Attempted Calculation of the Effect of 4,4'-Substituents on the Enthalpies of Activation for Inversion of Some Biphenyl Derivatives

JÖRGEN R. PEDERSEN

Department of Organic Chemistry, University of Göteborg and Chalmers Institute of Technology, Fack, S-402 20 Göteborg 5, Sweden

Westheimer and Mayer's minimization procedure for calculating the enthalpy of activation for inversion of *ortho*-halogenated biphenyls has been extended to include variation of the delocalization energy of the planar transition state. The delocalization energy of the planar transition state has been estimated by semi-empirical quantum chemical calculations on a number of biphenyls with polar substituents in the 4,4'-positions. The results are compared with available experimental information, and the effect of different substituents is discussed. Finally a tentative explanation of the apparent unresolvability of 2,2'-dibromo-4,4'-diaminobiphenyl is afforded, and the possibility of its resolution is predicted.

The nature of the effect of *ortho*-substituents on the inversion of biphenyls was resolved 25 years ago by Westheimer and Mayer's calculation of the activation energy for inversion of 4,4'-dicarboxy-2,2'-dibromobiphenyl.[1,2] This work was followed by calculation of the buttressing effect by Rieger and Westheimer,[3] and was later refined by Howlett,[4] who calculated the activation energies for inversion of a large number of *ortho*-halogenated biphenyls using better values for the van der Waals potentials than were available to Westheimer.

These authors either ignored the effect of change in the delocalization energy as the molecule becomes planar in the transition state [1-3] or treated it as a constant, independent of the length of the pivot bond.[4] The latter is a very reasonable approximation, as long as the effect of 4,4'-substituents is not explicitly taken into account, since it is well known that p-p orbital overlap changes very little with variation in bond length at the distances (≈ 1.50 Å) that separate the two rings.

The nature of the effect of polar substituents in the 4- and 4'-positions is still under debate. The success of Westheimer and Mayer's method suggested to the present author that it might be extended to include the change in

electronic energy with change in pivot-bond length and used to predict the effect of substituents in these positions.

The treatment proposed here is essentially Westheimer and Mayer's method for calculating the minimum energy of activation for inversion of biphenyl derivatives, but with the delocalization energy over the 1,1'-bond of the planar transition state treated as a function of the 1,1'-bond length. The model uses 2,2'-dibromobiphenyl as a reference, and a value for the delocalization energy in this compound is chosen to yield a reasonable length for the 1,1'-bond.

The inversion of the *ortho*-dihalogenated biphenyl molecule is assumed to involve passage through a planar * transition state with the conformation shown in Fig. 1. According to Howlett,[4] the difference between the energies
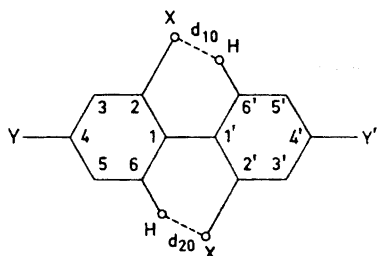

Fig. 1. Planar transition state for 2,2'-dihalogeno-4,4'-disubstituted biphenyl. d_{10} and d_{20} are the nonbonded distances in absence of distortions due to nonbonded halogen-hydrogen repulsion and π-electron overlap over the 1,1'-bond.

of the planar transition state and the orthogonal ground state may be considered as the sum of four independent magnitudes.

1. Repulsive van der Waals forces between substituents in the *ortho*-positions.

2. Deformations extending, in the case of a real system, over all the normal coordinates of the molecule, leading to a lowering of the energy increase caused by 1.

3. Stabilization energy of the planar state caused by π-overlap between the rings.

4. The alteration in dipole-dipole interaction between the *ortho*-carbon-halogen bonds as their relative orientation changes.

Howlett minimized with respect to the first and second magnitudes by Westheimer and Mayer's minimization procedure, and dealt with the third and fourth by assuming them to be constants which he added to the result. This involved little error as he treated only biphenyls without substituents in positions other than *ortho* to the 1,1'-bond.

The treatment here is identical with that of Howlett [4] except that the third magnitude is taken to be a function of the stretching of the 1,1'-bond in the minimization procedure. Accordingly, the energy of a biphenyl molecule in the planar state in excess of that of the (assumed) orthogonal ground state is written as:

$$\Delta E = 1/2 \sum_i k_i q_i^2 + A_1 \exp\left(-d_1/\varrho_1\right) + A_2 \exp\left(-d_2/\varrho_2\right) -$$

$$- DE_\pi \exp\left(-2Bq_1\right) - E_{\text{dipole}} - E_{\text{orthogonal}} \tag{1}$$

* For an opposing view see Ref. 5.

In this expression k_i is the force constant for normal coordinate i while q_i is the deformation along the coordinate. A_i and ϱ_i are parameters in the approximation of the van der Waals repulsion; d_i is the corresponding non-bonded distance. DE_π is the overlap energy between the rings of the planar transition state when the pivot bond is unstretched ($q_1 = 0$), and B is an empirical parameter by means of which the exponential approximates the change in overlap energy as the 1,1'-bond is stretched (compressed). Dewar [6] has shown that such a change is approximately proportional to the square of the 1,1'-resonance integral. Similarly Suzuki [7] points out that the extra resonance energy over the 1,1'-bond in biphenyl is almost completely proportional to the square of this overlap integral. Consequently $2B$ was chosen for the exponential decay of the overlap energy as the 1,1'-bond is stretched, B being assigned the value 3.0323 Å^{-1} suggested by Allinger for the exponential decay of the resonance integral.[8] E_{dipole} is the decrease in dipole-dipole interaction energy due to the *ortho*-halogen substituents when the molecule passes into the transoid transition state. $E_{\mathrm{orthogonal}}$ is the energy of the orthogonal ground state caused by small residual deformations. The distances d_i are, for small displacements, approximated as linear functions of the deformations, thus:

$$d_1 = d_{10} + \sum_i b_i q_i \text{ and } d_2 = d_{20} + \sum_i c_i q_i \qquad (2)$$

where d_{10} and d_{20} are intermolecular distances (defined in Fig. 1) in the absence of deformations due to nonbonded halogen-hydrogen repulsion and π-electron overlap over the 1,1'-bond, b_i and c_i are geometrical factors and summation extends over all normal coordinates. All interatomic distances and angles in the absence of the above deformations are the same as used in the quantum chemical computations, see below.

The energy is minimized with respect to coordinates other than q_i by setting $\partial \Delta E / \partial q_i = 0$ ($i \neq 1$), thus

$$0 = \partial \Delta E / \partial q_i = k_i q_i - (A_1 b_i / \varrho_1) \exp(-d_1/\varrho_1) - (A_2 c_i / \varrho_2) \exp(-d_2/\varrho_2) \qquad (3)$$
$$(i \neq 1)$$

The set of equations (3) is solved by an iterative computer program for discrete values of q_1. The assumed value of q_1 and the computed values of q_i ($i \neq 1$), d_1 and d_2 are substituted into (1) to find the energy. A subroutine finds the minimum energy and the corresponding value of q_1, and the cycle is repeated with smaller intervals in q_1 around the value giving the first minimum energy. Iteration is terminated when two subsequent minimum energies differ by less than 1 cal mol^{-1}.

The values for the van der Waals potentials, force constants, E_{dipole} and $E_{\mathrm{orthogonal}}$ that were taken from Howlett [4] are listed in Tables 1, 2, and 3. The normal coordinates are numbered according to Westheimer and Mayer;[1] the force constants for the benzene rings and the pivot bond are adopted from their work and listed in Table 4. In addition, their approximation of treating only in-plane distortions is assumed valid.

The overlap energy between the rings in the planar transition state. This quantity is obviously not directly calculable; it is the difference in energy

Table 1. van der Waals potential parameters.[4]

Atoms	$10^{11} \times A$ (erg molecule^{-1})	ϱ (Å)
H···Br	14.4	0.4379
H···I	53.7	0.3983

Table 2. Assumed force constants.[4]

Bond	k (mdyn Å^{-1})	Interbond angle	$10^{11} \times k$ (dyn cm rad^{-2})
C−H	5.02	C−C−H	0.86
C−Br	3.3	C−C−Br	0.97
C−I	2.8	C−C−I	0.84

Table 3. Energy components.[4]

ortho-Substituents	$E_{orthogonal}$ (kcal mol^{-1})	E_{dipole} (kcal mol^{-1})
2,2′-Dibromo	1.32	0.13
2,2′-Diiodo	1.72	0.10

Table 4. Normal-coordinate force constants for pivot bond and benzene vibrations, numbered according to Westheimer *et al.*[1-3]

Coordinate	Force constant	
I	5.5	mdyn Å^{-1}
II	1.13×10^{-11}	dyn cm rad^{-2}
$q_1{}^a$	45.9	mdyn Å^{-1}
$q(6+8)$	13.7	mdyn Å^{-1}
$q(6+8)^*$	450.0	mdyn Å^{-1}
q_{12}	46.2	mdyn Å^{-1}
q_{19}	74.6	mdyn Å^{-1}

a This normal coordinate does *not* correspond to the deformation variable with the same notation, used in the present paper. The latter variable corresponds to I above.

between the actual (assumed) planar transition state and a hypothetical planar transition state without overlap but with the same geometry.

In the model used in the estimation of the overlap between the rings, unsubstituted biphenyl is used as a reference and a value $DE_{\pi u}$ is chosen as the overlap energy between the rings of the transition state of this compound. This choice was dictated by the fact that neither the INDO nor the CNDO/2 approximation can include the heavy halogen atoms. The overlap energies of the different 4,4'-substituted biphenyls are then estimated relative to it according to formula (4).

$$DE_{\pi s} = DE_{\pi u} + H_u - H_s \qquad (4)$$

Here H equals the binding energy of the planar transition state with conjugation minus the binding energy of the orthogonal ground state, and the subscripts u and s stand for unsubstituted and substituted, respectively. The binding energes were calculated using Pople's INDO method.[9,10] The length of the 1,1'-bond in the orthogonal ground state as well as in the planar transition state was taken to be 1.50 Å.

The assumptions behind these choices are as follows. The desired overlap energy is not calculable. The difference in energy between a planar transition state with overlap and an orthogonal ground state with identical bond lengths is calculable, however, and the assumption is that the influence of the substituents on the energy of the orthogonal ground state should be similar to their influence on the energy of the desired hypothetical transition state without overlap, as indicated in Fig. 2 (the level spacing is assumed to be the same to the left and to the right). By using a suitable value for $DE_{\pi u}$, the
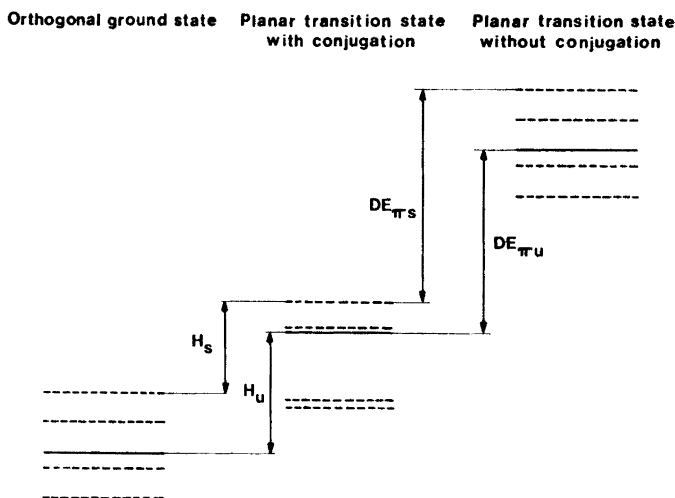

Fig. 2. Energy-level diagram for the definition of the overlap energy between the rings in the planar transition state. $DE_{\pi u}$ is the chosen value for DE_π in the reference, H_s is the difference in binding energy between the planar and the orthogonal conformation of a substituted biphenyl and H_u is the same quantity for the reference.

level for the energy of a planar unsubstituted biphenyl without conjugation between the rings is fixed (full-drawn line), and by the aforementioned assumptions the remaining energy levels for the substituted planar biphenyls without conjugation between the rings are established in relation to it. This model assumes also that any substituent influence on the coulomb energy is the same in the hypothetical planar non-conjugated transition state and the orthogonal ground state in spite of the difference in geometry. Actually, calculations of the coulomb-energy differences, due only to change in geometry between the two conformations concerned, show that this is not true. The differences are very slight, however, except for the doubly charged ions and dicarboxybiphenyl.

The magnitude of $DE_{\pi u}$ in eqn. (4) was chosen so as to yield the minimum energy for planar 2,2'-dibromobiphenyl at a 1,1'-bond length of 1.507 Å. The reason for this choice was that planar 2,2'-dibromobiphenyl with no 4,4'-substituents was most likely to have a pivot bond length not much larger than that in planar biphenyl. The 1,1'-bond length of planar biphenyl is not known with precision, but the molecule appears to be planar or very close to planar in crystalline form, as determined by X-ray crystallography. Some recent values of the 1,1'-bond length are 1.494, 1.506 and 1.507 Å.[11-13] It is pointed out that the data are not sufficiently precise to decide unequivocally if the molecule is completely planar in the crystal. The exact geometry of the transition state for inversion of biphenyls in solution is of course completely unknown. It is not likely, however, that the 1,1'-bond length in an *ortho*-halogenated biphenyl without polar substituents in the 4,4'-positions should become shorter during the inversion than the 1,1'-bond length of planar (or almost planar) biphenyl albeit in crystalline form. A numerical value of 3.7×10^{-13} erg molecule^{-1} for $DE_{\pi u}$ resulted in a 1,1'-bond length of 1.507 Å for planar 2,2'-dibromobiphenyl at the energy minimum. Consequently, this value for $DE_{\pi u}$ was adopted in all the calculations. The 1,1'-bond in the transition state of 2,2'-dibromobiphenyl may of course be longer than 1.507 Å, but the calculations show that the pivot-bond stretching due to the halogen-hydrogen repulsion is generally as small as a few hundredths of an Ångström unit. The somewhat arbitrary choice, however, largely affects the reference level for the calculated $\Delta H^{\ddagger}$ for inversion, but the differences in levels for differently 4,4'-substituted dibromo and diiodobiphenyls are not significantly affected.

RESULTS AND DISCUSSION

The calculated barriers to inversion and the 1,1'-bond lengths for 2,2'-dibromo- and 2,2'-diiodobiphenyls, using the extended version of Westheimer and Mayer's minimization method, are found to be linear functions of $DE\pi$ in the interval of interest (3.0×10^{-13} erg molecule$^{-1} < DE_{\pi} > 5.0 \times 10^{-13}$ erg molecule^{-1}). The expressions for $\Delta H^{\ddagger} = (\Delta E)_{min}$ and q_1 obtained by a least-squares fitting to the calculated values are listed in Table 5. The root-mean-square deviation of the straight line from the originally calculated values is given in the last column. The functions could not be expected to remain linear

Table 5. Linear equations fitted (by the method of least squares) to calculated values for $\Delta H^{\ddagger}$ and q_1.[a,b]

2,2'-Substituents	Linear equation	Root-mean-square deviation from originally calculated values
Dibromo	$\Delta H^{\ddagger} = -1.4395 \times 10^{13} \times DE_{\pi} + 32.61$	± 0.03
Dibromo	$q_1 = -0.0145 \times 10^{13} \times DE_{\pi} + 0.0610$	± 0.0002
Diiodo	$\Delta H^{\ddagger} = -1.4185 \times 10^{13} \times DE_{\pi} + 39.79$	± 0.03
Diiodo	$q_1 = -0.0140 \times 10^{13} \times DE_{\pi} + 0.0614$	± 0.0003

[a] The following units are used: for $\Delta H^{\ddagger}$ kcal mol^{-1}, for DE_{π} erg molecule^{-1} and for q_1 Å.
[b] The lines were fitted to nine calculated points evenly distributed in the interval 3.0×10^{-13} erg molecule$^{-1} \le DE_{\pi} \le 5.0 \times 10^{-13}$ erg molecule^{-1}.

outside the stated interval. This is immaterial, however, since the values for DE_{π} are not likely to vary outside this range.

The binding energies for the orthogonal and planar conformations of different 4,4'-disubstituted biphenyls with no *ortho*-substituents were calculated by Pople's INDO method using the program CNINDO. The original atomic parameters proposed by Pople *et al.* were used.[9,10] The standard bond lengths and bond angles proposed by Pople [9] were used for all bonds except the pivot bond length which was chosen as 1.50 Å in agreement with the model used for the computation of the overlap energy DE_{π}.

From the calculated charge distributions for different 4,4'-disubstituted biphenyls, it was found that the substituents altered the charge distribution of the planar transition state in another way than that of the orthogonal ground state. This difference is caused both by change in geometry and by change in overlap between the two rings, therefore the effect on the hypothetical planar transition state cannot readily be gauged. In order to estimate the importance of these effects, the change in coulomb energy due to geometrical alteration and the change due to the combined causes were separately calculated.

The coulomb energy of a conformation of any particular biphenyl can be calculated employing the equation:

$$C = \sum_i \sum_j e_i e_j / r_{ij} \tag{5}$$

where e_i is the formal charge on atom i and r_{ij} is the distance between atoms i and j.

The coulomb energy change due to change in geometry alone was defined according to eqn. (6).

$$P = C^s_{\text{planar}} - C^s_{\text{orthogonal}} - (C^u_{\text{planar}} - C^u_{\text{orthogonal}}) \tag{6}$$

In this expression C is the coulomb energy of one conformation, calculated employing eqn. (5) with the index i running over all the atoms on one side of the pivot bond and the index j over all the atoms on the other side. The

formal-charge pattern of the orthogonal ground state was applied for the calculation of the coulomb energy of both the ground state and the planar transition state. The superscripts s and u stand, as before, for substituted and unsubstituted, respectively.

The partial coulomb energy change was defined according to eqn. (7).

$$P_{\text{partial}} = C^{\text{s}}_{\text{planar,conj.}} - C^{\text{s}}_{\text{orthogonal}} - (C^{\text{u}}_{\text{planar,conj.}} - C^{\text{u}}_{\text{orthogonal}}) \tag{7}$$

In this expression the symbols have the same general meaning as before, but the subscript conj. indicates that the coulomb energy is calculated from eqn. (5) employing the actual formal charge pattern for the planar conformation, i.e., including the effect of conjugation between the rings. As before only coulomb interaction between atoms in different rings is included.
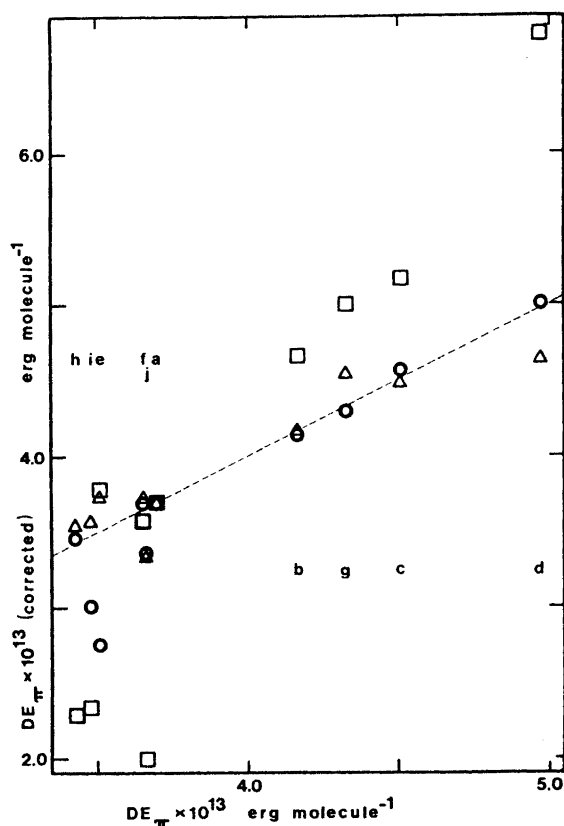

Fig. 3. Correlation diagram for DE_π corrected for change in coulomb energy due to geometry change alone (○), for the partial coulomb energy change (△) and the total coulomb energy change (□) versus uncorrected DE_π. The line with unit slope is drawn for comparison. (a) Biphenyl; (b) 4-aminobiphenyl; (c) 4,4'-diaminobiphenyl; (d) 4-amino-4'-ammoniumbiphenyl; (e) 4,4'-diammoniumbiphenyl; (f) 4-nitrobiphenyl; (g) 4-amino-4'-nitrobiphenyl; (h) 4,4'-dinitrobiphenyl; (i) 4,4'-dicarboxybiphenyl; (j) 4,4'-dicarboxybiphenyl dianion.

The total coulomb energy change was defined according to eqn. (7) using the actual formal charge pattern for the conformation in question as before but now with the indices i and j running over all pairs of atoms in the molecule.

The correlation diagram in Fig. 3 shows the three sets of values of DE_π, obtained by correction for the change in coulomb energy in the three different ways, plotted against the uncorrected values of DE_π. The correlation is roughly linear for all three sets, and it therefore seems likely that the effect on the hypothetical planar transition state without overlap will not change the order of the estimated DE_π values. The uncorrected values are used in the following.

The calculated barriers to inversion and the length of the 1,1'-bonds for different biphenyls are given in Tables 6 and 7 together with the available experimental activation parameters for inversion. From the digram in Fig. 4 it is seen that there is a correlation between calculated and experimental values.
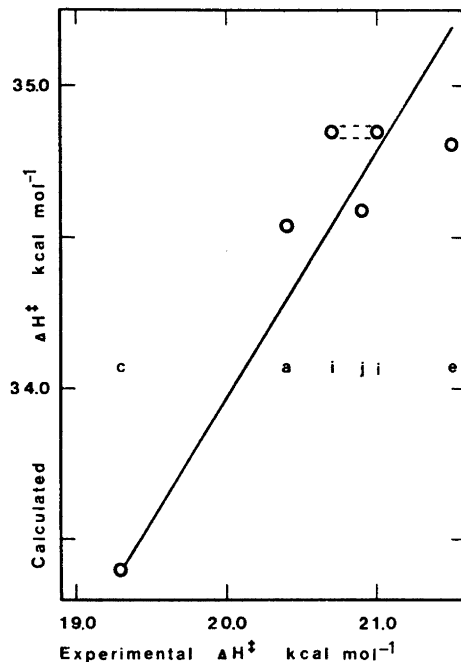

Fig. 4. Correlation diagram for diiodo-biphenyls. Calculated $\Delta H^{\neq}$ for inversion *versus* experimental values. The letters represent the same 4,4'-substitution pattern as in Fig. 3.

The differences between calculated and experimentally determined values for the barriers to inversion are seen to be larger than for the results obtained by Howlett using the same van der Waals parameters but neglecting the overlap over the 1,1'-bond. This is partly due to the shorter 1,1'-bond distance of 1.50 Å used in this treatment for the undeformed transition state. The non-bonded distances d_{10} and d_{20} are thus slightly shorter at the start, and this raises the energy.

What is of particular interest in this treatment, however, is not the absolute level of the barrier but the relative barrier heights for biphenyls with different

polar substituents in the 4,4'-positions. From Tables 6 and 7 it is seen that there is close parallelism between the results for 2,2'-dibromo- and 2,2'-diiodobiphenyls, as could be anticipated. For this reason, and because of the scarcity of experimental data for 2,2'-dibromobiphenyls, the following discussion will largely be restricted to the relative barrier heights for 2,2'-diiodobiphenyls. If not otherwise stated, $\Delta\Delta H^{\ddagger}$ is always calculated as the difference between $\Delta H^{\ddagger}$ for the 4,4'-substituted-2,2'-diiodobiphenyl under consideration and $\Delta H^{\ddagger}$ for 2,2'-diiodobiphenyl.

Table 6. Calculated and experimental inversion barriers and calculated 1,1'-bond length for transition state of 2,2'-dibromobiphenyls

Substituents		Calculated	Experimental		Calculated
4	4'	$\Delta H^{\ddagger}$ kcal mol^{-1}	$\Delta H^{\ddagger}$ kcal mol^{-1}	$\Delta G^{\ddagger}$ kcal mol^{-1}	1,1'-bond length Å
H	H	27.29	—	—	1.5074
H	NH_2	26.62	—	—	1.5006
NH_2	NH_2	26.12	—	—	1.4956
NH_2	NH_3^+	25.45	—	—	1.4889
NH_3^+	NH_3^+	27.55	—	—	1.5100
H	NO_2	27.35	—	—	1.5080
NH_2	NO_2	26.38	—	—	1.4982
NO_2	NO_2	27.67	—	—	1.5113
CO_2H	CO_2H	27.60	17.38; 18.5	20.3[a,b]	1.5105
CO_2^-	CO_2^-	27.34	—	20.1[a]	1.5079

[a] Temperature 1°C; calculated from the rate constant given in Ref. 14. [b] Temperature 1°C; calculated from the rate constant given in Ref. 15.

Table 7. Calculated and experimental inversion barriers and calculated 1,1'-bond length for transition state of 2,2'-diiodobiphenyls.

Substituents		Calculated	Experimental		Calculated
4	4'	$\Delta H^{\ddagger}$ kcal mol^{-1}	$\Delta H^{\ddagger}$ [a] kcal mol^{-1}	$\Delta G^{\ddagger}$ [b] kcal mol^{-1}	1,1'-bond length Å
H	H	34.54	20.4[c]	23.7[c]	1.5096
H	NH_2	33.88	—	—	1.5031
NH_2	NH_2	33.40	19.3[c]	22.0[c]	1.4983
NH_2	NH_3^+	32.73	—	—	1.4918
NH_3^+	NH_3^+	34.81	21.5[d]	23.7[d]	1.5122
H	NO_2	34.60	—	—	1.5102
NH_2	NO_2	33.65	—	—	1.5008
NO_2	NO_2	34.93	—	—	1.5134
CO_2H	CO_2H	34.85	21.0[c]; 20.7[e]	23.9[c]; 23.6[e]	1.5127
CO_2^-	CO_2^-	34.59	20.9[f]	24.9[f]; (23.5[g])	1.5101

[a] Ref. 5. [b] Temperature 25°C; calculated from the data in Ref. 5. [c] DMF solution. [d] 0.5 N aq. ethanolic HCl. [e] EtOH solution. [f] 0.1 N aq. NaOH. [g] Ref. 16.

*Amino substituents.* Introduction of one 4-amino group in 2,2′-diiodobiphenyl results in a predicted $\Delta\Delta H^{\ddagger} = -0.66$ kcal mol^{-1}. Although no experimental evidence exists for the height of the barrier to inversion for 4-amino-2,2′-diiodobiphenyl, the effect is in the expected direction. Introduction of electron-releasing substituents into the 4-position of *ortho*-substituted biphenyls generally leads to a lowering of the barrier to inversion, as shown by the work of Hanford and Adams,[17] and more recent work by Michinori and Yamamoto.[18]

The predicted $\Delta\Delta H^{\ddagger} = -1.14$ kcal mol^{-1} on introduction of two amino groups is slightly less than twice the $\Delta\Delta H^{\ddagger}$ resulting from introduction of one amino group, suggesting that the effect is roughly additive with very little interaction between the two substituents in the 4,4′-positions. The agreement with the experimental $\Delta\Delta H^{\ddagger} = -1.1$ kcal mol^{-1} from the work of Harris *et al.*[5] is fair for this compound.

This treatment predicts a comparatively large decrease of the barrier to inversion on monoprotonation of 2,2′-diiodobenzidine, with $\Delta H^{\ddagger}$ for the monoprotonated species 0.67 kcal mol^{-1} lower than that for the free base. Here again there are no experimental data available for comparison with the model. However, substitution with two ammonium groups increases the barrier to inversion with a predicted $\Delta\Delta H^{\ddagger} = 0.27$ kcal mol^{-1}. This agrees qualitatively with the work of Harris *et al.*[5] 4,4′-Diammonium-2,2′-diiodobiphenyl has an energy barrier to inversion considerably higher than that of 2,2′-diiodobenzidine, with $\Delta\Delta H^{\ddagger} = 1.1$ kcal mol^{-1}. The experiment was done under conditions where 2,2′-diiodobenzidine presumably exists almost entirely as the dication in solution, and thus no conclusions concerning the barrier height for the monoprotonated species is possible. Circumstantial evidence in favor of a lower energy barrier to inversion for the monoprotonated species may perhaps be inferred from the fact that two groups of investigators [5,19] have reported failure to resolve 2,2′-dibromobenzidine despite numerous attempts. As mentioned, substitution with two ammonium groups in the 4,4′-positions raises the energy barrier to inversion for 2,2′-diiodobiphenyl, the enthalpy of activation being even higher than for the dianion of 4,4′-dicarboxy-2,2′-diiodobiphenyl, the species used in the optical resolution of 4,4′-dicarboxy-2,2′-diiodobiphenyl. One would expect a similar increase in the energy barrier to inversion for 2,2′-dibromobiphenyl on substitution with two ammonium groups in the 4,4′-positions. This should result in an enthalpy of activation for inversion of the same magnitude as that for 4,4′-dicarboxy-2,2′-dibromobiphenyl, *i.e.*, close to 18 kcal mol^{-1}, which is sufficient for resolution. A tentative explanation for the apparent unresolvability of 2,2′-dibromobenzidine could be that the monoprotonated species has a lower energy barrier to inversion than the free base. 4,4′-Diammonium-2,2′-dibromobiphenyl could be expected to have a quite low pK_a and would therefore tend to be in equilibrium with appreciable amounts of the monoprotonated species even in quite acidic solution, thus offering a lower-energy path for racemization. If this hypothesis is valid, then 2,2′-dibromobenzidine might be resolvable under conditions (strong resolving acid) making the diprotonated species predominant. It would also be very interesting to test the validity of the model by a study of the rate of racemization of 2,2′-diiodobenzidine as a function of H_0 to ascertain whether

the rate of racemization goes through a maximum in the region between the first and the second pK_a of the dication.

Nitro substituents. The calculated $\Delta\Delta H^{\ddagger} \approx 0.0$ kcal mol^{-1} on introduction of one nitro substituent in the 4-position of 2,2′-diiodobiphenyl may at first seem contrary to expectation. Introduction of one nitro substituent in the *para* position of a biphenyl is generally expected to increase the barrier. This expectation, however, is based on work by Kuhn and Albrecht,[20,21] who measured racemization rates of *1* and *1a* and noticed an increase of the barrier

1 Y = H

1a Y = NO$_2$
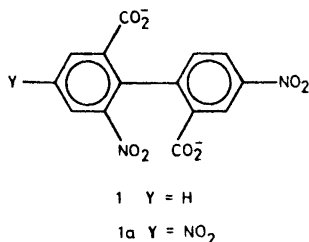
to inversion on introduction of a nitro substituent in the 4′-position of *1*. It is difficult to draw general conclusions from these examples since the racemization of *1* is subject to strong salt effects.[22] This is presumably the case with 1a also, although proof is lacking due to decomposition of the dipotassium salt of *1a*.[22] The calculated $\Delta\Delta H^{\ddagger} = 0.39$ kcal mol^{-1} for the introduction of two nitro substituents is in the expected direction. Recent work [22] has shown that the introduction of a 4′-nitro group into a diphenic acid already containing one nitro substituent increases the barrier to inversion by 0.8 kcal mol^{-1}. The change affects only the enthalpy of activation. The resulting diphenic acid concerned is not directly comparable to 4,4′-dinitro-2,2′-diiodobiphenyls because one nitro group is in the 6-position, but the effect of a 6-nitro group on the overlap energy would be expected to be similar to that of a 4-nitro substituent. The agreement between predicted effects of substitution and the sparse experimental evidence available seems to be fair for this class of substituents.

Unsymmetric 4,4′-substitution. An interesting point, which is still under debate, is whether the influence of polar 4- and 4′-substituents on the optical stability of biphenyls is exerted mainly through a change in conjugation of the transition state or by an inductive effect. If the substituents exert their influence on the racemization rate mainly through a mesomeric effect, then this factor should be enhanced if the nature of the substituents allows cumulative conjugation. On the other hand if the effect is mainly inductive in nature then the two different substituents should not interact and their effect on the racemization rate should merely be additive. The predicted $\Delta\Delta H^{\ddagger} = -0.89$ kcal mol^{-1} for 4-amino-4′-nitro-2,2′-diiodobiphenyl is less than the predicted $\Delta\Delta H^{\ddagger}$ for 4,4′-diamino-2,2′-diiodobiphenyl. This is not consistent with a predominating mesomeric effect with the two substituents interacting through cumulative conjugation and hence contrary to qualitative predictions [23] based

on elementary resonance theory. Unfortunately the validity of the prediction cannot be verified as no racemization data exist for this compound.

Carboxylic substituents. The predicted $\Delta\Delta H^{\ddagger} = 0.31$ kcal mol^{-1} for 4,4'-dicarboxy-2,2'-diiodobiphenyl and $\Delta\Delta H^{\ddagger} = 0.05$ kcal mol^{-1} for its dianion are in the expected direction, although the result for the dianion is far from good. The experimental $\Delta\Delta H^{\ddagger} = 0.6$ kcal mol^{-1} in DMF solution for the acid and $\Delta\Delta H^{\ddagger} = 0.5$ kcal mol^{-1} for the dianion in 0.5 N aq. NaOH solution are in the same order as the prediction. The reverse is true, however, if we choose the value for inversion of the acid in ethanol. The picture is clarified somewhat by the fact that the rate of inversion for the dianion is subject to strong salt effects as shown by the work of Berntsson *et al.*[16] Their work, however, permits only the calculation of a thermodynamically better defined $\Delta G^{\ddagger} = 23.5$ kcal mol^{-1} (25°C) for inversion at zero ionic strength. This is less than $\Delta G^{\ddagger}$ for inversion of the diacid both in DMF and ethanol solutions.[5] Furthermore, the work of Melander and Carter [14] on 4,4'-dicarboxy-2,2'-dibromobiphenyl supports the impression that the barrier to inversion is slightly lower for the dianion than for the diacid. The conclusion is that there is fair agreement between the predicted effects and known facts for this class of compounds also.

CONCLUSION

Westheimer and Mayer's minimization method [1] for calculation of energy barriers to inversion for *ortho*-halogenated biphenyls has been extended to include variation of the delocalization energy of the postulated planar transition state. It was the expectation of the present author that, by inclusion of this variable into the treatment, it might be possible to rationalize the available experimental data on the effect of polar 4,4'-substituents upon these barriers. The model used here to describe the configurational inversion of hindered biphenyls is moderately successful in relating the optical stability to the nature of the substituents in these positions. This lends some credibility to the predictions which cannot, at the present time, be tested by comparison with experiment.

Judging from the predicted energy barriers to inversion, the effect of polar 4-substituents on the optical stability of biphenyls appears to be best interpreted as being mainly inductive in nature. One cannot, however, exclude the possibility that the basis for this rationale is an artifact introduced by the model used to estimate the delocalization energy over the 1,1'-bond in the postulated planar transition state. To settle this question it will be necessary to have experimentally determined activation parameters for the racemization of unsymmetrically substituted 2,2'-dihalogenobiphenyls, *e.g.* 4-amino-4'-nitro-2,2'-diiodobiphenyl, or to study the rate of racemization of 2,2'-diiodobenzidine as a function of H_0.

The models used are admittedly very crude, the approximations employed in the calculation of the overlap energy over the 1,1'-bond of the planar transition state being particularly severe. In addition, the postulated planar transition state and neglect of the out-of-plane deformation of the benzene rings in the ground state probably involve oversimplifications in the case of the 2,2'-

diiodobiphenyls. They are presumably the cause of the failure of this treatment to predict adequately the difference in the energy barriers between corresponding 2,2'-dibromo and 2.2'-diiodo compounds. The calculated differences are of the order of 7 kcal mol^{-1}, compared to the experimental differences of approximately 2.6 kcal mol^{-1}. The argument of Harris *et al.*[5] for an unsymmetric transition state, with the interfering groups passing one at a time, may be a more reasonable model for the diiodo compounds. At the same time one would not expect the delocalization energy for the latter model to differ very much from that of the planar model. On departure from the planar model, however, the calculations would become exceedingly complex.

Finally it may seem more reasonable to attempt a complete minimization of the energy of the transition state and the ground state by semiempirical quantum chemical calculations on the 2,2'-dihalogenobiphenyls as such. This is not possible at the present time, however, as the INDO approximation includes only fluorine and lower elements, and the CNDO/2 approximation includes only elements through chlorine. In addition, even if a complete treatment were possible, the cost in computer time would be at least between one and two powers of ten higher than for the present treatment.

REFERENCES

1. Westheimer, F. H. and Mayer, J. E. *J. Chem. Phys.* **14** (1946) 733.
2. Westheimer, F. H. *J. Chem. Phys.* **15** (1947) 252.
3. Rieger, M. and Westheimer, F. H. *J. Am. Chem. Soc.* **72** (1950) 19.
4. Howlett, K. E. *J. Chem. Soc.* **1960** 1055.
5. Chua Cheung King Ling and Harris, M. M. *J. Chem. Soc.* **1964** 1825.
6. Dewar, M. J. S. *J. Am. Chem. Soc.* **74** (1952) 3341.
7. Suzuki, H. *Electronic Absorption Spectra and Geometry of Organic Molecules*, Academic, New York 1967, p. 267.
8. Allinger, N. L. *J. Org. Chem.* **27** (1962) 443.
9. Pople, J. A. and Beveridge, D. L. *Approximate Molecular Orbital Theory*, McGaw, New York 1970.
10. Dobosh, P. A. *Program 141 CNINDO*, Quantum Chemistry Program Exchange, Indiana University 1971, vol. 7.
11. Robertson, G. B. *Nature* **191** (1961) 593.
12. Hargreaves, A. and Rizvi, S. H. *Acta Cryst.* **15** (1962) 346.
13. Trotter, J. *Acta Cryst.* **14** (1961) 1135.
14. Melander, L. and Carter, R. E. *Acta Chem. Scand.* **13** (1964) 1138.
15. Harris, M. M. and Mitchell, R. K. *J. Chem. Soc.* **1960** 1905.
16. Berntsson, P., Wanger, M. and Carter, R. E. *Acta Chem. Scand.* **21** (1967) 879.
17. Hanford, W. E. and Adams, R. *J. Am. Chem. Soc.* **57** (1935) 1592.

18. Michinori, O. and Yamamoto, G. *Bull. Chem. Soc. Japan* **44** (1971) 266.
19. Searle, N. E. and Adams, R. *J. Am. Chem. Soc.* **56** (1934) 2112.
20. Kuhn, R. and Albrecht, O. *Ann.* **455** (1927) 272.
21. Kuhn, R. and Albrecht, O. *Ann.* **458** (1927) 220.
22. Carter, R. E. and Berntsson, P. *Acta Chem. Scand.* **23** (1969) 499.
23. Westheimer, F. H. In Newman, M., Ed., *Steric Effects in Organic Chemistry*, Wiley, New York 1956, p. 551.