diquaternary salt and to test the latter for curare activity.

ADDED TO PROOF.—1-(β-Picolyl)-6,7-methylenedioxyisoquinoline was examined for antispasmodic activity by Dr. R. H. Dreisbach of the Department of Pharmacology of Stanford University Medical School. A 2% solution in propylene glycol was diluted with water to give solutions of the desired concentration. The compound relaxes previously untreated rabbit ileum (small intestine) and also antagonizes spasm induced by barium chloride. The concentration required to produce these effects is from two to five times greater than the concentration of papaverine required to produce the same effects. Thus a concentration of 0.002% was somewhat less effective in relaxing untreated intestine than a concentration of 0.001% of papaverine.

Experimental

N-(β-Pyridylacetyl)-homopiperonylamine.—β-Pyridyl methyl ketone was prepared by the procedure of Hurd and Webb[5] and converted to methyl β-pyridylacetate by the Willgerodt reaction using the procedure of Hartmann and Bosshard.[6] The ester was condensed with homopiperonylamine[2] by the procedure reported previously for the α-pyridyl derivative.[2] The product was crystallized from carbon tetrachloride to a constant melting point of 100–100.5°; yield 65%.

Anal.[7] Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67. Found: C, 67.55; H, 5.56.

1-(β-Picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (VI).—The above amide was cyclized by the procedure of Clemo, McIlwain and Morgan.[1] The product was crystallized from cyclohexane to a constant melting point of 117–119° (dec.); yield 89%.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30. Found: C, 72.65; H, 5.23.

The **dihydrochloride** of the base was prepared by adding an alcoholic solution of hydrogen chloride to an ether solution of the base. After crystallization from alcohol-ether, the light yellow crystals decomposed at 204°.

Anal. Calcd. for $C_{16}H_{16}Cl_2N_2O_2$: Cl, 20.92. Found: Cl, 20.82.

1-Nicotinyl-6,7-methylenedioxyisoquinoline (VII).—A modification of the procedure used by Buck, Haworth and Perkin[8] for the preparation of papaveraldine was followed in which the intermediate dihydro derivative was not isolated. A solution of 2.5 g. of 1-(β-picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline in 25 cc. of a 10% solution of potassium hydroxide in methyl alcohol was refluxed on the steam-bath for one hour. The solvent was evaporated by allowing a stream of air to pass over the solution, the solvent being renewed five times during the process. The resulting crystalline mass was filtered and recrystallized from methyl alcohol to give a yellow product weighing 1.4 g. and melting at 176–177°. The mother liquors gave another 0.12 g. making a total yield of 60%. Further recrystallizations did not change the melting point.

Anal. Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.06. Found: C, 69.34, 69.38; H, 3.75, 3.69; N, 9.52.

1-(β-Picolyl)-6,7-methylenedioxyisoquinoline (VIII).—A solution of 0.25 g. of 1-nicotinyl-6,7-methylenedioxyisoquinoline in 2.5 cc. of glacial acetic acid was stirred on the steam-bath while 1.2 g. of zinc powder was added over a period of three hours. The reaction mixture was filtered, the residue washed with hot water, and the zinc precipitated from the combined filtrates by passing in hydrogen sulfide. The filtrate was concentrated on the steam-bath, neutralized with sodium carbonate, an excess of ammonia added, and the mixture extracted with chloroform. After removal of the chloroform the residue was crystallized from petroleum solvent (b. p. 55–85°) to give 0.15 g., m. p. 133–135° (63%). This product resisted further reduction on treating with hydrogen bromide in acetic acid solution and adding zinc dust. Recrystallization did not raise the melting point.

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58. Found: C, 72.43; H, 4.72.

Attempts to prepare this compound directly by the dehydrogenation of 1-(β-picolyl)-3,4-dihydro-6,7-methylenedioxyisoquinoline (VI) with Raney nickel, Raney nickel and nitrobenzene, or by oxidation with nitric acid[9] were unsuccessful.

Absorption Spectra.—All of the absorption spectra were determined on freshly prepared solutions in 95% alcohol that had been distilled from potassium hydroxide. A Beckman Quartz Spectrophotometer, Model DU, was used. It was found that the intensities of the absorption maxima of some solutions decreased fairly rapidly on standing without change in the positions of the maxima.

Summary

1-(β-Picolyl)-6,7-methylenedioxyisoquinoline (VIII), a pyridyl analog of papaverine, has been synthesized.

STANFORD, CALIFORNIA RECEIVED MARCH 8, 1949

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(5) Hurd and Webb, THIS JOURNAL, **49**, 551 (1927).

(6) Hartmann and Bosshard, *Helv. Chim. Acta*, **24**, 28E (1941).

(7) All microanalyses by C. W. Koch, Albany, Calif.

(8) Buck, Haworth and Perkin, *J. Chem. Soc.*, **125**, 2176 (1924).

(9) Rodionov and Yavorskaya, *J. Gen. Chem.* (U. S. S. R.), **11**, 446 (1941); *C. A.*, **35**, 6592 (1941).

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Calculation and Determination of the Buttressing Effect for the Racemization of 2,2′,3,3′-Tetraiodo-5,5′-dicarboxybiphenyl

BY MARTIN RIEGER AND F. H. WESTHEIMER*

I. Introduction

Recently Westheimer and Mayer[1] developed a method for calculating the activation energy for the racemization of optically active biphenyl derivatives. In principle, the energy by which the planar configuration of a particular ortho substituted biphenyl exceeds that of the twisted form is expressed in terms of the force constants for the vibrations of the molecule and the van der Waals potential function for the interaction of the atoms which form the ortho substituents attached to the biphenyl skeleton. The activation energy for the racemization must be the minimum value of the excess energy of the planar form. The method, although approximate, involves no arbitrary parameters; it has been successfully applied[2] in calculating the activation energy for the racemization of 2,2′-dibromo-4,4′-dicarboxybiphenyl.

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* Harvard University Ph.D. 1935.

(1) Westheimer and Mayer, *J. Chem. Phys.*, **14**, 733 (1946).

(2) Westheimer, *ibid.*, **15**, 252 (1947).

In the picture of the racemization process obtained from these calculations, the distortions of the bond angles play a very important role. Thus, racemization of 2,2′-dibromo-4,4′-dicarboxybiphenyl (hereafter called the "dibromo acid") would be impossible were it not for a considerable distortion of the normal C—C—Br bond angles. That such bending occurs, at least to some extent, may be qualitatively inferred from the "buttressing effect" previously observed by Chien and Adams.[3] They found that, as a rule, biphenyls substituted in the 3- and 3′-positions racemize more slowly than similar compounds substituted in the 4- and 4′- or 5- and 5′-positions. This regularity suggests that the substituents in the 3- and 3′-positions buttress the substituents in the 2- and 2′- (ortho) positions, and thus tend to prevent the necessary distortion of bond angles. The effects observed by Adams and his coworkers, although unmistakable, are, in general, not very large. However, on the basis of the quantitative theory[1,2] for the racemization of optically active biphenyl derivatives, it has been possible to select a compound where the buttressing effect should be quite large, and to calculate the magnitude of the predicted effect.

For this purpose, 2,2′-diiodo-5,5′-dicarboxybiphenyl (hereafter called the "diiodo acid") and 2,2′,3,3′-tetraiodo-5,5′-dicarboxybiphenyl (hereafter called the "tetraiodo acid") were synthesized, resolved[4] and their rates of racemization determined. Here (see Figs. 1 and 2) the iodine atoms in the 2- and 2′-positions of the tetraiodo acid are buttressed by the adjacent iodine atoms in the 3- and 3′-positions whereas no such buttressing effect occurs in the diiodo acid. The activation energies for the racemization of both the diiodo and the tetraiodo acid were determined and compared with the calculated values. The calculated results are in reasonable agreement with the experimental findings, and account for the fact that the diiodo acid racemizes more than 30,000 times as fast as the tetraiodo acid. In this paper, the method of calculating the activation energies is presented in part II; the calculated results and the experimental findings are compared in part III; the details of the kinetic determinations are presented in part IV; and the derivation of the needed new equations is outlined in part V (the mathematical appendix).

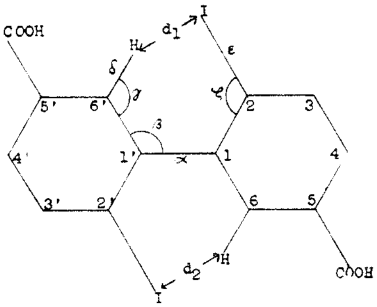

Fig. 1.

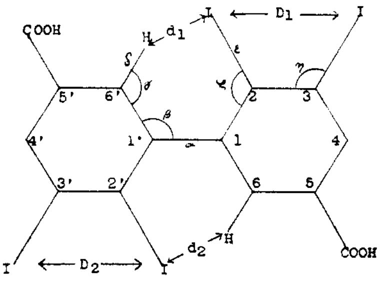

Fig. 2.

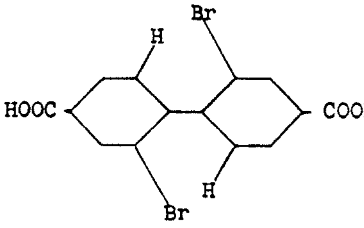

Fig. 3.

II. The Calculation of Activation Energies

The equations needed to calculate the activation energy for the racemization of the diiodo acid are identical with those previously used for that of the dibromo acid; those needed to calculate the energy of activation for the racemization of the tetraiodo acid are derived in part V. The discussion here deals only with the force constants, etc., which enter the computations. In order to discuss the choice of these constants a few definitions are necessary.

The energy, E, by which the planar form of the diiodo acid exceeds the energy of the twisted form is expressed, in accordance with previous practice,[1] by the equation

$$E = {}^1/_2 \sum_i a_i q_i^2 + Ae^{-d_1/\rho} + Ae^{-d_2/\rho} \qquad (1)$$

where the q_i's are the normal coördinates for the vibration in question, and the sum of the exponential terms is an approximation (over the range here of interest) to the van der Waals repulsion between the groups which, in the planar configuration of the diphenyl, interfere with one another; these exponential terms are evaluated below. The distances d_1 and d_2 are illustrated in Fig. 1; they may be approximated by the equations

$$d_1 = d_0 + \sum_i b_i q_i \qquad d_2 = d_0 + \sum b_i' q_i \qquad (2)$$

where d_0 is the distance between the iodine and hydrogen atoms in a rigid, undistorted planar molecule of the diiodo acid, and the constants b_i (or b_i') are factors, calculated from the geom-

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(3) Chien and Adams, THIS JOURNAL, **56**, 1787 (1934).

(4) Rieger and Westheimer, **71**, 28 (1949).

TABLE I

GEOMETRIC FACTORS, B_i, AND FORCE CONSTANTS, a_i, FOR THE DIIODO ACID

Vibration number	b	b'	B	a_i	$B_i^2/a_i \times 10^5$
I	0.861	0.861	0.861	5.5×10^5 dyne/cm.	0.135
II	1.920×10^{-8}	-2.706×10^{-8}	-0.393×10^{-8}	1.13×10^{-11} dyne/cm./radian^2	.273
III	0.530×10^{-8}	0	0.265×10^{-8}	0.86×10^{-11} dyne/cm./radian^2	.165
IV	-0.859	0	-0.430	5.5×10^5 dyne/cm.	.074
V	0.01	0	Neglected	....	...
VI	2.016	0	1.008×10^{-8}	0.93×10^{-11} dyne cm./radian^2	2.192
Benzene ring deformations (for both rings)					0.548

etry of the molecule, which relate the magnitude of each displacement q_1 to the increase in the distance d_1 (or d_2) which accompanies the displacement in question. (For example, an increase of 0.01 radian in the C—C—I bond angle increases d_1 by 0.02016 Å. and d_2 by 0 Å.; the factors b and b' for this vibration are thus 2.016 and 0 Å./radian, respectively.) The constant B_i is defined as $(b_i + b_i')/2$. The problem of calculating the desired activation energy has been reduced[1,2] to the problem of selecting an appropriate set of coördinates for the molecule, estimating the force constant associated with changes in these coördinates, calculating from the geometry of the molecule the factors B_i, and evaluating the van der Waals potentials between the interfering iodine atoms or iodine and hydrogen atoms.

The Coördinates for the Diiodo Acid.—The coördinates here chosen are essentially the same as those previously chosen for the dibromo acid.[2] Vibration I corresponds to the stretching of the interannular bond, α, (see Fig. 1); vibration II to the deformation of the angles, β; vibration III to the deformation of the C—C—H angles, γ; vibration IV to the stretching (contraction) of the C—H bonds, δ; vibration V to the stretching (contraction) of the C—I bonds, ϵ; and vibration VI to the deformations of the C—C—I angles, ζ. The internal deformations of the benzene ring are taken into account by an approximate method. For the dibromo acid,[2] these deformations were computed by using a simplified potential function analogous to the one suggested for benzene by Wilson.[5] Fortunately, these previous calculations showed that the benzene ring is quite rigid, and that its deformations affect the calculated energy of activation only slightly. Here the deformations of the benzene ring were taken into account by assuming that the sum[1] of the terms B_i^2/a_i which refer to ring deformations is the same for the diiodo acid and the tetraiodo acid as it is for the dibromo acid. Since the sum of the terms in question is small, the error introduced by this approximation may be neglected.

The Force Constants for the Diiodo Acid.—The force constants, a_i, for the deformations I-VI cited above are the same as those previously[2] used (for the dibromo acid) except that the force constant for distorting the C—C—I angle, VI, is needed in place of that for distorting the C—C—Br angle. The former of these force constants is estimated by applying reasonable corrections to the force constant for distorting the C—C—I angle in aliphatic compounds, exactly as the latter was previously estimated from the force constant for distorting the C—C—Br angle in aliphatic compounds.[2,6] Admittedly, this method of estimating the force constant for the distortion of the C—C—I bond angle leaves much to be desired. But since no force constants have as yet been calculated from the Raman or infrared spectrum of any aromatic iodide, no more rigorous method is available. It is therefore fortunate that even a large error in the force constant produces only a small error in the calculated activation energy. Furthermore, a part at least of an error in the calculation of activation energies must cancel out when only the difference between two activation energies is considered.

The computed values for the constants B_i, the assumed values for the a_i and the corresponding values of B_i^2/a_i for the vibrations of the diiodo acid are presented in Table I. The value of B_i/a_i for vibrations II–VI have been doubled since there are two of each of these vibrations (one for each ring).

The Coördinates and Force Constants for the Tetraiodo Acid.—The energy, E, by which the planar form of the tetraiodo acid exceeds the energy of a (hypothetical) unstrained form is expressed by the equation

$$E' = {}^1/_2\sum_i a_i q_i^2 + Ae^{-d_1/\rho} + Ae^{-d_2/\rho} + Ge^{-D_1/\rho'} + Ge^{-D_2/\rho'} \quad (3)$$

The first four terms here have the same meaning as in equation (1); the sum of the additional exponential terms in G, D and ρ' is an approximation (over the range here of interest) to the van der Waals repulsion between two iodine atoms attached to adjacent carbon atoms of the benzene ring. The distances D_1 and D_2 are illustrated in Fig. 2; they may be approximated by the equations

$$D_1 = D_0 + \sum_i c_i q_i \qquad D_2 = D_0 + \sum_i c_i' q_i \quad (4)$$

where D_0 is the distance between a pair of iodine

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(5) Wilson, *Phys. Rev.*, **45**, 706 (1934).

(6) Kohlrausch, *Z. physik. Chem.*, **B30**, 305 (1935); Crawford and Brinkley, *J. Chem. Phys.*, **9**, 69 (1941).

atoms in a hypothetical molecule of diiodobenzene of which all the bond angles are 120°. The constants c_i (or c_i') are factors, calculable from the geometry of the molecule, which relate the magnitude of the displacements q_i to the increase (or decrease) in the distance D_1 (or D_2) which accompanies the displacement in question; C_i is defined as $(c_i + c_i')/2$. The only new vibration required by the problem for the tetraiodo acid is the distortion, VII, of the angle η (see Fig. 2). Since this vibration, like vibration VI, refers to the bending of a bond between an iodine atom and a carbon atom of a benzene ring, the force constant a_7 is identical with a_6. The additional data needed are presented in Table II. The values of C_i^2/a_i for vibrations VI and VII have been doubled, since there are two of each of these vibrations (one for each ring).

TABLE II

GEOMETRIC FACTORS, C_i, AND FORCE CONSTANTS, a_i, FOR THE TETRAIODO ACID

Vibration	C_i	a_i, dyne cm. radians²	$C_i^2/a_i \times 10^5$
VI	-0.875×10^{-8}	0.93×10^{-11}	1.646
VII	$.875 \times 10^{-8}$	$.93 \times 10^{-11}$	1.646

Van der Waals Potential Curves.—In order to evaluate the constants A and ρ in the exponential term $Ae^{-d/\rho}$ (of equations 1 and 3) it is necessary to know the van der Waals potential curve for iodine–hydrogen interactions; to evaluate G and ρ' in the exponential term $Ge^{-D/\rho'}$ (of equation 3) it is necessary to know the van der Waals potential curve for iodine–iodine interactions. Complete van der Waals potential curves for a pair of atoms contain one or more terms for attraction as well as terms for repulsion. As Hill[7] has pointed out, it is only over a limited range that a simple exponential term such as $Ae^{-d/\rho}$ is a good approximation to the complete van der Waals potential; it is precisely correct at only one point, namely, the one where the van der Waals energy, U, is equal to the parameter Z later described. In non-mathematical language, the exponential curve must precisely fit the van der Waals curve at the point corresponding to the distance between the ortho substituents in the activated complex. Here the exponential approximation is fitted to the true van der Waals curve by successive approximations. Hill's method,[7] which involves a complete van der Waals expression, is too cumbersome to be employed in the calculations for the tetraiodo acid. Since both the parameter Z and the distance between the interfering ortho substituents in the activated complex depend upon the compound under investigation, the same van der Waals curve may, at different points in the curve, be best fitted by somewhat different exponential approximations.

The complete van der Waals potential curve for the iodine–hydrogen interaction is not known with precision, but may be approximated in several ways; fortunately, the various approximations all lead to very nearly the same potential function. Hill[7] has expressed the van der Waals potential, U, by the equation

$$U = -\mu/d^6 + Pe^{-d/\rho} \tag{5}$$

and has shown how the constants μ, P and ρ may be estimated from the critical constants of the elements. Since the critical constants for iodine are not well known, Hill's method was here applied both in a modified and in unmodified form.

In the first or modified method, use was made of the fact that Hill had previously worked out (in part from racemization data) values for the constants for the chlorine–hydrogen and the bromine–hydrogen interactions. These data were here extrapolated to obtain the appropriate constants for the iodine–hydrogen interaction by assuming that the constants for iodine differ from those of bromine by the same amount that those of bromine differ from those of chlorine. The resulting potential expression, A, is given in Table III. For purposes of convenience, the minimum value of the energy for this (and for all other) potential functions is here set equal to zero. The iodine–hydrogen distance corresponding to this minimum energy for potential A is 3.35 Å., exactly equal to Pauling's[8] independent estimate of the sum of the van der Waals radii for iodine and hydrogen.

The second (unmodified) method used to determine the iodine–hydrogen interactions was to follow Hill exactly, and to select from the literature a best value for the critical temperature for iodine. The potential expression obtained by using 826°K. as the critical temperature[9] is labelled B in Table III.

Finally, the potential curve previously used[2] for the bromine–hydrogen interaction may be shifted so that the minimum on the curve falls at 3.35 Å. (the sum of the van der Waals radii[8] for iodine and hydrogen) instead of 3.15 Å. (the sum of the van der Waals radii for bromine and hydrogen). The potential thus obtained (which resembles the interaction of two neon atoms) is presented as C in Table III.

All three of these potential energy expressions A, B and C, give essentially concordant values for the computed energy of activation for the racemization of the diiodo acid. The value obtained with the potential function A is almost precisely that obtained experimentally, but uncertainties involved in the calculation do not permit a definite choice among the potential functions in question. However, the fact that three reasonable approximations to the iodine–hydrogen interaction all lead to reasonable values of the activation energy strongly supports the theory of the calculation.

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[7] Hill, *J. Chem. Phys.*, **16**, 399 (1948).

[8] L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939.

[9] Rassow, *Z. anorg. Chem.*, **114**, 117 (1920).

TABLE III

VAN DER WAALS POTENTIAL FUNCTIONS FOR IODINE–HYDROGEN INTERACTIONS

Source of function	Approximation fitted at $U = Z$ ergs/molecule $\times 10^{13}$	Designation	Where applied	Potential U, in ergs/molecule
Hill's method (extrapolation)		A		$-0.271 \times 10^{-10}/\mathrm{d}^6 + 90.3 \times 10^{-10}\,\mathrm{e}^{-\mathrm{d}/0.240}$
Approx. to A	2.46	A'	Diiodo acid	$3.72 \times 10^{-8}\,\mathrm{e}^{-\mathrm{d}/0.2032}$
Approx. to A	3.32	A''	Tetraiodo acid	$2.656 \times 10^{-8}\,\mathrm{e}^{-\mathrm{d}/0.2094}$
Hill's method (Critical T)		B		$-0.3572 \times 10^{-10}/\mathrm{d}^6 + 93.05 \times 10^{-10}\,\mathrm{e}^{-\mathrm{d}/0.2466}$
Approx. to B	2.66	B'	Diiodo acid	$4.18 \times 10^{-8}\,\mathrm{e}^{-\mathrm{d}/0.2068}$
Approx. to B	3.52	B''	Tetraiodo acid	$3.49 \times 10^{-8}\,\mathrm{e}^{-\mathrm{d}/0.2100}$
Approx. to neon potential		C	Diiodo acid	$8.20 \times 10^{-11}\,\mathrm{e}^{-\mathrm{d}/0.165}$
		FOR IODINE–IODINE INTERACTIONS		
Hill's method (Critical T)		D		$-6.16 \times 10^{-9}/D^6 + 3.58 \times 10^{-8}\,e^{-\mathrm{D}/0.3165}$
Approx. to D	3.61	D'	Tetraiodo acid	$4.765 \times 10^{-6}\,e^{-\mathrm{D}/0.2107}$
Approx. to D	0.62	D''	Diiodobenzene	$2.90 \times 10^{-5}\,e^{-\mathrm{D}/0.191}$
Huggins and Mayer		E		$-4.00 \times 10^{-10}/D^6 - 1.150 \times 10^{-9}/D^8 + 0.75 \times 10^{-12}\,e^{-(3.57 - D)/0.345}$
Approx. to E	3.184	E'	Tetraiodo acid	$2.59 \times 10^{-8}\,e^{-\mathrm{D}/0.278}$
Approx. to E		E''	Diiodobenzene	$6.92 \times 10^{-8}\,e^{-\mathrm{D}/0.250}$
Approx. to E	3.34	F'	Tetraiodo acid	$6.40 \times 10^{-7}\,e^{-\mathrm{D}/0.2225}$
Approx. to E	0.54	F''	Diiodobenzene	$6.93 \times 10^{-6}\,e^{-\mathrm{D}/0.1925}$

In order to calculate the activation energy for the racemization of the tetraiodo acid, the van der Waals interaction of two iodine atoms must be known. This potential may likewise be estimated in several ways. First, following Hills' method,[7] a potential can be obtained from the critical constants of iodine. This potential is presented as D in Table III. Second, the potential between two iodine atoms may be estimated from the van der Waals potential of two iodide ions. This latter potential, E, free from all electrostatic interactions, was calculated by Huggins and Mayer[10] from the compressibilities of the alkali halides. The minimum value of the van der Waals potential for two iodide ions falls at 4.98 Å., whereas twice the van der Waals radius for iodine[8] is 4.30 Å. That the van der Waals radius of an iodide ion should exceed that of a covalently bound iodine atom is to be expected, since the former is spherically symmetrical, whereas the maximum electron density for the latter necessarily falls within the covalent bond. There are two ways to estimate the interactions of bound iodine atoms from the known van der Waals interactions of the corresponding ions. One estimate, E', of the potential is obtained by shifting the curve for the interaction of iodide ions so that its minimum falls at 4.30 Å. Another estimate, F', is obtained by decreasing (by the factor 4.30/4.98) the distance corresponding to each energy value in the potential function. Exponential approximations to E are shown in Table III.

In addition to the uncertainties in the calculated energy of activation due to uncertainties in the van der Waals potentials and in force constants, a serious question arises because the calculation has here been treated as a classical rather than as a quantum-mechanical problem. The zero-point energies of both the twisted biphenyl molecule and of the planar activated complex are large, even compared with the activation energy for racemization; the present calculation is not even approximately correct unless these zero-point energies largely cancel. Such a cancellation of the zero-point energies, $\sum {}^1/_2 h\nu_i$, implies that the vibration frequencies in the activated complex do not differ very much from those in the twisted molecule. Although the complete calculation of all the vibration frequencies in the activated complex is extraordinarily difficult,[1] the following qualitative argument about them is probably justified. The frequencies of vibration most affected by the transition from twisted biphenyl to activated complex are those related to (1) the very low frequency twisting vibration in the non-planar biphenyl molecule, (2) the low frequency of bending of the C—C—I bond and (3) the moderate frequency of bending of the C—C—H bond. Vibration (1) is eliminated in the activated complex and the frequencies (2) and (3) somewhat increased. But since the frequencies of all of these vibrations are low, they contribute little to the zero-point energy, and changes in these frequencies cannot cause a large change in the zero-point energy.

The same conclusion can be reached empirically by noting that the experimentally determined entropy of activation for racemization is small; this implies that the vibration frequencies in the activated complex do not differ greatly from those in the twisted molecule, and hence that the zero-

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(10) Huggins and Mayer, *J. Chem. Phys.*, **1**, 643 (1933); Mayer, *ibid.*, **1**, 270 (1933).

point energies of molecule and activated complex largely cancel. Incidentally, Hill[11] considered the problem of zero-point energy with respect to his calculation of the steric energy difference between *cis-* and *trans*-butene-2, and concluded (empirically) that here, too, the zero-point energy difference is small.

III. The Calculated and Observed Activation Energies

The calculated and observed activation energies, together with the designations of the van der Waals potential functions used to obtain these energies, are assembled in Table IV. The buttressing energy is here defined as the difference between the activation energies for the racemizations of the tetraiodo and the diiodo acids. The observed value of this difference is given in the next to last column of the table; the calculated values are given in the last column. In determining these calculated differences, wherever the exponential function A' was used for the diiodo acid, the function A'' was used for the tetraiodo acid; and wherever B' was used for the diiodo acid, B'' was used for the tetraiodo acid. It should be noted (see part IV) that the activation energies here reported are not those for the racemization of the acids named, but those of their salts. Although the rate of racemization of each acid differs slightly from that of its salt,[12] it seems unlikely that there is any large difference between the activation energies for any corresponding pair.

TABLE IV

ACTIVATION ENERGIES AND BUTTRESSING ENERGY

Acid racemized	Activation energy obs. cal./mole	Activation energy calcd. cal./mole	Van der Waals functions used	Buttressing energy obs. cal./mole	Buttressing energy calcd. cal./mole
Diiodo	21600	21400	A'	..	...
Diiodo	21600	23600	B'	..	...
Diiodo	21600	23200	C'	..	...
Tetraiodo	28050	33100	A'', D', D''	6400	11700
Tetraiodo	28050	31900	B'', F', F''	6400	8300
Tetraiodo	28050	29050	A'', F', F''	6400	7600
Tetraiodo	28050	28600	A'', E', F''	6400	7200

The calculated values for the activation energies agree well with those determined experimentally. As previously[2] pointed out, uncertainties in the van der Waals potentials may easily cause an uncertainty of 3–4 kcal./mole in the calculated activation energy; most of the discrepancies between the calculated and observed values fall within this limit. The observed buttressing energy is large, and the calculated values are in reasonable agreement with experiment. It may be noted that this agreement is quite good when the iodine–iodine potential estimated from the data of Huggins and Mayer is used, but is only qualitative when potential D is employed. This result suggests that the potentials based on the compressibilities of alkali iodides are more accurate than those estimated from critical constants. However, the buttressing energy (as here determined) is a small difference between too large quantities; hence to account for its numerical value is a severe test for any method of computation. The agreement here obtained between the calculated and observed values of the buttressing energy strongly supports the considerations advanced for computing steric effects, and particularly the emphasis here placed upon the bending of bonds as a major element of steric strain.

The observed free energy, ΔF^*, energy, ΔE^*, and entropy, ΔS^*, of activation, and the calculated energy of activation for the racemizations of the dibromo, diiodo and tetraiodo acids are presented in Table V. Where more than one calculated value has been obtained, the largest and the smallest are given. The new experimental data support the expectation that $T\Delta S^*$ should be small compared with the activation energy of racemization, and suggest that, for the racemization of all similar biphenyls, the entropy of activation may be approximately 6 entropy units/mole. If such is the fact, then the activation energy for the racemization of the dibromo acid should be around 18 kcal./mole; this estimated value appears in parentheses in Table V.

TABLE V

THE FREE ENERGIES, ENTROPIES AND ENERGIES OF ACTIVATION

Acid racemized	ΔF^* observed, cal./mole	ΔS^* observed, e. u.	ΔE^* observed, cal./mole	ΔE^* calculated, cal./mole
Dibromo	19,500		(17,900)[a]	18,200
Diiodo	23,400	−6.14	21,600	21,400–23,600
Tetraiodo	30,400	−6.75	28,050	28,600–33,100

[a] Estimated (see text).

The theory here advanced accounts not only for the buttressing effect, but also for the difference between the activation energies for the racemizations of the dibromo and the diiodo acids. The calculated values for this difference range from 3200 to 5400 calories/mole; the "experimental" value (estimated from Table V) is 3700 calories/mole.

IV. The Determinations of the Rates of Racemization

The rates of racemization of the diiodo and tetraiodo acids themselves could not be measured satisfactorily because the free acids are only sparingly soluble in all the solvents investigated. A few determinations (see Tables VI and VIII) were made with supersaturated dioxane solutions; most of the work here reported deals with the rates of racemization of the sodium salts of the acids.

Technique.—Samples of the tetraiodo acid, dissolved in equivalent quantities of sodium hydroxide, were sealed in ampoules and placed in an oil-thermostat at 80.16° or at 99.72°. (In

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[11] Hill, *J. Chem. Phys.*, **16**, 938 (1948).

[12] Compare, Searle and Adams, THIS JOURNAL, **55**, 1649 (1933).

TABLE VI

RATES OF RACEMIZATION OF THE TETRAIODO ACID

G. acid/25 cc.	Rotation of acid	$10^3 k$ in hr.$^{-1}$	Error in k, % (least squares)	$-\log k\mu$	$-\log k_0$	μ	$\bar{\mu}$ (corrected)	Correction to $\log k\mu$, $L\Delta\mu$	$-\log k\bar{\mu}$	T, °K.	Activation energy
0.7240	−	3.453	0.85	2.4618	2.4030	0.1970	0.2000	−0.0008	2.4626[a]	353.32	
.6708	+	3.540	.75	2.4510	2.4030	.1914	.2000	− .0022	2.4532	353.32	28220
.9436	+	28.66	.23	1.5428	1.4930	.2200	.2000	+ .0050	1.5387	372.88	
.8265	−	29.00	..	1.5376	1.4930	.2024	.2000	+ .0006	1.5370	372.88	
.2672	+	3.603	.75	2.4434	2.4030	.1467	.1470	− .0001	2.4435	353.32	
.2840	−	3.622	..	2.4411	2.4030	.1484	.1470	+ .0004	2.4407	353.32	27910
.2786	−	29.31	..	1.5330	1.4930	.1462	.1470	− .0002	1.5332	372.88	
.2655	+	29.30	.69	1.5331	1.4930	.1466	.1470	− .0001	1.5332	372.88	
.5331	+	3.553	.63	2.4494	2.4030	.1758	.1800	− .0011	2.4505	353.32	28120
.5858	−	28.94	.70	1.5384	1.4930	.1815	.1800	+ .0004	1.5380	372.88	
.2720	+	3.863	1.08	2.4131	2.4030	.0439	.0400	+ .0010	2.4121	353.32	27990
.2390	−	31.39	0.88	1.5033	1.4930	.0384	.0400	− .0004	1.5037	372.88	
.5885	+	8.181[b]	..	....	....	....	....	......	.....	353.32	

[a] This result is in error by more than three standard deviations and was eliminated. [b] Rate of racemization of free acid in dioxane.

order to obtain clear liquids, it was occasionally necessary to filter these solutions.) The temperatures were kept constant to ±0.02°; they were measured by a thermometer which could be read to 0.02°, and which had been calibrated at the boiling points of water and of benzene. At recorded times, ampoules were withdrawn, cooled in ice-water to stop the racemization, and then opened; the optical activity was measured to about 0.003° in a Rudolph polarimeter. About ten readings were taken for each sample, and the results averaged. The resulting averaged optical rotations, α, and the corresponding times, t, were fitted by least squares to the first order kinetic equation

$$2.303 \ln \alpha = 2kt + a_0 \qquad (6)$$

where a_0 is the constant of integration. The rate constants so determined, and (in some instances) the probable error[13] determined by the method of least squares, are given in Table VI.

Since the diiodo acid racemizes rapidly, some modification of the above procedure was necessary when this compound was used. The acid, dissolved in 1% aqueous bicarbonate solution, was placed in a jacketed polarimeter tube, and the successive observed rotations were recorded. Experiment showed that the temperature inside the tube was within 0.01° of that of the thermostat; the thermometer was calibrated at the ice-point and at the transition point for Na_2SO_4–$Na_2SO_4 \cdot 10H_2O$. Rate determinations were carried out at 19.90, 24.39 and at 38.22°.

Whereas the solvent used in the racemization of the tetraiodo acid was water, the solvent used in the racemization of the diiodo acid contained 38.25 weight per cent. alcohol and 61.75 weight per cent. water. This solvent was chosen because in it the specific rotation of the diiodo acid was several times greater than it was in water; only by using aqueous alcohol was it possible to obtain rotations high enough to permit accurate rate determinations.

For a single rate experiment with the diiodo acid, eight or ten sets of determinations of optical activity were made over a period of about two half-lives of the solute. Each set consisted of four or more individual observations, taken a few minutes apart. However, since the racemization was rapid (especially at 39°) it was not correct to assume that the observations which constituted one set should be identical, and could therefore simply be averaged. On the other hand, the amount of racemization during the few minutes which elapsed between the first and last readings for each particular set was always small; it was therefore easy to correct all the observations to a common time. To do this, an average time, $\bar{t}$ was chosen for each set of readings. Then the natural logarithm of each observed rotation, $\ln \alpha_{obs}$, was corrected by adding to it the quantity $2\ k'\Delta t$, where k' is the approximate rate constant for the reaction and Δt is $t_{obs} - \bar{t}$. The average values of the rotations thus corrected and the corresponding values of $\bar{t}$ were fitted to equation (6) by the method of least squares. A typical example of such a rate determination is presented in Table VII.

The rate constants determined for the diiodo acid in the manner outlined above are recorded in Table VIII.

The data presented in Tables VI, VII and VIII clearly show that the racemization, as anticipated, is a first order reaction. Not only was a good first order rate constant obtained in each individual experiment (usually over a period of two or more half-lives), but the rate of each racemization, at constant ionic strength, was independent of the concentration of the optically active biphenyl employed. Regrettably, however, the rate of racemization was not strictly independent of the

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[13] Mather, "Statistical Methods in Biology," Interscience Publishing Co., New York, N. Y., 2nd ed., 1947, Chaper 8.

TABLE VII

A TYPICAL RATE DETERMINATION: THE RATE OF RACEMIZATION OF THE DIIODO ACID AT 19.90°

$t_{\text{obs.}}$	ln $\alpha_{\text{obs.}}$	$\bar{t}$	ln α_{corr}	Average ln α_{corr}
0.0	1.4446	0.0	1.4446	1.4501
4.4	1.4471		1.4543	
7.0	1.4385		1.4497	
9.0	1.4377		1.4522	
31.5	1.4071	35.0	1.4016	1.4004
33.6	1.4023		1.4002	
35.6	1.3981		1.3990	
37.6	1.3949		1.3990	
40.7	1.3935		1.4025	
67.7	1.3502	70.0	1.3465	1.3463
70.7	1.3387		1.3376	
73.0	1.3436	70.0	1.3484	
76.7	1.3415		1.3523	
123.4	1.2581	125.0	1.2556	1.2544
125.6	1.2540		1.2549	
127.9	1.2475		1.2521	
130.3	1.2470		1.2554	
172.6	1.1778	175.0	1.1739	1.1716
174.6	1.1706		1.1699	
177.4	1.1653		1.1693	
179.2	1.1665		1.1732	
284.5	0.9947	290.0	0.9883	0.9873
286.3	.9929		.9869	
288.0	.9880		.9848	
289.8	.9892		.9889	
332.2	.9236	335.0	.9192	.9217
335.2	.9208		.9210	
337.2	.9194		.9231	
340.6	.9150		.9240	
396.3	.8241	400.0	.8181	.8183
398.3	.8241		.8209	
401.0	.8200		.8223	
403.2	.8077		.8128	
466.6	.6991	470.0	.6935	.6972
468.8	.7002		.6993	
472.4	.6995		.7034	
475.2	.6841		.6924	
530.2	.5977	530.0	.5980	.5959
531.8	.5954		.5984	
533.5	.5862		.5918	
536.6	.5851		.5958	
651.7	.4002	655.0	.3949	.4013
654.8	.4041		.4039	
657.2	.4002		.4036	
659.0	.3960		.4025	
761.9	.2452	765.0	.2402	.2356
764.4	.2445		.2436	
766.5	.2183		.2208	
768.3	.2319		.2372	

$a_0 = 1.4522.$ $k = 8.014 \times 10^{-4}.$

ionic strength, μ, of the solution. Since the reactions are not only first order but almost certainly unimolecular, the rather large salt effect here observed is surprising.

The desired activation energies are clearly those for infinite dilution where $\mu = 0$. The extrapolation of the rate constants to infinite dilution is, however, difficult, because the experiments referring to the most dilute solutions are necessarily subject to the greatest errors; the optical activity of these dilute solutions is too low for precise measurement. Fortunately, as the data in Fig. 4 and in Tables VI and VIII show, the effect of ionic strength on the rate of a particular racemization process is independent of temperature.

The activation energy for each racemization process was therefore calculated by applying the Arrhenius equation to the data from a set of experiments conducted at various temperatures but at the same ionic strength. The rate determinations fall naturally into a few groups, and within each group there are several experiments carried out at almost identical ionic strengths. Although these small differences in ionic strength among the experiments of any one set might well have been neglected, the data were in fact corrected to definite and identical values of μ. The very small corrections necessary (see Tables VI and VIII) were applied in accordance with equation 7.

$$\log k\mu = \log k_0 + L\mu \qquad (7)$$

where $k\mu$ is the rate constant at the ionic strength μ, k_0 the corresponding constant at zero ionic strength, and L a proportionality factor which was found to be 0.250 for the diiodo acid and 0.330 for the tetraiodo acid.

The activation energies determined as outlined above are independent (within 100 calories) of ionic strength; the experimental values therefore correspond well to those at infinite dilution. The method here outlined for finding activation energies where $\mu = 0$ appears satisfactory; nevertheless extrapolation to infinite dilution may well involve an uncertainty of about one or two per cent. in the temperature coefficient for the rate of each racemization. This uncertainty is the major cause of the estimated uncertainty of ±300 calories in the activation energies here recorded.

V. Mathematical Appendix

For the tetraiodo acid,[14] the energy of activation is the difference between the minimum value of E' (see equation 3) and twice the strain energy of ortho diiodobenzene.

$$E^0 = E'^0 - 2E_{\text{ortho}} \qquad (8)$$

For convenience in notation, the symbols E_{d_0} and E_{D_0} are defined by the equations

$$E_{d_0} = Ae^{-d_0/\rho} \text{ and } E_{D_0} = Ge^{-D_0/\rho'} \qquad (9)$$

Equation (3) can be rewritten (with the aid of (2), (4) and (9)) as

$$E'^0 = \sum_i {}^1/_2\, a_i q_i^2 + E_{d_0} \exp\left(\frac{1}{\rho}\sum_i b_i q_i\right) +$$

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[14] The derivations here given parallel in part those given by T. L. Hill, *J. Chem. Phys.*, **16**, 938 (1948).

TABLE VIII

RATES OF RACEMIZATION OF THE DIIODO ACID

g. acid/5.5 cc. of solvent	$10^4 k$ (min.$^{-1}$)	Error in k, % (least squares)	$-\log k\mu$	$-\log k_0$	μ	$\bar{\mu}$ (corrected)	Correction to log $k\mu$, $L\,\Delta\bar{\mu}$	$-\log k\mu$	T, °K.	Activation energy	Per cent. error in activation energy
0.3922	8.015	0.40	3.0961	2.9218	0.529	0.530	−0.0003	+3.0964	293.06		
.3304	8.113	.64	3.0908	2.9218	.507	.530	− .0076	+3.1074	293.06		
.3655	69.44	..	2.1584	1.9832	.520	.530	− .0033	+2.1617	311.28	21630	0.42
.3803	69.38	.63	2.1588	1.9832	.536	.530	+ .0020	+2.1568	311.28		
.3890	13.56	..	2.8676	2.6928	.528	.530	− .0006	+2.8682	297.55		
.3945	8.024	.54	3.0956	2.9218	.531	.550	− .0063	+3.1019	293.06		
.4945	67.41	.24	2.1713	1.9832	.567	.550	+ .0056	+2.1657	311.28	21510	..
.4527	13.50	.29	2.8697	2.6928	.552	.550	+ .0006	+2.8691	297.55		
.1994	8.350	.85	3.0783	2.9218	.459	.460	− .0003	+3.0786	293.06		
.1990	73.62	.65	2.1330	1.9832	.458	.460	− .0006	+2.1336	311.28		
.2032	73.18	..	2.1356	1.9832	.460	.460	.0000	+2.1356	311.28	21720	.49
.1299	14.75	.51	2.8315	2.6928	.433	.460	− .0089	+2.8404	297.55		
.1969	14.62	..	2.8351	2.6928	.458	.460	− .0026	+2.8377	297.55		
.2107	14.13	..	2.8501	2.6928	.463	.460	+ .0010	+2.8491	297.55		
.2775[a]	16.72	.33	2.7768	2.6928	.252	...	......	......	297.55	...	..
.1940[b]	19.72	..	......	......	...	...	......	......	297.55	...	..

[a] In 7 cc. of solution containing theoretical amount of sodium hydroxide and ethanol–water mixture. [b] In 6 cc. of dioxane.

$$E_{d_0} \exp\left(-\frac{1}{\rho}\sum_i b_i' q_i\right) + E_{D_0} \exp\left(-\frac{1}{\rho'}\sum_i c_i q_i\right) + E_{D_0} \exp\left(-\frac{1}{\rho}\sum_i c_i' q_i\right) \quad (10)$$

In order to find the minimum value of E'^0, the partial derivative of E'^0 with respect to each of the coördinates q_i is set equal to zero. For the coördinate q_j

$$\frac{\partial E'^0}{\partial q_j} = 0 = a_j q_j - \left(\frac{b_j}{\rho}\right) E_{d_0} \exp\left(-\frac{1}{\rho}\sum_i b_i q_i^0\right) - \left(\frac{b_j'}{\rho}\right) E_{d_0} \exp\left(-\frac{1}{\rho}\sum_i b_i' q_i^0\right) - \left(\frac{c_j}{\rho}\right) E_{D_0} \exp\left(-\frac{1}{\rho'}\sum_i c_i q_i^0\right) - \left(\frac{c_j'}{\rho'}\right) E_{D_0} \exp\left(-\frac{1}{\rho'}\sum_i c_i' q_i^0\right) \quad (11)$$

Here the quantities $q^0{}_j$ represent the values of the respective coördinates in the activated complex. Two mathematical parameters, Y and Z, are now defined by equations (12) and (13).

$$Z = E_{d_0} \exp\left(-\frac{1}{\rho}\sum_i b_i q_i^0\right) = E_{d_0} \exp\left(-\frac{1}{\rho}\sum_i b_i' q_i^0\right) \quad (12)$$

$$Y = E_{D_0} \exp\left(-\frac{1}{\rho'}\sum_i c_i q_i^0\right) = E_{D_0} \exp\left(-\frac{1}{\rho'}\sum_i c_i' q_i^0\right) \quad (13)$$

Here the constant Y represents the van der Waals energy of repulsion between two neighboring iodine atoms, in the activated complex. Because of symmetry, Y can be expressed in terms either of the constants c_i or of the constants c_i'. A similar argument for Z has previously been presented.[1,2] From equations (11), (12) and (13)

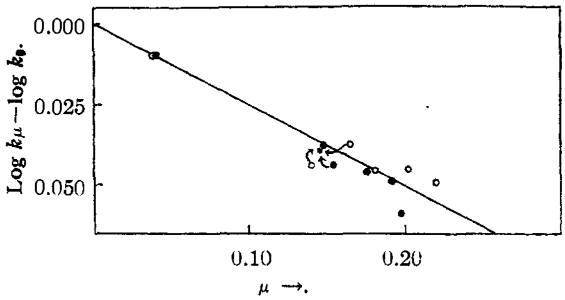

Fig. 4.—The effect of ionic strength on the rate of racemization of the sodium salt of the tetraiodo acid. The * represents the coincidence of three points (at the bases of the arrows): ●, data at 353.22°K.; ○, data at 372.88°K.

and from the definitions of B_i and C_i, it follows that

$$q_j^0 = \frac{2B_jZ}{a_j\rho} + \frac{2C_jY}{a_j\rho'} \quad (14)$$

Therefore, from (12) and (14)

$$Z = E_{d_0} \exp\left(-\frac{2Z}{\rho^2}\sum_i B_i^2/a_i - \frac{2Y}{\rho\rho'}\sum_i \frac{B_iC_i}{a_i}\right) \quad (15)$$

and from (13) and (14)

$$Y = E_{D_0} \exp\left(-\frac{2Y}{\rho'^2}\sum_i \frac{C_i^2}{a_i} - \frac{2Z}{\rho\rho'}\sum_i \frac{B_iC_i}{a_i}\right) \quad (16)$$

For convenience in notation, let

$$\chi = \frac{2}{\rho^2}\sum_i B_i^2/a_i \quad (17)$$

$$\psi = \frac{2}{\rho'^2}\sum_i C_i^2/a_i \quad (18)$$

$$\omega = \frac{2}{\rho\rho'}\sum_i B_iC_i/a_i \quad (19)$$

Then

$$Z = E_{d_0} \exp(-\chi Z - \omega Y) \quad (20)$$

$$Y = E_{D_0} \exp(-\psi Y - \omega Z) \quad (21)$$

Simultaneous solution of equations (20) and (21) gives equation (22).

$$\ln\left[\frac{1}{\omega}(\ln E_{\mathrm{d}_0} - \chi Z - \ln Z)\right] = \ln E_{\mathrm{D}_0} - \omega Z - \frac{\psi}{\omega}(\ln E_{\mathrm{d}_0} - \chi Z - \ln Z) \quad (22)$$

Since the constants E_{d_0}, E_{D_0}, χ, ψ and ω are all determined by the previous choices of the force constants, van der Waals potentials, etc., equation (22) can be solved numerically for Z; subsequently, either equation (20) or (21) can be solved numerically for Y. From equations (10), (14), (17), (18) and (19) it follows that

$$E'^0 = Z^2\chi + Y^2\psi + 2ZY\omega + 2Y + 2Z \quad (23)$$

The strain energy for diiodobenzene can also be determined by methods similar to those already presented[1,2]; this energy is found to be

$$E_{\mathrm{ortho}} = \frac{Y'^2}{2\rho'^2}\sum_{\mathrm{i}} \frac{C_{\mathrm{i}}^2}{a_{\mathrm{i}}} + Y' \quad (24)$$

where

$$Y' = E_{\mathrm{D}_0} \exp\left(-\frac{1}{\rho'}\sum_{\mathrm{i}} C_{\mathrm{i}}^2/a_{\mathrm{i}}\right) \quad (25)$$

For the calculations of Y', the iodine–iodine interactions were assumed to be the same as those used in the calculations of E'^0. However, as previously noted, it was necessary to use an exponential approximation to the van der Waals potential different from that used in determining the value of the strain energy for the tetraiodo acid; this statement follows at once from the fact that the iodine atoms are further apart in diiodobenzene than they are in the activated complex for the racemization of the tetraiodo acid. The exponential approximations used in determining the strain energy for diiodobenzene are given in Table III.

Acknowledgment.—The authors wish to express their enthusiastic thanks to Dr. Seymour Stein of the University of Illinois Neurological Institute, who loaned them the Rudolph polarimeter with which the rates here recorded were measured.

VII. Summary

J. E. Mayer and one of the authors recently developed a method for calculating the activation energies for the racemization of optically active derivatives of biphenyl. This theory emphasizes the importance of the bending of valence bonds, as well as overlap of atoms, as a major element in steric strain.

To test this theory, activation energies have been measured and calculated for the racemization of 2,2'-diiodo-5,5'-dicarboxybiphenyl and for 2,2',3,3'-tetraiodo-5,5'-dicarboxybiphenyl. For the latter compound, the iodine atoms in the 3- and 3'-positions "buttress" those in the 2- and 2'-(ortho) positions, and thereby retard the racemization process. In agreement with the qualitative argument presented above and with the quantitative calculations, the experimentally determined activation energy for the tetraiodo acid exceeds that for the diiodo acid by about 6.4 kcal./mole.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Preparation and Resolution of 2,2'-Diiodo-5,5'-dicarboxybiphenyl and of 2,2',3,3'-Tetraiodo-5,5'-dicarboxybiphenyl

BY MARTIN RIEGER AND F. H. WESTHEIMER*

In the preceding article,[1] the calculated and observed activation energies for the racemization of 2,2'-diiodo-5,5'-dicarboxybiphenyl (the "diiodo acid") and of 2,2',3,3'-tetraiodo-5,5'-dicarboxybiphenyl (the "tetraiodo acid") are reported. In this paper, the methods of preparing and resolving these compounds are described.

The general plan of the preparations is shown in Fig. 1. The central compound of this series is the dimethyl ester, XI, of 2,2'-diamino-5,5'-dicarboxybiphenyl. Both amino groups of this ester can be diazotized, and the resulting tetrazonium salt converted (by way of the iodonium iodide, XIII) to the ester, XIV, of the "diiodo acid." Alternatively, the amino ester, XI, can be iodinated to form the diiododiamino ester, XVI, which can then be converted (by way of the corresponding tetrazonium salt and the iodonium iodide, XVII) to the ester, XVIII, of the "tetraiodo acid." It has been assumed that, in the iodination of 2,2'-diamino-5,5'-dicarbomethoxybiphenyl (XI), the iodine atoms are introduced into the 3 and 3' positions. Since, in the diamino ester, XI, the position para and one of the positions ortho to each amino group are blocked, it is expected that the iodination will occur as indicated above.

The precursor for the diamino ester, XI, is the dinitro ester, V. The latter compound had previously been prepared by Case and Koft.[2] The first step in their synthesis was the nitration of *o*-tolidine (VI) to form a dinitro-*o*-tolidine to which they (as well as earlier workers) ascribe the structure VII. On deamination, this dinitro-*o*-tolidine yields a dinitroditolyl to which these

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* Harvard University Ph.D. 1935.

(1) Rieger and Westheimer, **72**, 19 (1950).

(2) Case and Koft, THIS JOURNAL, **63**, 508 (1941).