# 354. *The Mechanism of Racemisation of 2,2′-Di-iodobiphenyl.*

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2,2′-Di-iodobiphenyl has been prepared in the optically active state, and its racemisation studied. The transition state for racemisation of 2,2′-disubstituted biphenyls is reconsidered in the light of the effects of 4,4′-substituents on the rate constant for racemisation of 2,2′-di-iodobiphenyl.

The merit of a model put forward to describe the configurational inversion of an optically active biphenyl can be tested by means of the success with which it can relate change in optical stability to change in the nature and position of substituents in the biphenyl skeleton.[1-3] The inversion, $R \rightleftarrows S$, of a suitably substituted biphenyl was one of the earliest processes for which a reasonably acceptable transition state could be drawn; most writers have considered it to contain the two benzene rings and the atoms directly attached to them in one plane, bond-bending, bond-stretching, and atomic compression taking place to allow the transient planar arrangement. Baddeley,[4] however, recognised that if out-of-plane bending about the 1,1′-bond could take place it would facilitate racemisation, and drew attention to some comparative racemisation rates measured by Adams and his co-workers[5] which could be interpreted in this way. However, the *o*-substituents ($-NO_2$, $-OMe$, $-CO_2H$) in the compounds quoted may affect the optical stability in various ways. It is not known which pair of substituents passes each other in each compound; each group has a primary steric effect; each is capable of taking part in conjugation across the 1,1′-bond in different degrees; each is non-spherical, and can itself vary its degree of planarity with its attached benzene ring with consequential variation of both steric and conjugation effects; each may be capable of promoting bond-bending. Crawford and Smyth[6] put forward a geometrically similar view, as regards the molecular skeleton, when they suggested that the racemisation of biquinolyls and bi-isoquinolyls was assisted by the attack of hydrogen ion at one of the carbon atoms of the interannular bond, changing the hybridisation from $sp^2$ to $sp^3$. Neither of these ideas has received general acceptance; this is partly because the supporting evidence does not bear exclusively upon the one factor, no experiments having yet been designed which can do this.

[1] Adams and Yuan, *Chem. Rev.*, 1933, **12**, 261.

[2] Eliel, " Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, pp. 156—164.

[3] Westheimer, " Steric Effects in Organic Chemistry," ed. Newman, Wiley, New York, 1956, pp. 542—555.

[4] Baddeley, *Nature*, 1946, **157**, 694.

[5] Adams and Hale, *J. Amer. Chem. Soc.*, 1939, **61**, 2825; Adams and Finger, *ibid.*, 1939, **61**, 2828.

[6] Crawford and Smyth, *Chem. and Ind.*, 1954, 346; *J.*, 1954, 3464.

Studies of biphenyl racemisation are usually carried out on solutions. The investigation carried out by Leffler and his co-workers [7,8] indicates a significant dependence upon solvation in some of the racemisations; however, the biphenyls used carry polar, even ionisable, groups in the blocking positions, thus complicating any steric interpretation.

Probably, the main reason why suggestions involving out-of-plane bond-bending have been neglected, lies in the remarkable success of Westheimer [3] and his co-workers in calculating the enthalpies of activation for racemisation of 2,2'dibromobiphenyl and 2,2'-di-iodobiphenyl. The striking agreement with experimental values [9,10] made the acceptance of the premises on which the calculations were based almost axiomatic, *viz.*: that the ground state of the molecule is unstrained; that the transition state is planar, deformation taking place within the plane; and that the gain in resonance energy in going from the ground state to the transition state is negligible. Calculations on the Westheimer pattern but with added refinements—dipolar interaction terms in the ground and transition states, recognition of small van der Waals non-bonding interactions and in-plane deformations in the ground state, introduction of a resonance-energy stabilisation term in the transition state, and the use of revised van der Waals potential functions—have been carried out by Howlett.[11] The results for 2,2'-dibromo- and 2,2'-di-iodobiphenyl gave $\Delta H^{\ddagger} = 20{\cdot}8$ and $26{\cdot}4$ kcal. mole$^{-1}$, respectively ($E_{\text{rac}}$ 21·4 and 27·0 kcal. mole$^{-1}$). The numerical values depend upon the figure, 6·95 kcal. mole$^{-1}$,[12] used for the resonance stabilisation energy in the transition state; opinions vary about this quantity, *e.g.*, Mislow and his co-workers [13] used 4 kcal. mole$^{-1}$ [14] in calculating the energy barrier to racemisation of a biphenyl carrying a 2,2'-bridge, where the ground-state interplanar angle is 49·4°. It is possible that in calculations on highly hindered biphenyls, it is not justifiable to use a figure that was estimated for biphenyl itself. Westheimer omitted the factor altogether, and his results agree very well with experiment; if resonance-stabilisation factors are to be introduced into his calculations, so also must some compensating factors.

1,1'-Binaphthyl-8,8'-dicarboxylic acid racemises "abnormally" easily; the racemisation parameters can be reasonably interpreted, in a qualitative way, if it is assumed that out-of-plane as well as in-plane bending can take place and that the ground state has a considerable strain energy.[15,16] In view of this, it seemed to us that the postulate of out-of-plane bending to facilitate racemisation in the biphenyl series should be examined afresh.

As a beginning, we have prepared 2,2'-di-iodobiphenyl and a series of 4,4'-di-symmetrically substituted 2,2'-di-iodobiphenyls in the optically active state and have determined their velocity constants for racemisation, over a range of temperature, in *NN*-dimethylformamide solution. These compounds were chosen in an attempt to approach as closely as possible to the variation of a single factor which might influence racemisation rate, this factor being the nature of the 4,4'-substituents. Halogen atoms were selected for the blocking positions because we considered that they would themselves have little conjugative interaction with the molecular skeleton; fluorine and chlorine appear to be too small to give observable optical activity and bromine is on the verge of accurate measurement in the 4,4'-dicarboxylic acid, so that iodine was the inevitable choice. Since the 4- and 4'-groups in each compound are identical, the incursion of major resonance effects across the 1,1'-bonds is unlikely.

*NN*-Dimethylformamide was chosen as solvent because all the compounds were

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[7] Leffler and Graham, *J. Phys. Chem.*, 1959, **63**, 687; Graham and Leffler, *ibid.*, 1959, **63**, 1274; Leffler and Graybill, *ibid.*, 1959, **63**, 1457; Graybill and Leffler, *ibid.*, 1959, **63**, 1461.

[8] Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, 1961, p. 307.

[9] Searle and Adams, *J. Amer. Chem. Soc.*, 1934, **56**, 2112.

[10] (*a*) Harris, *Proc. Chem. Soc.*, 1959, 367; (*b*) Harris and Mitchell, *J.*, 1960, 1905.

[11] Howlett, *J.*, 1960, 1055, and personal communication.

[12] Guy, *J. Chim. phys.*, 1949, **46**, 469.

[13] Mislow, Hyden, and Schaefer, *J. Amer. Chem. Soc.*, 1962, **84**, 1449.

[14] Adrian, *J. Chem. Phys.*, 1958, **28**, 608.

[15] Cooke and Harris, *J.*, 1963, 2365.

[16] Harris and Cheung King Ling, *Chem. and Ind.*, 1962, 1378.

soluble in it to a workable concentration. In spite of attempts to limit structural variation so as to isolate a single factor, there is at least one unwanted extra variation, that of different degrees of interaction of the solvent with the solute, on account of the different nature of the 4,4'-groups; we see no way of eliminating this factor at present.

Optical activity was introduced by optical activation of 2,2'-di-iodobiphenyl-4,4'-dicarboxylic acid or of 2,2'-di-iodobenzidine; replacement or modification of the carboxyl- or amino-groups was then carried out in such a way as to retain sufficient optical activity for measurement of velocity constants for racemisation. Discussion of the synthetic problems is given later.

The results of racemisation experiments are summarised in Table 1.

TABLE 1.

Racemisation of 4,4'-disubstituted 2,2'-di-iodobiphenyls.*

| No. | 4,4'-substituents | Solvent | $t_{\frac{1}{2}}$ † (min.) at 25° | $\Delta F^{\ddagger}$ (kcal. mole$^{-1}$) at 25° | $\Delta H^{\ddagger}$ (kcal. mole$^{-1}$) | $\Delta S^{\ddagger}$ (e.u.) at 25° | $E_{rac}$ (kcal. mole$^{-1}$) | $\log_{10} A$ (sec.$^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| 1 | $-CO_2Me$ | DMF § | 104 | 22·9 | 21·7(5) | −3·9 | 22·3(5) | 12·4 |
| 2 | $-CO_2H$ | ,, | 104 | 22·9 | 21·0(5) | −6·1 | 21·6(5) | 11·9 |
| 3 | −H | ,, | 95 | 22·8 | 20·4 | −8·0(5) | 21 | 11·5 |
| 4 | −NH·COMe | ,, | 14·5 | 21·7 | 20·0 | −5·7 | 20·6 | 12·0 |
| 5 | $-NH_2$ | ,, | 5·3 | 21·1 | 19·3 | −6·0(5) | 19·9 | 11·9 |
| 6 | $-CO_2H$ | EtOH | 85 | 22·7 | 20·7 | −6·9 | 21·3 | 11·7 |
| 7 | $-CO_2^-$ | 0·1N aq. NaOH | 151 | 23·1 | 20·9 | −7·4 | 21·5 | 11·6 |
| 8 | $-NH_3^+$ | 0·5N aq. alc. HCl | 93 | 22·8 | 21·5 | −4·1 | 22·2 | 12·3(5) |
| | | Racemisation of 4,4'-disubstituted 2,2'-dibromobiphenyl. | | | | | | |
| 9 | $-CO_2H$ | EtOH | | 19·9 | 18·5 | −4·9 | 19 | 12·1 |

* Arrhenius parameters are given together with transition-state theory functions; both forms of expression are widely used in discussing optical stability, and each figure has its own particular usefulness when attempting to assign causes to variation in optical stability. † The half-lives at 25° were not measured directly at exactly this temperature, but were obtained by reading ln *k* (25°) from the graph of ln *k* against $1/T$ in each case. This explains any small apparent discrepancies between the half-lives in Table 1 and individual determinations given in the Experimental section. § DMF, *NN*-dimethylformamide.

The values of the free energy of racemisation, $\Delta F^{\ddagger}$, in dimethylformamide (Nos. 1—5) are very close together; the reality of the differences is most easily appreciated by considering the half-lives at 25°. The figures for $\Delta H^{\ddagger}$ (and $E_{rac}$) lie in the same numerical order as those for $\Delta F^{\ddagger}$; in other words, enthalpy (or activation energy) differences are primarily responsible for the differences in stability, with small modifications from $\Delta S^{\ddagger}$, the entropy factor.

It has been suggested that, for the 1,1'-binaphthyl series,[15,16] the experimentally determined activation energy for racemisation, $E_{rac}$, is equal to $E_{ster} - E_r - E_{gs}$, where $E_{ster}$ is the energy due to strain and compression in the transition state, $E_{gs}$ is that in the ground state, and $E_r$ is the gain in resonance energy in the transition state; in the compounds which contain *peri*-substituents, the ground-state energy is considerable and lowers significantly the energy barrier to racemisation, $E_{rac}$. Also, as a result of out-of-plane deformations, the obstacles on either side of the pivot bond can be passed one at a time instead of simultaneously.

With regard to the ground state for 2,2'-di-iodobiphenyl, the conclusion from studies of electron diffraction on the vapour,[17] of dipole moments,[18] and of ultraviolet spectra,[19] assuming always that the two benzene rings are co-axial, is that the planes of the benzene rings lie a little to the *cis*-side of the orthogonal position. Recent *X*-ray crystallographic work on aromatic molecules can add refinement to this picture, in the following way. The

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[17] Bastiansen, *Acta Chem. Scand.*, 1950, **4**, 926.

[18] Littlejohn and Smith, *J.*, 1954, 2552.

[19] Beaven and Hall, *J.*, 1956, 4637.

work of Ferguson and Sim,[20] on *o*-halogenobenzoic acids has shown that the extra-annular bonds in *o*-chlorobenzoic acid and *o*-bromobenzoic acid are both splayed out in the main plane and also slightly displaced from it. The out-of-plane displacement, although small, is larger for C–Br than for C–Cl, and might reasonably be inferred to be even larger for C–I in the same circumstances. Table 2 shows the information together with other relevant data. Out-of-plane distortion of this kind has recently been invoked to explain the otherwise unexpectedly large dissociation constants of *o*-halogenobenzoic and 2-naphthoic acids.[21]

TABLE 2.

| | Cl | Br | I |
|---|---|---|---|
| C–Hal bond length [22] | 1·69 Å | 1·86 Å | 2·02 Å |
| C–Hal out-of-plane displacement in *o*-halogenobenzoic acid | 1·2° | 1·9° | — |
| C–C out-of-plane displacement in *o*-halogenobenzoic acid | 2° | 2° | — |
| Splaying angle between C–Hal and C–C | 67·4° | 68·3° | — |
| Angle of tilt of $CO_2H$ group to plane | 13·7° | 18·3° | — |
| $\Delta H^\ddagger$ (kcal. mole$^{-1}$) for 2,2′-dihalogenobiphenyl-4,4′-dicarboxylic acid in EtOH (exptl.) | — | 18·5 [10] | 20·7 |
| $\Delta H^\ddagger$ (kcal. mole$^{-1}$) for 2,2′-dihalogenobiphenyl (exptl.) | — | — | 20·4 |
| $\Delta H^\ddagger$ (kcal. mole$^{-1}$) for 2,2′-dihalogenobiphenyl (calc.) | —<br>16·6 [11] | 18·2 [3]<br>20·8 [11] | 21·4—23·6 [3]<br>26·4 [11] |

If it is assumed that the bulk effect of a phenyl group *ortho* to a halogen atom on a benzene ring is at least as large as that of a carboxylic acid group, then 2,2′-dichloro-, -dibromo-, and -di-iodobiphenyls must be slightly distorted in the ground state in the same way as these carboxylic acids. The distortion in each phenyl unit can be in either of two asymmetric conformations, *d* or *l*; [16] there are therefore three possible bent conformations of the whole molecule, *dd*, *ll*, or *dl*, each of which can be rotated about the 1,1′-bond and has *R*- and *S*-configurations of minimum energy. At the extreme left of Fig. 1 is shown one of the conformations, the *R*-configuration, in the ground state. In this near-orthogonal position, conjugation between the rings will not be possible; the 1,1′-bond is, presumably, single.

We now consider the transition state. When biphenyl itself is held in a plane, in the crystal, when conjugation across the 1,1′-bond should be a maximum, the length of the 1,1′-bond is generally agreed to be close to the estimated $sp^2$–$sp^2$ single-bond length [23] 1·506,[24] 1·494,[25] and 1·507 Å [26] being recent experimental figures. It is unlikely that the 1,1′-bond in the transition state for 2,2′-di-iodobiphenyl would be shorter than this, and unlikely, therefore, that there is much, if any, shortening of the 1,1′-bond when the molecule passes from the ground state to the transition state. It seems reasonable to suggest that magnification of the tiny distortions of the ground state, together with rotation about the 1,1′-bond, leads to the possible transition and intermediate states. There are three possible intermediate states, *dd*, *ll*, and *dl*, for configurational inversion $R \rightleftharpoons S$ by the *trans*-route (2-I passing 2′H and 2′I passing 2-H), which is more probable than the *cis*-route; whilst in the *dd* or *ll* conformer both barriers to rotation have to be passed simultaneously, in the *dl* conformer their points of *maximum* interference can be passed one at a time, making this energetically the easiest path. The sequence of diagrams in Fig. 1 represents an exaggerated picture of this process, and the accompanying energy changes, neglecting $E_r$, are represented schematically in Fig. 2.

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[20] Ferguson and Sim, *Acta Cryst.*, 1961, **14**, 1262; *ibid.*, 1962, **15**, 346; Ferguson and Monteath Robertson, *Adv. Phys. Org. Chem.*, 1963, **1**, 203.

[21] Hoop and Tedder, *J.*, 1963, 4853, 4857.

[22] " Tables of Interatomic Distances and Configurations in Molecules and Ions," ed. Sutton, *Chem. Soc. Spec. Publn.*, No. 11, 1958.

[23] Summarised by Streitwieser, ref. 8, p. 165.

[24] Hargreaves and Rizvi, *Acta Cryst.*, 1962, **15**, 365.

[25] G. B. Robertson, *Nature*, 1961, **191**, 593.

[26] Trotter, *Acta Cryst.*, 1961, **14**, 1135.

This mechanism would be assisted, and the racemisation accelerated, by factors which facilitate bond-bending at the 1- and 1'-positions. With regard to the effect on $\Delta F^{\ddagger}$ of the 4,4'-substituents (Table 1) it is apparent that the order in which they increase the racemisation velocity, $-NH_2 > -NHCOMe > -H > -CO_2H \simeq -CO_2Me$, parallels their electron-releasing power as judged by their influence in electrophilic aromatic substitution.[27] The groups $-NH_2$ and $-NH{\cdot}COMe$ accelerate the process appreciably; $-CO_2H$ and $-CO_2Me$ slow it down a little. Over the range $-NH_2$ to $-CO_2Me$, $\Delta H^{\ddagger}$ varies by 2·45 kcal. mole$^{-1}$, a substantial fraction of the total energy barrier.

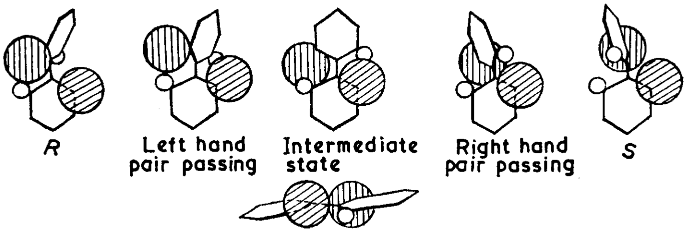

FIG. 1. A suggested model for configurational inversion of 2,2'-dihalogenobiphenyls.

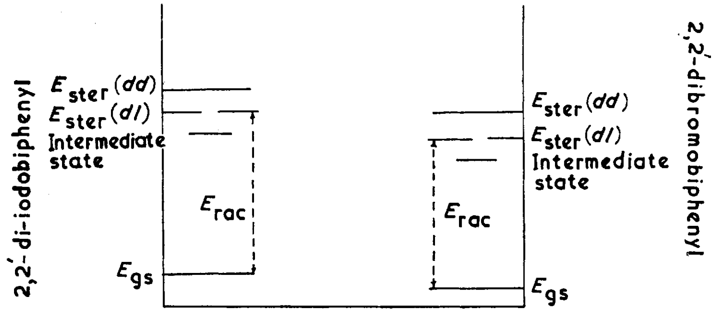

FIG. 2. The energy changes (neglecting $E_r$) accompanying the configurational inversion of 2,2'-dihalogenobiphenyls, depicted in Fig. 1 where the halogen is bromine or iodine.

Electron-release by the $-NH_2$ group might conceivably lower $E_{rac}$ in one or both of the following ways. Conjugation of the type shown in (I) would lower $E_{rac}$ by increasing the numerical value of $E_r$. Ultraviolet-spectroscopic studies[28] of biphenyls carrying no 2,2'-substituents have shown that all 4,4'-substituents, irrespective of their nature, increase conjugation between the rings to some extent. This in itself could not, then, explain the oppositely directed influences of 4,4'-diamino- and 4,4'-dicarboxy-groups. The ultraviolet spectra of 2,2'-dihalogenobiphenyls, studied by Beaven and Hall,[19] show a conjugation band diminishing in intensity through the difluoro-, dichloro-, and dibromo-compounds, being absent in the di-iodo-compounds where there is no evidence for conjugation at all. It is doubtful whether this evidence is relevant to a study of the transition state. If the 1,1'-bond in 2,2'-di-iodobiphenyl is even longer than in biphenyl itself, and the central region is distorted, conjugation across the 1,1'-bond is probably restricted and is distinctly less than that operative in the transition state in biphenyl itself.

The other kind of electron-releasing effect allows the participation of canonical structures (II) or (III) (according to the conformation of the molecule); these would increase the $sp^3$ character of the hybridisation at C-1 and C-1', thus releasing strain in the transition state by permitting the magnification of distortions already present in the ground state.

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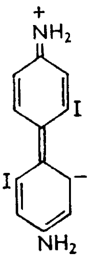
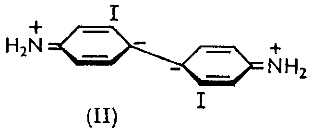
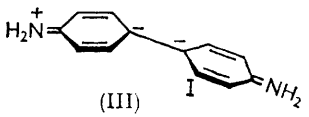
[27] de la Mare and Ridd, " Aromatic Substitution," Butterworths, London, 1959, ch. 10.

[28] Williamson and Rodebush, *J. Amer. Chem. Soc.*, 1941, **63**, 3018.

Electron-withdrawing groups in the 4,4′-positions would oppose this tendency. Although conjugation of the type shown in (I) cannot be dismissed, the experimental evidence is compatible with a bending-mechanism, as Baddeley suggested,[4] facilitated by electron-release. The postulate is supported by experimental evidence from the 1,1′-binaphthyl series, where electron-attracting groups in non-blocking positions in the naphthalene nuclei have a decelerating effect,[15,16] in comparison with 1,1′-binaphthyl itself, while the electron-releasing amino-group accelerates racemisation.[29]


(I)


(II)


(III)

Participation by the solvent, to any great extent, in the transition state for these racemisations is not evident, although it may have some small effect. Thus, changing the solvent from *NN*-dimethylformamide to ethanol in the racemisation of the 4,4′-acid (Table 1) makes very little difference to $\Delta F^{\ddagger}$; $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ undergo small changes. The likelihood of *NN*-dimethylformamide associating with aromatic $-CO_2H$ or $-NH_2$ groups at room temperature is very small; [30] it cannot be a proton donor, therefore association at the 1,1′-positions, already crowded, seems improbable. When optically active 4,4′-di-amino-2,2′-iodobiphenyl is dissolved in 0·5N-hydrochloric acid [Table 1, (8)], it racemises more slowly than in *NN*-dimethylformamide; if protons participate under these conditions to assist bending of the 1,1′-bond, their accelerating effect must be smaller than the decelerating effect due to electron-withdrawal by $-NH_3^+$.

The difference between the experimental $E_{rac}$ values for comparable 2,2′-dibromo- and 2,2′-di-iodo-compounds, 2·6 kcal. mole$^{-1}$, is small. This suggests that there may be a further easing factor in the iodo-racemisations, which diminishes the gap between $E_{ster}$ and $E_{gs}$ relatively more than in the bromo-compounds; this could be the greater deformability of the iodine atoms themselves under the strong pressures in the transition state.

We have been no more successful than previous workers,[9] in spite of many attempts, in demonstrating optical activity in 2,2′-dibromobenzidine. The drop in $\Delta F^{\ddagger}$ in the di-iodo-series when 4,4′-dicarboxy-groups are replaced by amino-groups is $22{\cdot}9 - 21{\cdot}1 = 1{\cdot}8$ kcal. mole$^{-1}$. If a similar drop took place in the dibromo-series, the dibromobenzidine would racemise with a free energy of activation of $19{\cdot}9 - 1{\cdot}8 = 18{\cdot}1$ kcal. mole$^{-1}$. A recent compilation [31] showed a $\Delta F^{\ddagger}$ value of 19·7 kcal. mole$^{-1}$ as the lowest so far observed in racemisation. Our negative result, then, lends some support to the theory of acceleration by amino-groups.

The $-CO_2H$ and $-CO_2Me$ groups, electron-attracting, exert only a very small effect on $\Delta H^{\ddagger}$; it would seem that the same may be true for the nitro-group [32] in these circumstances.

Apart from 2,2′-di-iodosubstituted biphenyls, the Arrhenius parameters for racemisation are known for only a few 2,2′-disubstituted compounds; they are compared with those for 2,2′-di-iodobiphenyl in Table 3. The most effective steric barriers appear to be $-CMe_3$ and $-NMe_3^+$. Two $-CMe_3$ groups, in the 2- and 2′-positions, confer such stability that the compounds have shown no tendency to racemise at all.[33] The $-CF_3$ group lies between

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[29] Theilacker and Hopp, *Ber.*, 1959, **92**, 2293.
[30] Becker and Davidson, *J. Amer. Chem. Soc.*, 1963, **85**, 159.
[31] Hall and Harris, *J.*, 1960, 490.
[32] Brooks, Harris, and Howlett, *J.*, 1957, 1934.
[33] Lesslie and Mayer, *J.*, 1962, 1401.

TABLE 3.

Racemisation of 2,2′-disubstituted biphenyls in solution.

| Substituent | | | | | $E$ | $\log_{10} A$ |
|---|---|---|---|---|---|---|
| 2 | 2′ | 4 | 4′ | Solvent | (kcal. mole$^{-1}$) | (sec.$^{-1}$) |
| I | I [a] | H | H | DMF [g] | 20·9 | 11·4 |
| I | I [a] | $NH_2$ | $NH_2$ | DMF | 19·9 | 11·9 |
| Br | Br [b] | $CO_2H$ | $CO_2H$ | Ethanol | 19 | 12·1 |
| $CF_3$ | $CF_3$ [c] | $NH_2$ | $NH_2$ | Ethanol | 19·5 | 9·9 |
| $CMe_3$ | $CO_2H$ [d] | H | H | Ethanol | 24 | 12·2 |
| $CMe_3$ | $NO_2$ [e] | H | $CO_2H$ | Toluene | 25·4 | 12·9 |
| $NMe_2$ | $NMe_3^+$ | H | H | Water | 27·6 | 12·2 |

[a] Present work. [b] Ref. 9. [c] Hall and Harris, *Proc. Chem. Soc.*, 1959, 396. [d] Lesslie and Mayer, *J.*, 1961, 611. [e] Ref. 33. Shaw and Turner, *J.*, 1933, 135; refs. 7 and 31. [g] DMF, *NN*-dimethylformamide.

Br and I, but the possibility of its " cog-wheeling " past the 6- and 6′-hydrogen atoms cannot be dismissed: this group, being strongly electron-attracting, would operate against the 4,4′-amino-groups in promoting bond-bending.

*Synthesis of Optically Active Materials.*—(±)-2,2′-*Di-iodobiphenyl*-4,4′-*dicarboxylic acid* was prepared by the method previously employed,[34,35] but with substantial modifications. Methyl instead of ethyl esters were used throughout; Raney nickel with hydrazine hydrate [36] proved to be a uniformly more satisfactory means of reducing dimethyl 2,2′-dinitrobiphenyl-4,4′-dicarboxylate than catalytic hydrogenation, which often stopped at the cinnoline stage. Attempts to make the 2,2′-di-iodo-acid by direct iodination of diethyl biphenyl-4,4′-dicarboxylate, which we were prompted to try since direct bromination can be effected,[10] gave poor results, the best being a small yield of impure mono-iodo-product when the conditions described by Tronov and Novikov [37] were used, so this line of approach was abandoned. The optically active acid was obtained through the brucine salt; treatment with diazomethane gave the optically active methyl ester.

(±)-2,2′-*Di-iodobenzidine* was made by two methods, the Curtius reaction of the azide of 2,2′-di-iodobiphenyl-4,4′-dicarboxylic acid and the benzidine rearrangement of 3,3′-di-iodohydrazobenzene; the first process, despite its many stages, proved to be the more satisfactory. The optically active bases were prepared through their hydrogen (+)-tartrates, which crystallised with a wide variety of specific rotations; in general, slower crystallisation gave a hydrogen (+)-tartrate of higher rotation. We have no means of assessing the degree of optical purity of specimens of (+)-base and (—)-base obtained from the tartrates.

Deamination by the diazo-process, using hypophosphorous acid, gave 2,2′-di-iodobiphenyl in the optically active state; the preparation and the purification were carried out as rapidly and at as low a temperature as possible. It was less wasteful of optical activity to use the optically active hydrogen (+)-tartrate, in hydrochloric acid, directly for the diazotisation, than to separate the (+)- or the (—)-base first. All the specimens of 2,2′-di-iodobiphenyl (from 13 deaminations) showed optical activity; the infrared spectrum of the optically active material was identical with that of a specimen of the racemic compound obtained from a different source.*

## EXPERIMENTAL

*Polarimetric Work.*—All polarimetric readings were taken by use of the mercury green line, $\lambda = 5461$ Å, with a polarimeter specially designed (Bellingham and Stanley) on a heavy base

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* The authors thank Dr. J. W. Smith, Dr. D. M. Hall, and Miss Prakobsantisukh for specimens of this compound.

[34] Reverdin, *Ber.*, 1897, **30**, 3002.

[35] Searle and Adams, *J. Amer. Chem. Soc.*, 1933, **55**, 1649.

[36] Balcom and Furst, *J. Amer. Chem. Soc.*, 1953, **75**, 4334; Moore and Furst, *J. Org. Chem.*, 1958, **23**, 1504; *Org. Synth.*, Coll. Vol. III, 181.

[37] Tronov and Novikov, *Tomsk Polytech. Zhav Obshchei Khim.*, 1953, **23**, 1022 (*Chem. Abs.*, 1954, 7483).

for use with a variety of thermostatic apparatus. All measurements were made at a controlled temperature: those above 20°, by using a 2-dm., jacketed, centre-filling tube with fused end-plates (Hilger), a Braun Circotherm pump circulating hot water, thermostatically controlled, from a large Dewar flask; those below 20°, by using a low-temperature 2-dm. tube [10b] and a Colora KT-40 thermostat fitted with a circulating pump delivering a fast stream of the coolant liquid, methanol. All racemisations followed the unimolecular law without deviation; they were followed to zero rotation, and the racemised substance was shown to be chemically identical with the original optically active material. The energy of activation, $E_{\text{rac}}$, was obtained from the rate constants for racemisation, both by least-squares calculation and by the graphical method. $\Delta F^‡$, $\Delta H^‡$, and $\Delta S^‡$ were calculated according to the procedure previously summarised.[31]

*Methyl* 4-*Iodo*-3-*nitrobenzoate*.—Methyl 4-iodobenzoate (58 g.) was dissolved in concentrated sulphuric acid (75 c.c.) and a mixture of concentrated nitric acid (30 c.c.) and concentrated sulphuric acid (30 c.c.) added gradually with stirring, keeping the temperature below 6°. The first drop of nitrating mixture caused the solution to turn black; it became more viscous until 1/3 of the nitrating mixture had been added, further addition then being accompanied by decrease in viscosity and change of colour to reddish brown. After being stirred for 30 min. and standing for 2 hr. in ice–water, during which time a yellow precipitate began to appear, the mixture was poured on to crushed ice. Crystallisation of the yellow solid from methanol gave the iodo-nitro-ester (42 g., 62%), m. p. 104—106°. Reverdin [34] obtained such an ester, yellow plates, m. p. 103·5°, but did not specify the position of the nitro-group: it is now clear that this is the 3-position (see below). On standing, the methanolic mother-liquor deposited a by-product, which gave pale yellow needles, m. p. 182° (decomp.) from methanol (Found: C, 33·3; H, 2·1; N, 2·4; I, 43·3%). A similar unidentified by-product (colourless) was obtained on nitration of ethyl 4-iodobenzoate, and had m. p. 146—148° (decomp.) (Found: C, 35·7; H, 2·8; N, 2·8; I, 41·9%).

*Dimethyl* 2,2′-*Dinitrobiphenyl*-4,4′-*dicarboxylate*.—Methyl 4-iodo-3-nitrobenzoate (50 g.) was heated to 170° and copper bronze (40 g.) added, while stirring, at such a rate as to keep the internal temperature between 180 and 195° (bath temperature, 165—175°). After heating to 190° for 15 min., extraction with chloroform and crystallisation from aqueous acetone gave dimethyl 2,2′-dinitrobiphenyl-4,4′-dicarboxylate (23 g.), m. p. 159—161°.

*Dimethyl* 2,2′-*Diaminobiphenyl*-4,4′-*dicarboxylate*.—The above dinitro-ester (18 g.) was reduced, by using Raney nickel and hydrazine hydrate (100%, 65 c.c.),[36] to give a solid (12·5 g.), m. p. 174—176°, which consisted of two crystalline forms, long bright yellow *needles* and pale yellow *rhombohedra*; their infrared spectra in Nujol mulls showed small differences, but after the needle form was heated above its melting point and cooled, its infrared spectrum and its appearance were identical with those of the other form (Found: C, 64·1; H, 5·5; N, 9·4. $C_{16}H_{16}N_2O_4$ requires C, 64·0; H, 5·4; N, 9·3%). (Diethyl 2,2′-diaminobiphenyl-4,4′-dicarboxylate was similarly prepared from its corresponding dinitro-ester; it crystallised in plates, m. p. 112—115°, and in needles, m. p. 99—100°. The lower-melting form solidified above its melting point to give the higher-melting form, when its infrared spectrum, previously slightly different, became identical with that of the higher-melting form).

(±)-*Dimethyl* 2,2′-*di-iodobiphenyl*-4,4′-*dicarboxylate*.—Double diazotisation of the diamino-compound (15 g.), followed by reaction with sodium iodide, gave dimethyl 2,2′-di-iodobiphenyl-4,4′-dicarboxylate (7·7 g.), m. p. 152·5—154·5°, and 4,4′-di(methoxycarbonyl)biphenylene-iodonium iodide (8·5 g.), m. p. 220—224° (decomp.), separable by Soxhlet extraction and crystallisation from ethanol; the iodonium iodide (25 g.), on thermal rearrangement, gave *dimethyl* 2,2′-*di-iodobiphenyl*-4,4′-*dicarboxylate* (13·3 g. after crystallisation) (Found: C, 36·5; H, 2·5; O, 12·3; I, 48·5. $C_{16}H_{12}I_2O_4$ requires C, 36·8; H, 2·3; O, 12·3; I, 48·6%). Hydrolysis of this ester with 10% alcoholic potash gave (±)-2,2′-di-iodobiphenyl-4,4′-dicarboxylic acid [35] which crystallised from methanol in microcrystalline needles changing to rhombohedra above 250° and melting at 324—326°.

2(?)-*Iodobiphenyl*-4,4′-*dicarboxylic Acid*.—Diethyl biphenyl-4,4′-dicarboxylate [35] (30 g.), when treated with iodine and nitric acid,[37] gave the *monoiodo-diester* (1 g.), m. p. 94—96° (Found: C, 50·8; H, 3·9; I, 27·7. $C_{18}H_{17}O_4I$ requires C, 51·0; H, 4·0; I, 29·9%), and the *monoiodo-diacid* (2·8 g.), m. p. 334—337° (Found: C, 46·3; H, 2·8; I, 33·7. $C_{14}H_9O_4I$ requires C, 48·8; H, 2·5; I, 34·5%).

(±)-2,2′-*Di-iodobenzidine*.—(*a*) 2,2′-di-iodobiphenyl-4,4′-di-carboxylic acid (10 g.), heated under reflux on a steam-bath with thionyl chloride (30 c.c.) for 5 hr. gave the di(acid chloride)

(10·6 g.) m. p. 116—118° (from acetone). Activated sodium azide[38] (3 g.), in ice-cold water, was added to this chloride, dissolved in acetone (250 c.c.). After 15 min., water (500 c.c.) was gradually added; the solid azide separated and was dried in a vacuum (10·5 g.), m. p. 114° (decomp.). The total quantity of the azide was decomposed by heating in dry toluene (15 c.c.) at 110—110°; hot 50% aqueous sodium hydroxide (40 c.c.) was then added, with stirring, and the mixture boiled for 15 min. The solid from the aqueous layer was combined with that obtained by evaporation of the toluene layer, and purified by cystallisation of the hydrochloride, giving (±)-2,2′-*di-iodobenzidine* (8·1 g.), m. p. 168—170° (from aqueous methanol) (Found: C, 33·4; H, 2·4; N, 6·3; I, 57·8. $C_{12}H_{10}N_2I_2$ requires C, 33·1; H, 2·3; N, 6·4; I, 58·2%).

(*b*) 3,3′-Di-iodoazoxybenzene (30 g.) in ether (750 c.c.) was reduced with zinc and acetic acid, and the ethereal solution was evaporated to 100 c.c. under nitrogen. This solution was then added dropwise to cold, concentrated hydrochloric acid (250 c.c.) under nitrogen, with stirring. After 1 hr. the precipitate was filtered off, and extrated with dilute hydrochloric acid. Addition of ammonia gave 2,2′-di-iodobenzidine (7·1 g.), m. p. 168—170°.

From the concentrated hydrochloric acid solution, further crops separated; from one of these a *base* isomeric with 2,2′-di-iodobenzidine was isolated, m. p. 196—198° (Found: C, 33·1; H, 2·4; N, 6·4; I, 58·0. $C_{12}H_{10}N_2I_2$ requires C, 33·1; H, 2·3; N, 6·4; I, 58·2%). Deamination gave 2,2′-di-iodobiphenyl, m. p. and mixed m. p., 108°; the base is therefore either 2,2′-diamino or 2,4′-diamino-6,6′-di-iodobiphenyl.

2,2′-Dibromobenzidine,[9] m. p. 151—152·5°, was prepared in 36·6% yield by the benzidine rearrangement of 3,3′-dibromohydrazobenzene.[39] Attempted optical activation as the mono-(+)-camphor-10-sulphonate[9] or di(+)-α-bromocamphor-π-sulphonate[9] failed, as did also attempts with the dihydrogen (+)-tartrate [m. p. 163—164°, $[\alpha]_{5461}^{25}$ +0·8° (in ethanol)] and the di-mandelate.

Heating of 2,2′-dibromobenzidine (5 g.) for 1 hr. under reflux with trimethylphosphate (50 c.c.), and then for a further 2 hr. with 30% sodium hydroxide, gave 2,2′-*dibromo*-NNN′N′-*tetramethylbenzidine* (3·3 g.), m. p. 184° (from ethanol) (Found: C, 48·3; H, 4·4; N, 7·1; Br, 40·6. $C_{16}H_{18}N_2Br_2$ requires C, 48·3; H, 4·6; N, 7·0; Br, 40·1%).

This compound, on heating with methyl iodide at 70—80° for 6 hr., gave the *dimethiodide*, m. p. 200—213° (decomp.), depending upon the rate of heating (Found: C, 37·7; H, 3·6; N, 5·1; Hal, 54·1. $C_{18}H_{24}N_2Br_2I_2$ requires C, 37·8; H, 3·9; N, 5·2; Hal, 53·1%). Treatment with silver (+)-α-bromo-camphor-π-sulphonate gave a salt melting first at 138°, resolidifying, and remelting at 191°; it showed no mutarotation in solution.

*Optically Active Compounds.*—(−)-2,2′-*Di-iodobiphenyl*-4,4′-*dicarboxylic acid*. The (±)-acid (6 g.) and anhydrous brucine (9·6 g., 2·4 mol.) were dissolved in ethanol (S.V.R.) (500 c.c.) and left to stand at room temperature for several days. Asymmetric transformation gave crystalline dibrucine(−)-acid (15·4 g.), m. p. 180—215°, mutarotating in chloroform containing 2½% ethanol, $k^{26\cdot7} = 0\cdot014$ min.$^{-1}$, $[\alpha]^{26\cdot7}$ −33° (by extrapolation to zero time). The salt (3·35 g.) was stirred in 98% formic acid for 2 min. and poured, with stirring, into a mixture of ice and concentrated hydrochloric acid; the precipitated acid after having been washed free from brucine and dried in a vacuum, weighed 1·2 g., m. p. 333—336° (Found: C, 33·7; H, 1·7; I, 51·4. $C_{14}H_8O_2I_2$ requires C, 34·0; H, 1·6; I, 51·4%), $[\alpha]^{25}$ −61 to −67° (*c* 0·823, ethanol). Racemisation rates were observed in *NN*-dimethylformamide, in ethanol, and in 0·1N-aqueous sodium hydroxide, as shown below. The Arrhenius parameters and transition-state theory functions calculated from these data are given in Table 1.

| *NN*-Dimethylformamide | | | Ethanol | | | 0·1N-aqueous NaOH | | |
|---|---|---|---|---|---|---|---|---|
| Temp. | $10^4 k$ (sec.$^{-1}$) | $t_{\frac{1}{2}}$ (min.) | Temp. | $10^4 k$ (sec.$^{-1}$) | $t_{\frac{1}{2}}$ (min.) | Temp. | $10^4 k$ (sec.$^{-1}$) | $t_{\frac{1}{2}}$ (min.) |
| 36·2° | 4·08 | 28·3 | 25·2° | 1·38 | 83·6 | 30·5° | 1·44 | 81·2 |
| 40·0 | 6·48 | 17·8 | 30·8 | 2·66 | 43·4 | 35·1 | 2·54 | 45·4 |
| 44·3 | 10·00 | 11·6 | 35·9 | 4·90 | 23·6 | 40·1 | 4·45 | 25·9 |
| 48·2 | 15·35 | 7·5 | 40·1 | 7·84 | 14·7 | 46·2 | 8·47 | 13·6 |
| 52·2 | 23·2 | 5·0 | 45·3 | 13·4 | 8·6 | 50·2 | 12·9 | 9·0 |
| 56·2 | 35·6 | 3·2 | 50·4 | 22·6 | 5·1 | 55·2 | 22·0 | 5·2 |
| | | | 56·0 | 39·6 | 2·9 | 61·0 | 37·4 | 3·1 |

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[38] Hall, Mahboob, and Turner, *J.*, 1950, 1844; Nelles, *Ber.*, 1932, **65**, 1345.

[39] Khalifa, *J.*, 1960, 1854.

(−)-*Dimethyl* 2,2′-*di-iodobiphenyl*-4,4′-*dicarboxylate.* The powdered (−)-acid (1 g.) was added gradually, while stirring, to an ethereal solution of diazomethane (0·2 g., 2·4 mol. in 10 c.c.) cooled to −10°. A first crop of crystalline (−)-ester (0·55 g.) separated after 15 min., m. p. 152—154°, $[\alpha]^{20}$ −1·4°; a second crop was obtained by cold evaporation of the filtrate, 0·4 g., m. p. 151—154°, $[\alpha]^{20°}$ −19·3° (Found: C, 36·5; H, 2·5; O, 12·3; I, 48·5. $C_{16}H_{12}O_4I_2$ requires C, 36·8; H, 2·3; O, 12·3; I, 48·6%). Racemisation rates were observed in *NN*-dimethylformamide, as shown below.

| Temp. | 25·9° | 35·1 | 38·8 | 42·8 | 44·3 | 45·5 |
|---|---|---|---|---|---|---|
| $10^4 k$ (sec.$^{-1}$) | 1·21 | 3·95 | 5·57 | 9·49 | 10·7 | 12·7 |
| $t_{\frac{1}{2}}$ (min.) | 95·7 | 29·3 | 20·7 | 12·2 | 10·8 | 9·1 |

(+)- *and* (−)-2,2′-*Di-iodobenzidine.* These compounds were obtained by second-order asymmetric transformation as the *di-*[*hydrogen* (+)-*tartrate*], m. p. 182° [from ethanol (S.V.R.)] (Found: C, 32·3; H, 3·7; N, 3·2; I, 32·3. $C_{20}H_{22}O_{12}N_2I_2$ requires C, 32·6; H, 3·0; N, 3·8; I, 34·5%). In one experiment, (±)-2,2′-di-iodobenzidine (8·7 g.) and (+)-tartaric acid (6·0 g.; 2 mols) yielded a first crop of (11·7 g.), m. p. 182° (decomp.), and a second crop of (3·0 g.), m. p. 182° (decomp.). Ten such preparations of di-hydrogen (+)-tartrate were carried out; sometimes the salt of the (+)-base and sometimes that of the (−)-base crystallised. A salt having $[\alpha]^{20\cdot5}$ −18·4° in dimethylformamide, ground with aqueous ammonia, gave (−)-*base*, m. p. 167—170°, $[\alpha]^{15\cdot2}$ −14·0°; a salt having $[\alpha]^{22}$ +12·6° gave (+)-*base*, $[\alpha]^{19}$ +16·2° (all specific rotations extrapolated to zero time) (Found: C, 33·4; H, 2·8; N, 6·4; I, 58·0. $C_{12}H_{10}N_2I_2$ requires C, 33·1; H, 2·3; N, 6·4; I, 58·2%). Racemisation rates were observed in *NN*-dimethyformamide and in 0·5N-aqueous alcoholic hydrochloric acid, as shown below.

| *NN*-Dimethylformamide | | | | | | 0·5N-Hydrochloric acid | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Temp. | $10^4 k$ (sec.$^{-1}$) | $t_{\frac{1}{2}}$ (min.) | Temp. | $10^4 k$ (sec.$^{-1}$) | $t_{\frac{1}{2}}$ (min.) | Temp. | $10^4 k$ (sec.$^{-1}$) | $t_{\frac{1}{2}}$ (min.) | Temp. | $10^4 k$ (sec.$^{-1}$) | $t_{\frac{1}{2}}$ (min.) |
| −0·3° | 0·99 | 116·3 | 15·4 | 6·96 | 16·6 | 26·6° | 1·73 | 66·8 | 42·4 | 10·77 | 10·7 |
| 4·7 | 1·87 | 61·8 | 20·2 | 13·2 | 8·8 | 30·8 | 2·84 | 40·7 | 45·3 | 15·6 | 7·4 |
| 7·4 | 2·69 | 42·9 | 24·9 | 21·6 | 5·4 | 34·9 | 4·78 | 24·2 | 50·2 | 25·3 | 4·6 |
| 11·0 | 3·90 | 29·6 | | | | 38·2 | 6·72 | 17·2 | | | |

(+)-4,4′-*Diacetamido*-2,2′-*di-iodobiphenyl.* This compound was prepared by adding (+)-2,2′-di-iodobenzidine (4·2 g., $[\alpha]^{7\cdot4}$ +69·2°), dissolved in *NN*-dimethylformamide, to glacial acetic acid (28 c.c.) and acetic anhydride (56 c.c.) cooled to −20°. The reaction mixture gradually became cloudy and solid separated (together with some crystalline acetic acid). Addition to ice (600 c.c.) and hydrochloric acid gave the (+)-*diacetamido derivative* (5·0 g.), m. p. (after dehydration in a vacuum) 292—295°, $[\alpha]^{32}$ +25·5° (Found: C, 36·9; H, 2·65; N, 5·2; I, 48·2; O, 6·3. $C_{16}H_{14}O_2N_2I_2$ requires C, 37·1; H, 2·7; N, 5·4; I, 48·2; O, 6·1%). Racemisation rates were observed in *NN*-dimethylformamide solution, as shown below.

| Temp. | 12·2° | 16·05 | 19·8 | 24·0 | 27·9 | 32·1 | 36·0 |
|---|---|---|---|---|---|---|---|
| $10^4 k$ (sec.$^{-1}$) | 1·68 | 2·76 | 4·18 | 7·26 | 10·9 | 18·2 | 27·1 |
| $t_{\frac{1}{2}}$ (min.) | 68·6 | 41·9 | 27·6 | 15·9 | 10·6 | 6·3 | 4·3 |

(+)- *and* (−)-2,2′-*Di-iodobiphenyl.*—(−)-2,2′-Di-iodobenzidine di-hydrogen (+)-tartrate (1·7 g.) was cooled to −25° and concentrated hydrochloric acid (2·5 c.c.) added with stirring; to this paste, concentrated aqueous sodium nitrite (0·9 g.) was gradually added, and the resulting solution was poured into cold (−25°) hypophosphorous acid (30 c.c.). Freshly prepared cuprous oxide was then gradually added; after an interval varying between 10 and 30 min., vigorous frothing occurred with separation of a solid which was filtered off and washed with water, cold 10% aqueous sodium hydroxide, and water, and then dried (0·85 g.), dissolved in cold benzene (15 c.c.), and run down a short column of charcoal under gentle suction. Portions (30 c.c.) were diluted with light petroleum (b. p. 40—60°) and evaporated in a cool air stream; the total time for purification was 30—40 min. and gave (−)-2,2′-*di-iodobiphenyl* (0·56 g.), m. p. 102—106° (Found: C, 35·4; H, 1·9; I, 62·8. $C_{12}H_8I_2$ requires C, 35·5; H, 2·0; I, 62·5%). This experiment was repeated 13 times using different specimens of optically active (+)-tartrate. The recovered di-iodobiphenyl always showed optical activity, although sometimes the rotation was small. The value of [α] (by extrapolation to zero time) varied from −2·5 to −7·9°

and +2·8 to +15·1°. The five specimens of largest rotation were used to observe the rates of racemisation in *NN*-dimethylformamide, as shown below.

| | | | | | |
|---|---|---|---|---|---|
| Temp. | 25·4° | 25·5 | 26·0 | 35·2 | 42·2 |
| First reading | −0·26 | −0·55 | +0·29 | +0·83 | +0·33 |
| $10^4$ *k* (sec.$^{-1}$) | 1·34 | 1·27 | 1·36 | 3·95 | 8·14 |
| $t_{\frac{1}{2}}$ (min.) | 86·5 | 91 | 84·8 | 29·2 | 14·2 |

Whence $E$ = 20·9 kcal. mole$^{-1}$. If all 13 values of *k* (*i.e.*, including those measured on very small rotations) are used in a mean-square calculation, the value of $E$ is 20·7 kcal. mole$^{-1}$.

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