STUDY OF CHIROPTICAL PROPERTIES OF SOME PIPERIDINE DERIVATIVES*

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Received January 7th, 1982

Chiroptical properties of (*S*)-(−)-1-methyl-2-phenylpiperidine and (*S*)-(−)-1-methyl-2-(2-tolyl)-piperidine have been studied. The preferred conformations have been calculated in gradient way on the basis of the CNDO/2 method, and the rotational forces have been calculated for them by direct procedure using the CNDO/S-CI wave function. For comparison of theory and experiment, molar fractions of the individual conformers have been calculated and used together with the rotational forces for construction of the CD spectrum which has been compared with the experimental CD spectrum. Absolute configurations of the mentioned compounds have been determined by chemical correlation.

When comparing theoretical values of rotational forces with an experimental CD spectrum, the latter is usually separated into Gaussian or Lorentz bands, and these separated bands are compared with individual rotational forces obtained by calculation. This procedure is correct with the compounds which can exist in only one conformation or those having one dominant conformation (*e.g.*[1]). With flexible molecules, of course, such case can occur when two or more conformers will have electronic transitions at the same wavelength. If we try to separate the resulting CD curve into individual subcurves, the solution is ambiguous, since the subcurves are linearly dependent, and more than one solution exist. Therefore, we chose another way for comparison of the calculated and experimental CD curves.

In calculating the CD spectrum we start with the presumption that each conformer of the flexible compound contributes its Cotton effects to the resulting spectrum which is then a superposition of all the said effects. The individual contributions of conformers depend not only on magnitude and sign of the rotational force of the considered transition but also on molar population of the conformer, *i.e.*, its molar fraction. As the experimental CD spectrum is measured at low concentrations when the Lambert–Beer law is obeyed, it can be stated that the contribution of each conformer is directly proportional to its mole fraction.

* Part LVIII in the series on Asymmetric Reactions; Part LVII: This Journal *44*, 2946 (1979).

The optimized geometries were taken as the basis for calculation of rotational forces. The calculation of the excited states was carried out according to Bené and Jaffé[2]. The CNDO/S wave function (for which we used the parametrization by Jaffé and coworkers[3], the repulsion integrals being calculated according to Mataga and Nishimoto[4]) was treated by the method of configuration interaction. Always 36 singlet excited configurations were used which were formed by combination of 6 highest occupied and 6 lowest unoccupied MO's. This number of configurations was shown by Richardson and coworkers[5] to be quite sufficient for the studied type of compounds. The wave function traeted by the LCI method (limited configuration interaction) was used for direct calculation of rotational forces according to Hoffmann and Gould[6] by a modified program[1], using the following formula:

$$R_{0j} = -1{\cdot}8413 \,.\, 10^{-22} \sum_{r,s} c_{\psi_r} c_{\psi_s} \langle \psi_0 | \nabla | \psi_r \rangle \langle \psi_s | \boldsymbol{r} \times \nabla | \psi_0 \rangle \Delta E_{r0} \,, \qquad (1)$$

where R means the rotational force (in SI units $C^2\ m^3\ s^{-1}$), c are the corresponding LCI coefficients, E is the diagonal element of the LCI matrix, and ψ are coefficients of the wave function corresponding to the singlet excited configurations. The rotational forces obtained in this way can be recalculated to molar ellipticity[7],

$$[\Theta]^0_{ij} = R_{ij}\lambda^0_{ij}(2{\cdot}3216 \,.\, 10^{-57} \sqrt{(\pi)}\, H^0_{ij})^{-1} \,, \qquad (2)$$

where λ^0 stands for wavelength (nm) of the electronic transition, and H^0 is the band half-width (nm). The individual bands are then superposed from the known wavelengths, band half-widths, molar ellipticities (deg m^2 mol^{-1}), and mole fractions to give the resulting spectrum (summation for all the conformers):

$$\text{resulting spectrum} = \sum_{i=1}^{n} \{c_i [\Theta]^0_i \exp(-2{\cdot}772\lambda_i^2 |H_i^2|\} \,. \qquad (3)$$

Equation (*3*) describes the course of the resulting CD curve depending on wavelength, the units of the calculated spectrum being identical with those of experimental spectrum. Obviously, comparison of the two curves cannot serve for comparing vibrational transitions of the aromatic chromophore, but we must focus our attention to the "envelope curves" only. For a $\pi-\pi^*$ transition, the band half-width is usually chosen 14 nm (ref.[8]) or 16 nm (ref.[9]). The half-width choice within the limits from 14 nm to 17 nm does not affect substantially the resulting CD spectrum.

Calculation of Mole Fractions of the Conformers

Equilibrium between two conformers is characterized by the equilibrium constant

$$K = [C_B]/[C_A] \,, \qquad (4)$$

which can be expressed by the Gibbs energy of the system:

$$K = \exp\left(-\Delta G/RT\right), \tag{5}$$

where generally

$$\Delta G = \Delta H - T\Delta S. \tag{6}$$

The individual terms can be determined from Eq. (7),

$$\Delta H = E_B - E_A, \tag{7}$$

where E are energies of the conformers calculated by the CNDO/2 method. As this energy must be known with relatively high accuracy (see Appendix 1), it is not sufficient to optimize one or two degrees of freedom of the molecular geometry, but it is necessary to optimize all coordinates of atoms. To obtain the accurate energies, we used the gradient optimization of molecular geometry based on CNDO/2 (ref.[10]). Both the energies and the optimized geometries of the conformers obtained in this way served as a basis for calculation of the rotational forces.

The entropy term of Eq. (6) consists of a rotational, a vibrational, and a translational contributions. The last contribution is zero in our case, *i.e.*, at equilibrium of the two conformers:

$$\Delta S_{\text{transl}} = 0. \tag{8}$$

The vibrational contribution depends on wave numbers of the vibrations and is expressed by Eq. (9),

$$\Delta S_{\text{vib}} = R[\sum(A/(e^A - 1) - \ln(1 - e^A)], \tag{9}$$

where

$$A = \boldsymbol{h}c\nu/\boldsymbol{k}T,$$

ν is wave number of the vibration, $\boldsymbol{h}$, c, $\boldsymbol{k}$, T have the usual physical meaning, and the summation is carried out over all the vibrations in the molecule. This contribution was neglected, *i.e.* $\Delta S_{\text{vib}} = 0$, whereby an error of 1% was introduced into the overall calculation of the equilibrium constant and, hence, into the value of mole fractions (see Appendix 2).

The rotational contribution to entropy is given by Eq. (10),

$$\Delta S_{\text{rot}} = 0{\cdot}5R \ln\left(I_a^B I_b^B I_c^B / I_a^A I_b^A I_c^A\right), \tag{10}$$

where I's are the main rotation moments of the conformers A and B (the origin of coordinates being placed at the centre of gravity of the molecular geometry).

The individual moments can be calculated from the known optimized coordinates of the conformers and atomic masses of the atoms. As in most cases the origin of coordinates is not in the centre of gravity of the conformer, it is necessary to calculate, besides the main moments of inertia (I_{xx}, I_{yy}, I_{zz}), also the deviation moments of inertia I_{xy}, I_{yz}, and I_{xz} (see Appendix 3). Then the product $I_a I_b I_c$ is given by Eq. (*11*).

$$I_a I_b I_c = \begin{vmatrix} +I_{xx} & -I_{xy} & -I_{xz} \\ -I_{xy} & +I_{yy} & -I_{yz} \\ -I_{xz} & -I_{yz} & +I_{zz} \end{vmatrix} \qquad (11)$$

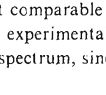
Using Eqs (*5*) through (*11*) we obtain the expression Eq. (*12*) for calculation of the equilibrium constant,

$$K = \exp\left(-[(E_B - E_A) - T\Delta S_{rot}]/RT\right), \qquad (12)$$

where the translational and rotational contributions to entropy are calculated precisely, the vibrational contribution is loaded with a small error (see Appendix 2), and the enthalpy term is loaded with the error given by accuracy of calculation of the optimized geometries of the conformers (see Appendix 1). The resulting calculated curve of CD spectrum is thus loaded with an error of about 1%, which is negligible for comparisons with the experimental spectrum. For a greater number of conformers the calculation of mole fractions is quite analogous, the starting equilibrium being more complex only.

From Eq. (*12*) it follows that the enthalpy term plays a dominant role, whereas the entropy term does not make itself felt until at comparable energies of the conformers. Also the Eq. (*12*) enables to compare the experimental spectrum measured at the absolute temperature T with the calculated spectrum, since absolute temperature is involved in Eq. (*12*).

I, R = C_6H_5
II, R = 2-CH_3—C_6H_4



III, R = C_6H_5
IV, R = 2-CH_3—C_6H_4

Calculation of the Preferred Conformations and CD *Spectrum of 1-Methyl-2-phenylpiperidine* (I)

1-Methyl-2-phenylpiperidine is a relatively flexible compound. Energy of its molecule will be most affected by the following degrees of freedom: rotation of phenyl

group, configuration of methyl group at nitrogen atom, and conformation of the six-membered ring (and the therewith connected position of phenyl group – equatorial or axial). The following variations were considered for the basic assessment of the geometries: *1*) the phenyl group axial or equatorial, *2*) the methyl group axial or equatorial, and *3*) the conformation of six-membered ring boat, chair, or twist boat. For all these conformations (twelve combinations) the dependence of energy of the molecule on rotation (*i.e.* angle) of phenyl group was followed by the EHT method. Nineteen geometries were obtained whose energies form minima at the energy hypersurface. For further calculation seven geometries only were taken into account (*Ia*–*Ig*) which have the lowest energy values (*Id* is given for illustration), and these geometries were used as the starting assessment for the optimization gradient procedure[10] working on the basis of CNDO/2 in the standard parametrization[11]. In the seven cases calculated the six-membered ring has a somewhat distorted chair conformation. The distortion is due to sterical requirements of the bulky phenyl substituent. The β angle included by the opposite bonds $C_{(1)}$—$C_{(2)}$ and $C_{(4)}$—$C_{(5)}$ of the six-membered ring varies within the limits from 3° to 14° (Table I). The calculated values of energies of the conformers, α angles, rotational forces, wavelengths of electronic transitions, and recalculated molar ellipticities are given in Table I. Fig. 1 represents course of experimental CD curve of compound *I* (in cyclohexane) along with that of the theoretically calculated CD spectrum. The two curves show a very good agreement.

Calculation of the Preferred Conformations and CD *Spectrum of* 1-*Methyl*-2-(2-*tolyl*)*piperidine* (II)

Energy of the molecule is affected by rotation of the tolyl group, configuration of the methyl group at nitrogen atom, and by conformation of the six-membered ring. Dependence of the energy of the molecule on the rotation of tolyl group was followed by the EHT method. Out of the 26 geometries obtained, whose energies correspond to local minima at the energy hypersurface, three conformers (*IIa*–*IIc*) with the lowest energy were taken as starting point for the gradient optimization procedure. The obtained three optimized geometries were used for calculation of the rotational forces and wavelengths of the electronic transitions. In all the three cases the piperidine ring has (as in *I*) the shape of slightly distorted chair. Also effect of 2-tolyl as a substituent is greater, since one conformation is wholly preferred in the case of *II* (namely *IIa*), in contrast to the compound *I* whose conformations *Ia* and *Id* have close energy values. The other conformers of the compound *II* have so high energies that their effect on the resulting CD spectrum does not make itself felt. The calculated values are given in Table I. Fig. 2 gives both the experimental and the theoretical course of the CD curve for compound *II*, and the two curves agree very well.

TABLE I

The calculated values for (*R*)-(+)-1-methyl-2-phenylpiperidine (*I*) and (*S*)-(−)-1-methyl-2-(2-tolyl)piperidine (*II*)

Conformer	Energy kJ mol^{-1}	α degrees	β degrees	Dipole moment C m . 10^{-30}	Mol. fraction	Rotational force C^2 m^3 s^{-1} . . 10^{-56}	λ nm	$[\Theta]$ deg. m^2 mol^{-1}
Ia	3·94	74	8	5·08	0·1816	− 4·8	261·58	−0·18
Ib	30·95	176	11	5·85	0·000003	6·0	260·28	0·22
Ic	25·28	179	5	4·76	0·000027	11·6	266·05	0·44
Id	0·00	124	3	4·50	0·81839	10·8	263·47	0·41
Ie	42·99	64	12	4·78	0·00000002	− 148·1	261·61	−5·16
If	41·84	153	8	5·91	0·00000003	4·5	262·86	0·17
Ig	41·02	65	14	6·60	0·00000004	− 2·6	260·57	−0·10
IIa	0·00	93	9	—	0·99999996	− 2·6	268·19	−0·10
IIb	45·04	304	3	—	0·00000001	2·1	265·61	0·08
IIc	42·03	189	14	—	0·00000003	− 1·5	264·51	−0·06

Synthesis of Compounds I *and* II *and Determination of Their Absolute Configurations*

Reactions of N-methyl-2-piperidone with the respective Grignard reagents gave the corresponding unsaturated bases, 1-methyl-2-phenyl-2-piperideine (*III*) and 1-methyl-2-(2-tolyl)-2-piperideine (*IV*), which were reduced with formic acid to give the racemic bases 1-methyl-2-phenylpiperidine (*I*) and 1-methyl-2-(2-tolyl)piperidine (*II*). The saturated bases were resolved to optical antipodes with (−)-dibenzoyltartaric acid. Absolute configuration of the optically active compounds *I* and *II* was determined by their chemical correlation with N-methylpipecolinic acid whose absolute configuration is known[12]. The phenyl (2-tolyl) group was degraded oxidatively to carboxyl after previous substitution. The starting bases were nitrated with nitric acid, the nitro derivatives were reduced to amines; their diazotization and hydrolysis gave the respective phenols which were oxidized with chromium trioxide in sulphuric acid medium. 1-Methyl-2-pipecolinic acid was isolated after transformation to ethyl ester[13]. In this way it was proved unambiguously that the laevorotatory compounds *I* and *II* have absolute configuration *S*.

CONCLUSIONS

The described calculation method of CD spectra of the compounds *I* and *II* proved to be satisfactory, since the agreement between the experimental and the calculated curves is obvious. Thus the separation of CD spectrum into individual Gaussian

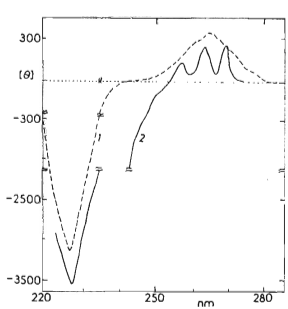


FIG. 1

CD Spectrum of (*S*)-(−)-1-methyl-2-phenylpiperidine. *2* experimental (in cyclohexane), *1* calculated

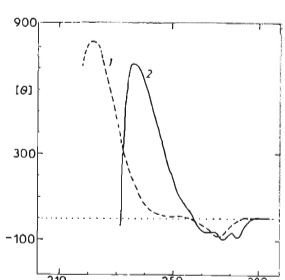


FIG. 2

CD Spectrum of (*S*)-(−)-1-methyl-2-(2-tolyl)-piperidine. *2* experimental (in cyclohexane), *1* calculated

bands (which is uncertain for conformationally flexible compounds) could be removed. The comparison of theoretical and experimental values is also more correct here, because introduction of the entropy term into calculation of molar fractions enables to take into account the temperature at which the experimental spectrum is measured. The determination of absolute configuration of compounds *I* and *II* confirmed the known fact that introduction of methyl group in *ortho* position of an aromatic chromophore changes (at the maintained absolute configuration of the compound) the sign of the first Cotton effect in CD spectrum. The calculation confirmed this fact. Another communication[14] deals with the problem whether the said property is due to changed conformation or to changed direction of the vectors of transition dipole moments or to some other circumstance.

EXPERIMENTAL

(*S*)-(−)-1-Methyl-2-phenylpiperidine (*I*)

The solution of Grignard reagent prepared from 30·4 g magnesium, 164·3 g bromobenzene and 350 ml ether was treated with 30·0 g 1-methyl-2-piperidone (b.p. 98—101°C/2 kPa) added drop by drop. The ether was distilled off, the mixture was poured onto ice, alkalized with 40·0 g barium hydroxide, the base was steam-distilled, the distillate was neutralized with 5M-HCl and concentrated; biphenyl was extracted with benzene and the solution was evaporated until dry. Yield 48·0 g (86%) 1-methyl-2-phenyl-1-piperideinium chloride.

1-Methyl-2-phenyl-1-piperideinium chloride (48·0 g) was heated with 125 ml 98% formic acid and 100 g freshly remelted potassium formate at 150—180°C 8 h to give 30·1 g (75·5%) 1-methyl-2-phenylpiperidine, b.p. 100—103°C/1·5 kPa. For $C_{12}H_{17}N$ (175·3) calculated: 82·23% C, 9·78% H, 7·99% N; found: 82·06% C, 9·82% H, 7·89% N.

Solution of 30·7 g (−)-dibenzoyltartaric acid in 150 ml ethanol was mixed with 15·0 g 1-methyl-2-phenylpiperidine in 25 ml ethanol to give 26·7 g salt with m.p. 162·5—163·5°C which increased to 176·0—176·5°C after four crystallizations from methanol; $[\alpha]_D^{22}$ −89·5° (c = 1·3, methanol). For $C_{30}H_{31}NO_8$ (553·5) calculated: 67·54% C, 5·85% H, 2·63% N; found: 67·94% C, 5·90% H, 2·57% N.

The salt was converted to 2·9 g base *I*, b.p. 95—98°C/1·6 kPa, $[\alpha]_D^{21}$ −154·4° (net substance). For $C_{12}H_{17}N$ (175·3) calculated: 82·23% C, 9·78% H, 7·99% N; found: 82·58% C, 9·70% H, 7·97% N. ^{1}H NMR spectrum (ppm, C^2HCl_3): 7·28 (s, 5 H), 2·0 (s, 3 H), 1·24—1·88 (m, 6 H), 2·99 (m, 2 H), 1·9—2·4 (m, 1 H).

(*S*)-(−)-1-Methyl-2-(2-tolyl)piperidine (*II*)

The solution of Grignard reagent prepared from 19·5 g magnesium and 136·0 g 2-bromotoluene in 550 ml ether reacted as above with 30·0 g 1-methyl-2-piperidone to give 30·0 g (50%) 1-methyl-2-(2-tolyl)-1-piperideinium chloride. The product was heated with 90 g 98% formic acid and 60·0 g remelted potassium formate at 160°C 8 h to give 16·3 g (64%) 1-methyl-2-(2-tolyl)-piperidine, b.p. 122—124°C/1·73 kPa. The prepared base (15·9 g) was dissolved in 50 ml ethanol and treated with solution of 30·1 g (−)-dibenzoyltartaric acid in 200 ml ethanol to give 27·0 g acid salt which separated on standing overnight; m.p. 161·5—162·5°C. Four crystallizations from methanol gave 7·8 g salt melting at 167·5—168·5°C, $[\alpha]_D^{21}$ −77·8° (c = 1·7, methanol). For $C_{31}H_{33}NO_8$ (547·5) calculated: 68·00% C, 6·07% H; found: 68·14% C, 6·25% H.

The above salt was converted into 2·0 g base *II*, b.p. 108–110°C/1·3 kPa, $[\alpha]_D^{23}$ −108·7° (net substance). For $C_{13}H_{19}N$ (189·3) calculated: 82·48% C, 10·11% H, 7·40% N; found: 82·39% C, 10·21% H, 7·19% N. ^{1}H NMR spectrum (ppm, C^2HCl_3): 3·04 (d, 2 H, J = 12 Hz), 2·34 (s, 3 H), 7·48 (d, 1 H, J = 6 Hz), 7·08 (s, 3 H), 2·0 (s, 3 H), 1·94–2·28 (m, 1 H), 1·18–1·92 (m, 6 H).

Correlation of (*S*)-(−)-1-Methyl-2-phenylpiperidine ((*S*)-*I*) with Ethyl (*S*)-(−)-1-Methyl-2-pipecolinate

7·0 g (*S*)-*I* $[\alpha]_D^{22}$ −58·0°, net substance) was dissolved in 5 ml chloroform and nitrated with a mixture of 6 ml nitric acid (ϱ_{20} = 1·4 g cm^{-3}) and 8·4 ml concentrated sulphuric acid with cooling at 5–10°C; then the reaction mixture was stirred at room temperature 1 h and boiled 20 min. After dilution with water and alkalization, the product was extracted with 5 × 50 ml chloroform. Chloroform was evaporated, and the raw nitro derivative was dissolved in 60 ml 25% HCl and refluxed with 20·0 g mossy tin 4 h. After cooling the base was liberated and steam-distilled, the distillate was acidified and concentrated, alkalized with sodium hydroxide, and extracted with ether. The extract was dried and evaporated, the residue was distilled with column to give 5·4 g amine, b.p. 97–107°C/0·062 kPa, m.p. 77–78°C. For $C_{12}H_{18}N_2$ (190·3) calculated: 75·74% C, 9·54% H, 14·72% N; found: 75·96% C, 9·73% H, 14·63% N.

5·1 g amine was dissolved in 100 ml 3M-H_2SO_4, the solution was cooled at 0°C and diazotized by addition of 2·0 g sodium nitrite dissolved in 15 ml water. The diazonium salt formed was hydrolyzed by one hour refluxing. The solution was concentrated to a half volume and treated with 20 ml concentrated sulphuric acid. This solution was added with cooling and shaking into a suspension of 25·0 g chromium trioxide in 50 ml concentrated sulphuric acid and 10 ml water, whereupon the mixture was boiled 4 h. After cooling the mixture was diluted with water, and SO_4^{2-} and Cr^{3+} ions were removed by precipitation with hot barium hydroxide solution: the precipitate was filtered and washed twice with hot water, and the combined filtrates were evaporated. The evaporation residue was rid of water (as water–ethanol–benzene azeotrope) and mixed with 50 ml ethanol, saturated with gaseous hydrogen chloride and refluxed 4 h. The mixture was concentrated, the residue was evaporated and dissolved in 15 ml water and washed with ether. After alkalization with potassium carbonate, the ester was extracted with 5 × 50 ml ether, the aqueous layer was treated with 1·5 ml 10% sodium hydroxide and again extracted with 3 × 50 ml ether. The combined ether extracts were dried over sodium sulphate, ether was evaporated, and the residue was distilled through a column to give 0·87 g ester, b.p. 83–90°C/1·7 kPa, $[\alpha]_D^{20}$ −4·72° (net substance).

Correlation of (*R*)-(+)-1-Methyl-2-(2-tolyl)piperidine ((*R*)-*II*) with Ethyl (*R*)-(+)-1-Methyl-2-pipecolinate

7·65 g (*R*)-*II*, $[\alpha]_D^{23}$ +31·9° (net substance) was treated as in the above case. Reduction of the nitro derivative gave 2·9 g amine, b.p. 121–127°C/0·2 kPa. The ethyl ester (0·24 g) had b.p. 83–91°C/1·5 kPa, $[\alpha]_D^{23}$ +3·13° (c = 9·2, ethanol). For $C_9H_{17}NO_2$ (171·2) calculated: 63·12% C, 10·01% H, 8·18% N; found: 63·36% C, 10·19% H, 8·34% N. ^{1}H NMR spectrum (ppm, C^2HCl_3): 2·3 (s, 3 H), 1·30 (t, 3 H, J = 6 Hz), 1·46–2·00 (m, 6 H), 2·62–3·08 (m, 2 H), 2·44 (s, 1 H), 4·24 (q, 2 H, J = 7 Hz).

APPENDIX

1) Calculation of energy and geometry optimization by the gradient method[10] necessitates to carry out the calculations to relatively small gradients. In our case the value 1 kJ mol^{-1} . nm^{-1}

was chosen for the Euclidian gradient norm, the maximum change of value of one coordinate being 0·0001 nm. In this case the energy calculation is loaded with the following error (*e.g.* for the compound *II*, number of atoms 33, *i.e.* 99 coordinates):

$$\|G\| = (\sum(\partial E/\partial s_i)^2)^{1/2} \doteq (\sum(\Delta E/\Delta s_i)^2)^{1/2} \qquad (A\text{-}1)$$

$$\Delta E = \|G\| \,.\, (\sum(1/\Delta s_i^2))^{-1/2} \qquad (A\text{-}2)$$

and with the use of triangular inequality

$$\Delta E \leqq \|G\| \,.\, (1/\sum(1/\Delta s_i)) \,, \qquad (A\text{-}3)$$

where G is gradient, E is energy of the compound, and s are the individual optimized coordinates. On introducing the values $n = 99$, $\|G\| = |1{\cdot}0|$, and $\Delta s = 0{\cdot}0001$ we obtain for the error of the calculated energy the value $\Delta E = 0{\cdot}01$ kJ mol^{-1}. Thus the error for two conformers is 0·02 kJ . . mol^{-1} at the most, which is the same as the error of enthalpy term in calculation of the equilibrium constants. The molar fractions are then computed with a quite negligible error of about 0·02%.

2) Conformational changes are accompanied relatively rarely by changes in vibration frequences, nevertheless, the calculation error due to these changes must be considered. Moreover, in the molecules studied one section of the molecule behaves vibrationally quite independently (phenyl or 2-tolyl groups), and conformation changes have almost no effect on this section and its vibrations. Let us calculate the approximate error in free energy due to neglection of the entropic vibrational contribution ($\Delta S_{vib} = 0$), *e.g.*, for the compound *II*. The molecule has 33 atoms, *i.e.* 93 degrees of freedom. Let us have an average vibration scale from about 600 cm^{-1} to 3 500 cm^{-1}; then for two conformers differing *e.g.* by 10 cm^{-1} in ten vibrations, the error in calculation of equilibrium constant by Eq. (*9*) will be about 0·7%.

3) Let the coordinates of the centre of gravity of the molecule be denoted with the index 0; then the coordinates of atoms are:

$$x_0 = (\sum m_i x_i')/M \quad y_0 = (\sum m_i y_i')/M \quad z_0 = (\sum m_i z_i')/M \,, \qquad (A\text{-}4)$$

where m means atomic mass of the individual atoms, M is the molecular mass of the compound ($M = \sum m_i$). On going from the coordinates x', y', z' which are quite general, to the coordinate system x, y, z whose origin is identical with the centre of gravity of the molecule, we must carry out the transformation:

$$x = x' - x_0 \quad y = y' - y_0 \quad z = z' - z_0 \,. \qquad (A\text{-}5)$$

For the main moments of inertia we obtain:

$$I_{xx} = \sum m_i(y_i^2 + z_i^2) \,, \qquad (A\text{-}6)$$

$$I_{yy} = \sum m_i(x_i^2 + z_i^2) \,, \qquad (A\text{-}7)$$

$$I_{zz} = \sum m_i(x_i^2 + y_i^2) \,, \qquad (A\text{-}8)$$

and for the deviation moments:

$$I_{xy} = \sum m_i x_i y_i \,, \qquad (A\text{-}9)$$

$$I_{xz} = \sum m_i x_i z_i \,, \qquad (A\text{-}10)$$

$$I_{yz} = \sum m_i y_i z_i \,. \qquad (A\text{-}11)$$

Let us then carry out substitution for I_{xx} from (*A-5*) and (*A-6*) to obtain

$$I_{xx} = \sum m_i(y_i' - y_0)^2 + \sum m_i(z_i' - z_0)^2 . \qquad (A\text{-}12)$$

By multiplication of the expressions in brackets, substitution of y_0 and z_0 with the use of (*A-4*), and with respect to the equality $M = \sum m_i$ we obtain:

$$I_{xx} = \sum m_i(y_i'^2 + z_i'^2) - 1/M(\sum m_i y_i')^2 - 1/M(\sum m_i z_i')^2 \qquad (A\text{-}13)$$

In this way we leave the coordinates bound by the condition that the origin of coordinates must be identical with the centre of gravity of the molecule. In similar way we can obtain the expressions independent of choice of coordinates also for the other main and deviation moments of inertia. For calculation of the product $I_a I_b I_c$, the equations (*A-13*) through (*A-18*) are introduced in Eq. (*11*).

$$I_{yy} = \sum m_i(x_i'^2 + z_i'^2) - 1/M(\sum m_i x_i')^2 - 1/M(\sum m_i z_i')^2 \qquad (A\text{-}14)$$

$$I_{zz} = \sum m_i(x_i'^2 + y_i'^2) - 1/M(\sum m_i x_i')^2 - 1/M(\sum m_i y_i')^2 \qquad (A\text{-}15)$$

$$I_{xy} = \sum m_i x_i' y_i' - 1/M(\sum m_i x_i')(\sum m_i y_i') \qquad (A\text{-}16)$$

$$I_{xz} = \sum m_i x_i' z_i' - 1/M(\sum m_i x_i')(\sum m_i z_i') \qquad (A\text{-}17)$$

$$I_{yz} = \sum m_i y_i' z_i' - 1/M(\sum m_i y_i')(\sum m_i z_i') \qquad (A\text{-}18)$$

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Translated by J. Panchartek.