to give non-equilibrium mixtures of the corresponding diastereoisomeric *trans*-dibromides (4) and (5) in ratios which differ somewhat according to the solvent and bromination agent employed, and to the position and polarity of the substituent in the substrate.[7,8,10] The isomers deriving from *anti*-parallel attack on the conformation with equatorial substituents (3) predominate in the mixtures, except for the case of the 3-t-butyl derivative (3e), which gives a slight excess of the diequatorial dibromide (5e). In no case was the formation of *cis*-dibromides observed, although the analytical procedures could have detected 1% of them. The data in Table 1 refer to brominations carried out with bromine in $CHCl_3$; the variations in diastereoisomer ratios with solvent and bromination procedure, and possible interpretations of the observed steric courses have been briefly discussed in preliminary communications,[10,11] and will be treated in greater detail elsewhere.

TABLE 1

Products of the bromine additions in $CHCl_3$ at 0°

Substrate	(4) : (5) ratio
(3a)	87 : 13
(3b)	94 : 6
(3c)	90 : 10
(3d)	78 : 22
(3e)	43 : 57

The dibromides (4) and (5) can be cleanly equilibrated by heating them in sealed tubes under nitrogen; side-products are not formed in appreciable amounts. The kinetics of the process was followed by an n.m.r. method, the analysis being carried out by integration of the signals of the protons α to the bromine. These signals are well separated in mixtures of (4) and (5), being broader and at higher field for the latter (axial protons) than for the former (equatorial protons) (see Table 3). Occasional checks carried out by g.l.c. fully confirmed the n.m.r. analyses. Equilibria were approached only from the side of the diaxial dibromides (4a)–(4d), which were easily isolated from mixtures by column chromatography, while the diequatorial isomers (5a)–(5d) could not be obtained pure in this way, because they were present in smaller amounts and apparently decomposed on the column. Only small samples of pure (5b) were separated by preparative g.l.c. The equilibration of (4e)–(5e) was carried out on the roughly equimolecular mixtures obtained in the bromination of (3e).



(3a - e) (4a - e) (5a - e)

a; $R^1 = H$; $R^2 = Me$
b; $R^1 = H$; $R^2 = t\text{-Bu}$
c; $R^1 = H$; $R^2 = CO_2Me$
d; $R^1 = Me$; $R^2 = H$
e; $R^1 = t\text{-Bu}$; $R^2 = H$

The rate and equilibrium constants and the activation parameters are shown in Table 2. Single runs usually exhibited clean first-order kinetics and the data thus obtained fitted rather satisfactorily the Arrhenius equation, as exemplified in Figure 1. The only mention in the literature of activation parameters in dibromide equilibrations is in the paper by Grob and Winstein,[4] who found E_a 25·5 kcal mol^{-1} and $\Delta S^{\ddagger}$ −5·1 cal K^{-1} mol^{-1} for the 5,6-dibromocholestanes; these data have a very approximate character, since they were based on kinetic runs at only two temperatures.

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[4] C. A. Grob and S. Winstein, *Helv. Chim. Acta*, 1952, **35**, 782.

[5] J. F. King and R. G. Pews, *Canad. J. Chem.*, 1965, **43**, 847.

[6] H. Kwart and L. B. Weisfeld, *J. Amer. Chem. Soc.*, 1956, **78**, 635.

[7] G. Bellucci, C. Giordano, A. Marsili, and G. Berti, *Tetrahedron*, 1969, **25**, 4515.

[8] G. Bellucci, G. Berti, F. Marioni, and A. Marsili, *Tetrahedron*, 1970, **26**, 4627.

[9] Unpublished work from this laboratory.

[10] P. L. Barili, G. Bellucci, G. Berti, F. Marioni, A. Marsili, and I. Morelli, *Chem. Comm.*, 1970, 1437.

[11] P. L. Barili, G. Bellucci, F. Marioni, and I. Morelli, *Chimica e Industria*, 1970, **52**, 708.

The data in Table 2 do not reveal very significant differences in rates and activation parameters for the first four pairs of dibromides, the moderate excess of diaxial isomers being consistent with the known preference for the *anti*-coplanar disposition of the halogen atoms, because of the dipole–dipole repulsion: values ranging between 18 and 62% diequatorial conformer have been calculated for *trans*-1,2-dibromocyclohexane by different methods and in different solvents.[12] The somewhat higher diaxial–diequatorial ratios found for (4c)–(5c) with respect to (4a,b)–(5a,b) can probably be attributed to interactions between the methoxycarbonyl and C–Br dipoles, but overall the size and polarity of substituents in the 4-position have little effect on the position of the equilibrium.

TABLE 2

$(5) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (4)$ equilibria [a]

Dibromides	T (K)	k_1 (s^{-1})	k_{-1} (s^{-1})	K_{eq}
(4a)–(5a)	393·2	2·06 ± 0·10 . 10^{-5}	1·11 ± 0·08 . 10^{-5}	65·0/35·0 (1·86 ± 0·10)
	408·2	0·97 ± 0·07 . 10^{-4}	0·53 ± 0·03 . 10^{-4}	64·7/35·3 (1·83 ± 0·10)
	423·2	3·96 ± 0·10 . 10^{-4}	2·14 ± 0·09 . 10^{-4}	65·0/35·0 (1·86 ± 0·10)
	438·2	1·48 ± 0·10 . 10^{-3}	0·79 ± 0·07 . 10^{-3}	65·0/35·0 (1·86 ± 0·10)
		E_a 32·4 ± 0·3	E_a 32·4 ± 0·2	
		$\Delta H^\ddagger$ 31·6 ± 0·3	$\Delta H^\ddagger$ 31·6 ± 0·2	
		$\Delta S^\ddagger$ −0·1 ± 0·7	$\Delta S^\ddagger$ −1·3 ± 0·6	
(4b)–(5b)	393·2	2·49 ± 0·13 . 10^{-5}	1·46 ± 0·05 . 10^{-5}	63·0/37·0 (1·70 ± 0·10)
	408·5	1·12 ± 0·05 . 10^{-4}	0·67 ± 0·04 . 10^{-4}	62·5/37·5 (1·67 ± 0·10)
	423·7	4·47 ± 0·54 . 10^{-4}	2·68 ± 0·30 . 10^{-4}	62·5/37·5 (1·67 ± 0·10)
	437·3	1·55 ± 0·08 . 10^{-3}	0·94 ± 0·06 . 10^{-3}	62·2/37·8 (1·64 ± 0·10)
		E_a 31·9 ± 0·4	E_a 32·4 ± 0·6	
		$\Delta H^\ddagger$ 31·0 ± 0·4	$\Delta H^\ddagger$ 31·6 ± 0·6	
		$\Delta S^\ddagger$ −1·2 ± 1·0	$\Delta S^\ddagger$ −0·8 ± 1·5	
(4c)–(5c)	393·2	2·39 ± 0·16 . 10^{-5}	0·89 ± 0·08 . 10^{-5}	72·9/27·1 (2·70 ± 0·10)
	408·2	1·33 ± 0·08 . 10^{-4}	0·51 ± 0·04 . 10^{-4}	72·1/27·9 (2·58 ± 0·10)
	423·2	5·89 ± 0·36 . 10^{-4}	2·32 ± 0·18 . 10^{-4}	71·7/28·3 (2·53 ± 0·10)
	438·2	2·22 ± 0·08 . 10^{-3}	0·88 ± 0·04 . 10^{-3}	71·7/28·3 (2·53 ± 0·10)
		E_a 34·4 ± 0·5	E_a 34·9 ± 0·7	
		$\Delta H^\ddagger$ 33·6 ± 0·5	$\Delta H^\ddagger$ 34·1 ± 0·7	
		$\Delta S^\ddagger$ +5·3 ± 1·3	$\Delta S^\ddagger$ +4·7 ± 1·6	
(4d)–(5d)	393·2	1·86 ± 0·09 . 10^{-5}	0·84 ± 0·06 . 10^{-5}	69·0/31·0 (2·23 ± 0·10)
	407·8	0·99 ± 0·09 . 10^{-4}	0·45 ± 0·04 . 10^{-4}	69·0/31·0 (2·23 ± 0·10)
	423·2	3·77 ± 0·21 . 10^{-4}	1·65 ± 0·06 . 10^{-4}	69·5/30·5 (2·28 ± 0·10)
	438·2	1·51 ± 0·20 . 10^{-3}	0·66 ± 0·10 . 10^{-3}	69·5/30·5 (2·28 ± 0·10)
		E_a 33·0 ± 0·9	E_a 32·8 ± 0·9	
		$\Delta H^\ddagger$ 32·2 ± 0·9	$\Delta H^\ddagger$ 32·0 ± 0·9	
		$\Delta S^\ddagger$ +1·3 ± 2·1	$\Delta S^\ddagger$ −0·8 ± 2·3	
(4e)–(5e)	355·2	5·71 ± 0·10 . 10^{-5}		
	359·8	1·10 ± 0·05 . 10^{-4}		
	368·0	2·45 ± 0·10 . 10^{-4}		
	382·6	8·44 ± 0·20 . 10^{-4}		
	393·2	1·84 ± 0·10 . 10^{-3}		
		E_a 25·0 ± 0·5		
		$\Delta H^\ddagger$ 24·3 ± 0·5		
		$\Delta S^\ddagger$ −9·7 ± 1·3		

[a] E_a and $\Delta H^\ddagger$ are expressed in kcal mol^{-1}, $\Delta S^\ddagger$ in cal K^{-1} mol^{-1}.

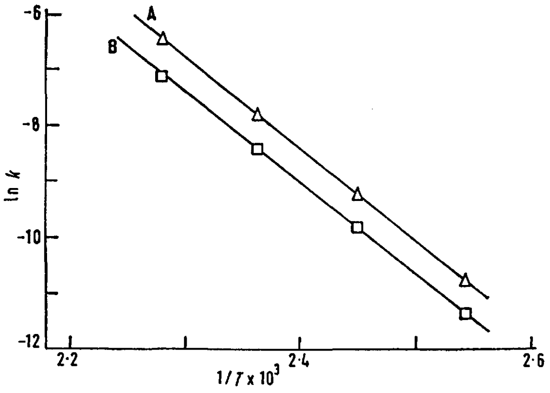

FIGURE 1 Plots of ln k_1 (A) and ln k_{-1} (B) *vs.* $1/T$ for (4a) $\rightleftharpoons$ (5a)

The situation is quite different for the 3-substituted derivatives. Whilst the behaviour of the 3-methyl dibromides is similar to that of the 4-substituted derivatives, the 3-t-butyldibromocyclohexanes (4e)–(5e) show markedly different behaviour in that the equilibrium is shifted completely in favour of the diaxial isomer. The less precise n.m.r. method sets a lower limit of 99% for this preference, while the g.l.c. method, which allows for a higher precision because of the very different retention times of (4e) and (5e) (relative retention time 1 : 2·5),

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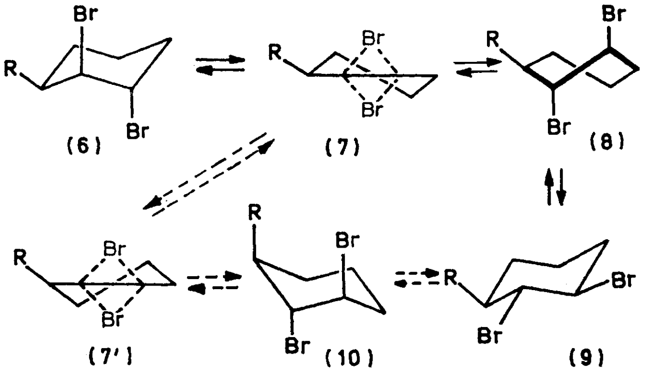
[12] P. Laszlo, *Progr. N.M.R. Spectroscopy*, 1967, **3**, 231; H. Booth, *ibid.*, 1969, **5**, 149; C. Altona, H. R. Buys, H. J. Hageman, and E. Havinga, *Tetrahedron*, 1967, **23**, 2265.

indicates that not more than 0·5% of the diequatorial isomer (5e) can be present at equilibrium. This appears to be by far the highest preference for a diaxial isomer in a cyclohexane system ever observed under equilibrium conditions. The activation parameters show that the *ca.* 100-fold increase in the diequatorial–diaxial conversion rate is due to the energy rather than the entropy term.



Scheme

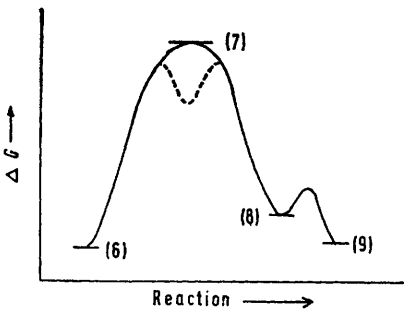


Figure 2

The equilibration of the cyclohexane dibromides can be visualized as shown in the Scheme. It requires an *anti*-parallel approach to the transition state, which is assumed to be similar to (7) under the conditions we employed (neat liquids), but could have some bromonium–bromide character in polar solvents. Whilst in the diaxial isomer (6) the bromine atoms are favourably disposed for conversion into the intermediate (or transition state) (7), the diequatorial isomer (9) requires prior conversion into a twist conformer (8) in order to reach the *anti*-coplanar disposition of the halogen atoms. The energy diagram is of the form shown in Figure 2 as proposed by King and Pews [5] for the steroid dibromides (the broken line refers to the possibility that a bromonium–bromide intermediate is actually formed). An alternative path involving interconversion of (7) and (7′) can be ruled out when R = alkyl, and is also rather unlikely for the racemization of dibromocyclohexane (R = H). The fact that the 4-methyl (4a,5a) and 4-t-butyl derivatives (4b,5b) have very similar equilibrium constants and activation parameters is in agreement with this hypothesis, since for (5b) conformation (10) would be of prohibitively high energy. In the case of the 3-t-butyl derivatives the negative value of $\Delta S^{\ddagger}$, implies a loss in degree of freedom in the transition state, which could indicate that a twist conformation (8) contributes to the conformational equilibrium of (5e), and the form of the energy diagram of Figure 2 should be so modified so that the levels of (8) and (9) are about equal. Evidence for the destabilization of the chair relative to a twist or boat form in t-butylcyclohexanes having a *trans*-substituent in the 2-position has recently been reported,[13] and preliminary data on the temperature dependence and coupling constants in the n.m.r. spectrum of (5e) seem to support this hypothesis.[14] Furthermore Pasto and Rao have shown that the equilibrium in the 2-t-butylcyclohexanols favours by *ca.* 0·55 kcal mol^{-1} the *cis*- over the *trans*-isomer,[15] this effect being attributed to the deformation of the ring near the t-butyl substituent,[16] which increases the *syn*-clinal interaction between the vicinal equatorial t-butyl and hydroxy-groups. However, even if this axial preference for the substituent in (2) can be greater for bromine than for hydroxy because of the greater steric requirements of the former, it is not possible to account for the more than 3 kcal mol^{-1} by which (4e) is more stable than (5e) on steric terms alone. It must be assumed that dipole–dipole interaction term plays a rather greater role in this case than in the 4-t-butyl dibromides, where it favours the diaxial isomer by only *ca.* 0·4 kcal mol^{-1}. A shortening of the distance between the two bromine atoms due to the ring deformation in (5e) may be responsible for its destabilization, but more reliable structural data on these compounds are obviously needed to explain the observed results in a satisfactory way.

EXPERIMENTAL

N.m.r. spectra were taken on neat liquids with a JEOL C-60 HL spectrometer. Preparative g.l.c. was carried out on a Perkin-Elmer F21 instrument, fitted with a 1-m steel column, i.d. 0·8 cm, packed with 5% SE 52 on 45—60 mesh Chromosorb A, 400 ml/min N_2, column temp. 100°, evaporator temp. 150°, collector temp. 150°.

Dibromides.—The preparation of the dibromides (4a) b.p. 62°/2 mm, n_D^{22} 1·5388, (4b) b.p. 74°/0·5 mm, n_D^{25} 1·5240, and (4d) b.p. 57°/0·6 mm, n_D^{25} 1·5415, by bromination of the corresponding olefins followed by chromatography on silica gel has already been described.[7,8]

r-1,t-2-*Dibromo*-t-4-*t-butylcyclohexane* (5b) was isolated by preparative g.l.c. from the equilibrated bromination mixture: m.p. 33—35° (from pentane at −60°) (Found:

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[13] R. D. Stolow, T. Groom, and D. I. Lewis, *Tetrahedron Letters*, 1969, 913; M. Tichý, J. Hapala, and J. Sicher, *ibid.*, p. 3739; R. D. Stolow, and J. L. Marini, *ibid.*, 1971, 1449.

[14] The n.m.r. spectra of the dibromides will be discussed in detail in a forthcoming publication.

[15] D. J. Pasto and R. D. Rao, *J. Amer. Chem. Soc.*, 1969, **91**, 2790; 1970, **92**, 5151.

[16] C. Altona and M. Sundaralingam, *Tetrahedron*, 1970, **26**, 925.

C, 40·6; H, 6·1; Br, 53·4. $C_{10}H_{18}Br_2$ requires C, 40·3; H, 6·1; Br, 53·6%).

Methyl t-3,c-4-*dibromo*-r-1-*cyclohexanecarboxylate* (4c) was obtained by addition of bromine to a chloroform solution of methyl 3-cyclohexenecarboxylate prepared by Fischer esterification of the commercially available acid. The gas-chromatographically pure isomer (4c) was isolated from its mixtures with (5c) by chromatography over silica gel (activity 1), with light petroleum (b.p. 30—50°)-benzene (7 : 3) as the eluant: b.p. 85—86°/0·1 mm, n_D^{25} 1·5375 (Found: C, 32·4; H, 4·1; Br, 53·5. $C_8H_{12}Br_2O_2$ requires C, 32·0; H, 4·0; Br, 53·3%).

TABLE 3

N.m.r. signals for protons α to bromine (δ in p.p.m.)

Compound	α-Hydrogens
(4a)	4·77—4·52
(5a)	4·30—3·63
(4b)	4·87—4·54
(5b)	4·34—3·66
(4c)	4·80—4·45
(5c)	4·28—3·89
(4d)	4·87—4·41
(5d)	4·36—3·48
(4e)	4·83—4·59
(5e)	4·57—3·97

r-1,t-2-*Dibromo*-t-3-*t-butylcyclohexane* (4e) was prepared by addition of bromine to a chloroform solution of 3-t-butylcyclohexene, obtained from 2-t-butylcyclohexanone tosylhydrazone with butyl-lithium.[17] Compound (4e) could be separated from the 57/43 mixture (n.m.r.) of (5e) and (4e) by elution with pentane from a silica gel column, but it was more convenient to obtain it by distillation after thermal equilibration of this mixture: b.p. 76—77°/0·5 mm, n_D^{24} 1·5290 (Found: C, 40·5; H, 6·2; Br, 53·2. $C_{10}H_{18}Br_2$ requires C, 40·3; H, 6·1; Br, 53·6%).

Thermal Isomerizations.—Samples of *ca.* 0·5 ml of the dibromides (4a)–(4d), or of a *ca.* 1 : 1 mixture of (4e) and (5e) were sealed under nitrogen in n.m.r. tubes and completely immersed in a thermostatted bath at the indicated temperatures (±0·2°). The tubes were withdrawn at intervals, rapidly cooled in ice–water, and the n.m.r. spectra taken; analysis was based on the integration of the signals of the protons α to halogen which were found in the ranges given in Table 3. Results were reproducible within ±1%. The heating was continued until four consecutive measurements indicated that equilibrium had been reached. The runs at the higher temperatures were carried out on two samples that were withdrawn from the bath alternatively. In these cases some darkening was observed, but n.m.r., g.l.p.c., or i.r. analysis did not reveal the formation of appreciable amounts of side-products, nor was the kinetics adversely affected.

The values of the equilibrium constants K_{eq} were calculated from four or more runs and are accurate to within ±0·1. All the isomerizations exhibited satisfactory first-order kinetics. For the equilibria (4a—d)–(5a—d) the rate constants k_1 and k_{-1} were determined from the equations:

$$k_1 + k_{-1} = \frac{1}{t} \ln \frac{x_e}{x_e - x}, \quad k_1/k_{-1} = K_{eq}$$

where x_e and x refer to mole fractions of the isomer (5), respectively at equilibrium and at the time t. The case of (4e)–(5e) in which the diequatorial–diaxial conversion is practically complete was treated as a simple irreversible first-order reaction. Seven or more measurements were carried out for each temperature and the best straight lines were calculated by the least-square method. The errors given in Table 2 are standard deviations.

Plots of ln$k$ against $1/T$ gave good straight lines, the slopes of which were calculated by the least-square method, errors being again expressed as standard deviations. The transition-state activation parameters, $\Delta H^\ddagger$ and $\Delta S^\ddagger$, were calculated from the Arrhenius activation parameters using the relationships [18]

$$\Delta H^\ddagger = E_a - RT$$
$$\Delta S^\ddagger = 4{\cdot}574 \log (A/T) - 49{\cdot}203$$

The temperature T was taken as 415·7 K for (4a—d)–(5a—d) and 374·2 K for (4e)–(5e).

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[1/1164 *Received, July 9th,* 1971]

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[17] J. C. Richer and C. Freppel, *Canad. J. Chem.*, 1968, **46**, 3709.

[18] S. Glasstone, J. J. Laidler, and H. Eyring, 'The Theory of Rate Processes,' McGraw-Hill, New York, 1941.