CONFORMATIONAL FLEXIBILITY IN OPEN CHAIN MOLECULES: CHIRAL AND ACHIRAL ALKANES

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Abstract—Conformational partition functions of chiral and achiral alkanes have been computed by using a continuum approach (instead of rotational isomeric state approximations). The accessible conformational space per bond depends upon the structure of the compound and is only in the range of 5–13% of the maximum accessible range. In order to partly overcome the intrinsic ambiguity of the term "conformational flexibility", the distinction between *number* flexibility (a measure of the number of accessible energy minima) and *space* flexibility (a measure of the total allotted space) is proposed. Further, the conformational versatility of each bond of a molecule is evaluated in terms of the *a priori* probability density function of that bond, and it is shown that the use of this function permits a comparison of the relative conformational flexibilities of the individual bonds, which is particularly useful for molecules having more than two rotation angles (where the conventional energy maps cannot be used). Optical rotations are calculated for a series of chiral alkanes by combining the continuum approach for conformational analysis and a recent optical activity calculation scheme. Contributions of single bonds to the molar optical rotation are evaluated and discussed. The influence of temperature upon conformational and chiral properties is evaluated.

In a previous paper[1] one of the authors attempted to order molecules according to an approximate scale of conformational flexibility/rigidity. That work had been carried out using the traditional 3-state isomeric state approximation in which bonds can assume only the 3 ideally staggered conformations (t, $g+$ and $g-$). The "flexibility number" F of a molecule having n torsion angles was simply evaluated as $F = \ln Z/n \cdot \ln 3$ where Z is the molecular conformational partition function, and F can vary between 0 (maximum rigidity) and 1 (maximum flexibility).

Although this work was instrumental in elucidating some of the concepts underlying conformational rigidity, its validity was limited by the approximations inherent in the simple 3-state rotational isomeric state scheme. The most drastic of these approximations is certainly that only one single value of the torsion angle is allowed for each bond instead of a continuous range of values. The limits of the 3-state rotational isomeric state scheme have been pointed out in the past by other authors,[2–8] and attempts to surpass its limitations in connection with optical activity calculations have been presented by Brewster.[4]

In small molecules it is possible to perform a conformational analysis without the limiting assumptions of a rotational isomeric state scheme, by detailed consideration of the potential energy hypersurface of the entire molecule. Such a continuum approach is used here.

The conformational potentials of a variety of alkanes have been evaluated by many authors and published in a series of papers.[9] The aim of this contribution is not to add one more estimate of the conformational energies of such compounds, but to elucidate in particular the following points: (a) the potential energy hypersurfaces of some alkane molecules, and the conformational "thermodynamic"[1] flexibility associated with it; (b) the conformational versatility of each individual bond, which

here will be presented in terms of "*a priori* probability density" of torsion angles; (c) the optical activity, calculated in a detailed manner for a series of paraffins containing *t*-butyl groups.

These computations consider the effect of temperature on the parameters.

BASIS OF THE CALCULATION

Conformational potential energy

The conformational potential energy of a structure in a specified conformation was estimated with "semiempirical potential functions" taken from the literature.[8] For these calculations the relative potential energy of a conformation is assumed to be the sum of contributions from "intrinsic torsional potentials" E_{tt} and "non-bonded interactions" E_{vdw} of atoms or groups that are separated by more than two bonds. For E_{tt} a threefold torsional potential with a barrier of 2.8 kcal mol^{-1} was used for each C–C bond. The nonbonded interactions E_{vdw} were assessed with the Lennard–Jones 6–12 pair potential.[8] Bond lengths and bond angles were held fixed at given values. Except for methyl groups that were approximated by a special pseudo-atom, all atoms were included explicitly. All parameters are tabulated in Table 1. We consider the calculated values to be reasonably reliable up to *ca* 5 kcal mol^{-1} over the absolute minima. Contributions of kinetic energy to the total conformational energy were ignored.
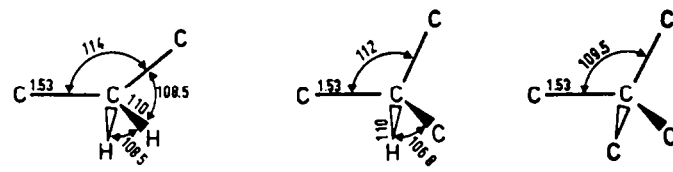
Calculation of optical rotation

The optical rotation of a given conformation of an alkane can be estimated with Brewster's uniform conductor model,[11,12] which is a development of an older concept.[10,13] In this "uniform conductor model" the contribution of an individual segment of three consecutive bonds (a "skew conformational unit") to the total (molar) optical rotation is

$$[\Delta m] = C_{ij} \sin \gamma$$

where γ is the dihedral angle and the square brackets

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Table 1. Parameters for the energy calculations

$$E_{ij} = a_{ij}/r_{ij}^{12} - c_{ij}/r_{ij}^{6}$$

a_{ij} (kcal $\mathring{A}^{12}$ mol^{-1})

	H	C	CH$_3$
H	7 279	56 770	147 738
C		398 343	968 311
CH$_3$			2 328 637

c_{ij} (kcal $\mathring{A}^{6}$ mol^{-1})

	H	C	CH$_3$
H	47.13	127.93	228.79
C		365.99	643.20
CH$_3$			1137.03

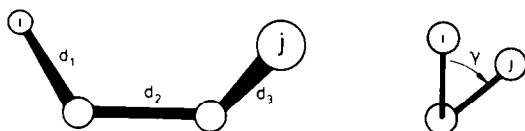$$E_{it}(\phi) = 1.4 \, (\, 1-\cos 3\phi) \qquad , \text{kcal mol}^{-1}$$

Fig. 1. Brewster's "skew conformational unit".

denote a molar quantity. For a unit with tetrahedral bond angles and two central C-atoms, C_{ij} becomes

$$C_{ij} \approx \frac{10^{10}}{\lambda^2} \frac{d_1 d_2 d_3}{(d_1 + d_2 + d_3)^2} f(\bar{n}) \sum_3 \Delta R \lambda$$

(see Fig. 1), where λ is the wavelength in $\mathring{A}$, the d_i are the bond lengths (in $\mathring{A}$) and ΔR_λ are bond- and group-refractivities of the three bonds (in units of ml mol^{-1}) and $f(\bar{n}) = (\bar{n}^2 + 2)^2/9\bar{n}$ where $\bar{n}$ is the refractive index of the medium. It varies slowly with $\bar{n}$ for $1 \leq \bar{n} \leq 2$, and we take $f(\bar{n}) = 1.25$ ($\hat{=} \bar{n} \approx 1.4062$) throughout this paper. The contribution of a bond, $[\Delta M]$, to the total molar optical rotation is the sum of all $[\Delta m]$ of "skew conformational units" that contain this bond as center. For alkanes, with torsion angles as defined below, one obtains

$$[\Delta M] = \sum_6 [\Delta m] = K_1 \sin \phi + K_2 \cos \phi$$
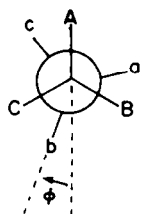
where

$$K_1 = (C_1 + C_3 - 2C_3)/2$$
$$K_2 = (C_1 - C_3)3^{1/2}/2$$

with

$$C_1 = C_{Aa} + C_{Bb} + C_{Cc}$$
$$C_2 = C_{aB} + C_{bC} + C_{cA}$$
$$C_3 = C_{Ab} + C_{Bc} + C_{Ca}$$

Values for C_{ij} for $\lambda = 589.3$ nm, that are calculated using Vogel *et al.*'s refractivity data,[14] are shown in Table 2. The computed optical rotation (in degrees cm^2 dmol^{-1}) for a structure (bond) and its enantiomeric structure are given as an example in Fig. 2.

The total molar optical rotation for a defined molecular conformation is the sum of all bond contributions:

$$[M] = \sum_n [\Delta M_n].$$

More details about this calculation scheme can be found in a recent work of one of us.[15]

Averages over conformation space

The absolute conformational potential minimum for a

Table 2. Constants C_{ij} for alkanes at $\lambda = 589.3$ nm

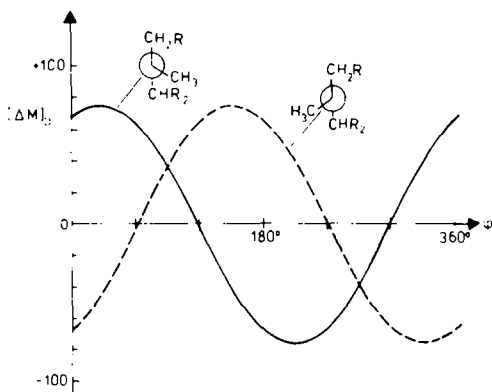| i	j	C_{ij}^a
H	H	224.3
H	CH$_2$	502.7
H	CH$_2$R	482.2
H	CHR$_2$	461.6
H	CR$_3$	441.1
CH$_3$	CH$_3$	864.2
CH$_3$	CH$_2$R	840.7
CH$_3$	CHR$_2$	817.1
CH$_3$	CR$_3$	793.6
CH$_2$R	CH$_2$R	817.1
CH$_2$R	CHR$_2$	793.6
CH$_2$R	CR$_3$	770.0
CHR$_2$	CHR$_2$	770.0
CHR$_2$	CR$_3$	746.4
CR$_3$	CR$_3$	722.9

^{a}In degrees cm^2 dmol^{-1}.

Fig. 2. Dependence of the optical rotation (in degrees $cm^2 dmol^{-1}$) from the torsion angle for two enantiomeric structural units.

given structure is called E_{min}, and the relative energy of a given conformation is

$$E^*(\phi) = E(\phi) - E_{min}$$

where the vector ϕ is composed of all values of ϕ_i for the bonds i, i.e. $\phi = (\phi_1, \phi_2, \ldots, \phi_n)$. The conformational partition function is then

$$Z = \int_{\{\phi\}} \exp(-E^*(\phi)/RT)\pi_i d\phi_i$$

where $\{\phi\}$ denotes the entire accessible ϕ-space. Integration was performed with the trapezoidal rule, and step sizes of usually 5–10°. The average optical rotation for the bond i is given by

$$\langle[\Delta M_i]\rangle = Z^{-1} \int_{\{\phi\}} [\Delta M_i] \exp(-E^*(\phi)/RT)\pi_i d\phi_i$$

and the average optical rotation of the whole molecule is just

$$\langle[M]\rangle = \sum_i \langle[\Delta M_i]\rangle.$$

For the actual calculation of $\langle[\Delta M_i]\rangle$ the trigonometric averages $\langle\sin\phi_i\rangle$ and $\langle\cos\phi_i\rangle$ were used.

Finally, we introduce an "*a priori* probability density function" for the angle ϕ_i, ψ_i, that is defined by

$$\psi_i = \psi_i(\phi') = Z^{-1} \int \exp(-E^*(\phi)/RT) \pi_{j\neq i} d\phi_j,$$

$$\{\phi\}|\phi_i = \phi'.$$

ψ_i measures the probability of the angle ϕ_i to assume the value ϕ'. It is normalized, so that

$$\int_{-\pi}^{+\pi} \psi_i d\phi_i = 1.$$

For compounds containing a t-butyl group and more than two torsion angles to be considered (as in the last 5 cases in Table 3), the conformational partition function of the whole molecule was assumed to be factorizable,

$$Z = Z'Z_{tb}$$

where Z_{tb} is the partition function of 2,2-dimethylbutane and Z' the corresponding value for the molecule that carries a methyl group instead of the t-butyl group. This approximation considerably shortens the numerical evaluations, and finds justification in the symmetry of the t-butyl group.

As already mentioned, an attempt to refine optical activity calculations beyond the limits of the 3-state rotational scheme has been presented by Brewster,[4] who introduces the concept of "conformational sept". The corresponding calculation procedure is also very successfull in predicting the optical rotation of paraffines.

GENERAL CONSIDERATIONS ON THE FLEXIBILITY OF ALKANES

In order to compare the conformational flexibility of different molecules we will use the function $z/2\pi$ where $z = \sqrt[n]{(Z)}$ and n is the number of bonds around which rotation is considered. The property $z/2\pi$ can vary between 0 and 1, and expresses the fraction of con-

Table 3. Conformational properties of alkanes

Compound[a]	$100 \cdot Z^{1/n}/2\pi$[b]	$d \ln Z^{1/n}/d \ln T$
— 2,2-dimethylbutane	11.8	—[c]
— 2,2,3-trimethylbutane	9.6	—[c]
4 n-pentane	13.0	0.852
5 2-methylpentane	10.8	0.768
5a 3-methylpentane	12.3	0.704
6 2,2-dimethylpentane	9.8	0.545
7 (S)-2,3-dimethylpentane	7.3	0.728
8 3,3-dimethylpentane	7.3	0.737
22 (R)-2,2,3-trimethylpentane	7.3	0.548
22a 2,3,3-trimethylpentane	6.3	0.633
22b 2,3,4-trimethylpentane	5.6	0.545
12a (3R,5S)-2,2,3,5-tetramethylheptane	7.7	0.487
12b (3S,5S)-2,2,3,5-tetramethylheptane	6.9	0.645
31 (3S,5S)-2,2,3,5,6-pentamethylheptane	7.4	0.424
25 2,2,3,5,7,8,8-heptamethylnonane(syndio)	6.9	0.339
14b (3S,5S,7R)-2,2,3,5,5,7,8-hexamethylnonane(iso)	7.0	0.504

[a]The same numerals as in Ref. 1 have been used (except that in Ref. 1 they are Roman).
[b]Calculated at 300 K.
[c]Not determined.
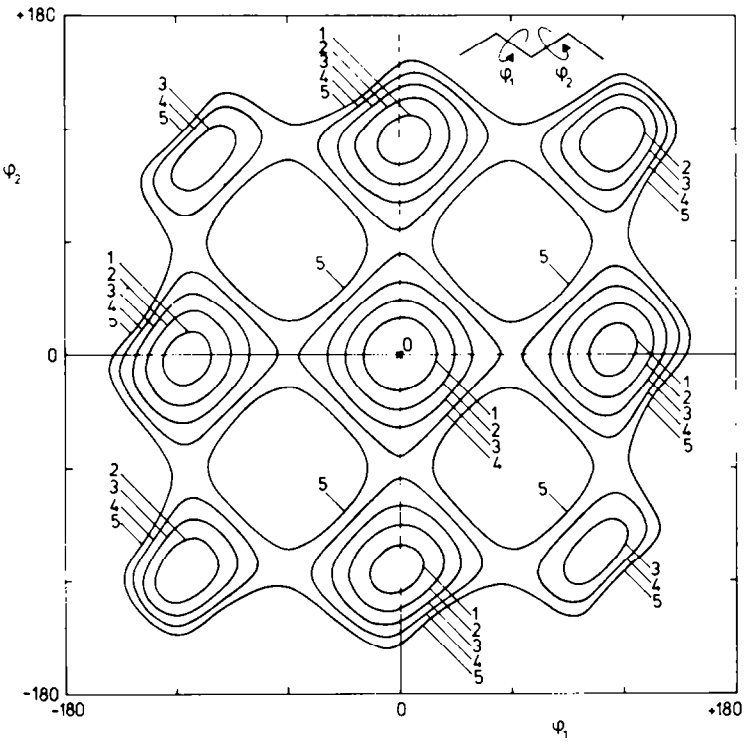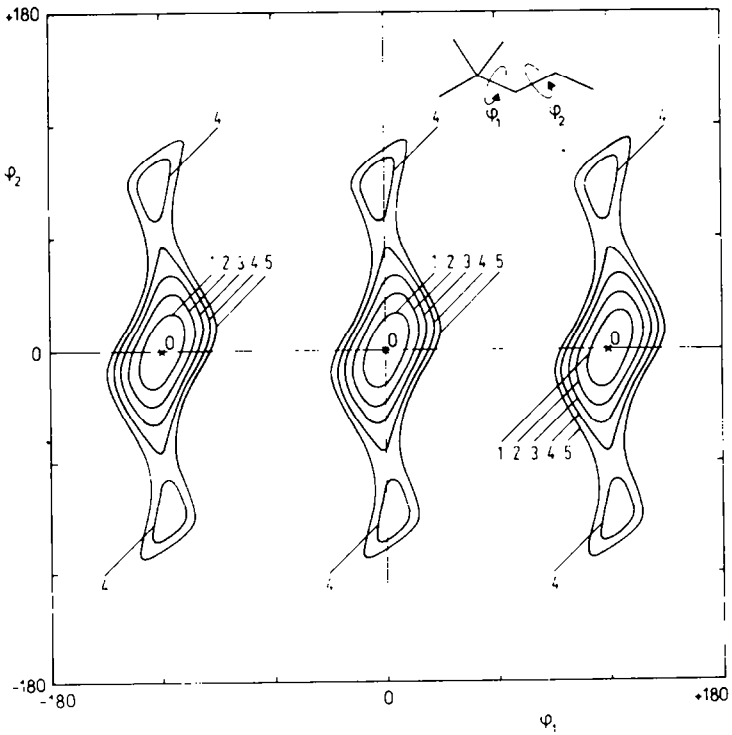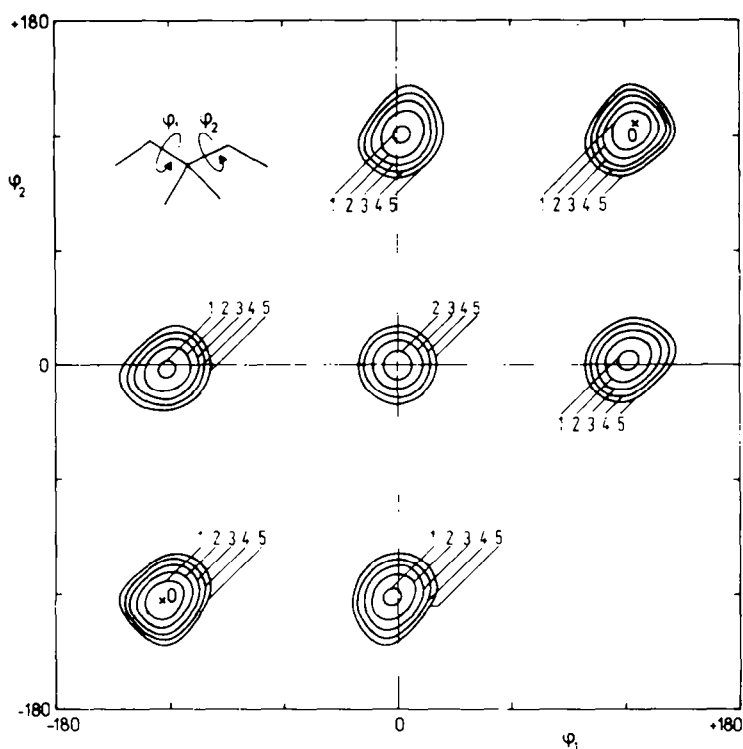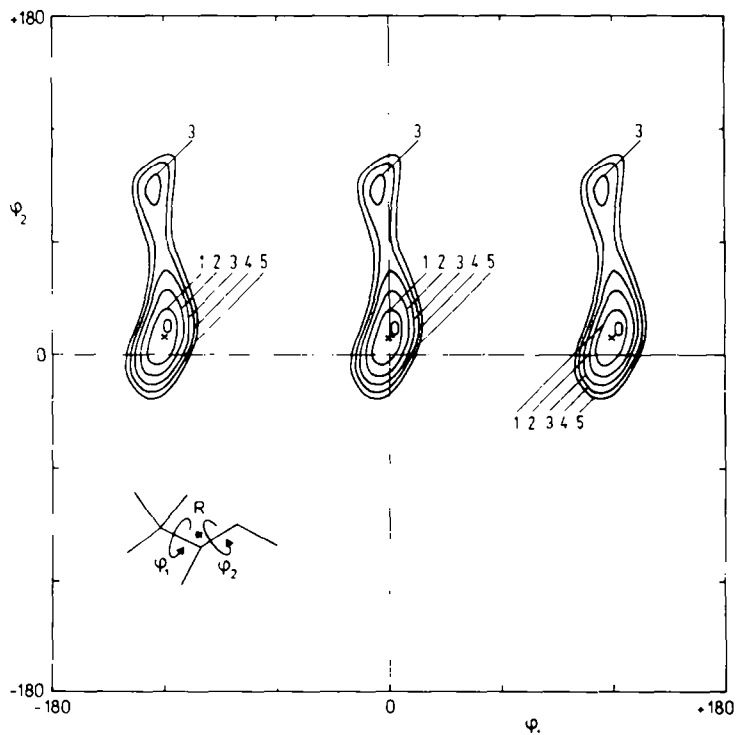
Fig. 3(a).

Fig. 3(b).

Fig. 3(c).

Fig. 3(d).

Fig. 3. Energy maps for n-pentane (a), 2,2-dimethylpentane (b), 3,3-dimethyl pentane (c), and (R)-2,2,3-trimethyl-pentane (d). Energies are calculated on a grid with 5° step width, and contours are drawn with intervals of 1 kcal/mol.

formation space accessible in average to a bond (with respect to the total space, which is 2π per bond).[3]

Table 3 reports $z/2\pi$ for some typical paraffines and the relative temperature coefficients $d \ln z/d \ln T$, whereas some energy maps are represented in Fig. 3.

The symmetry of the molecular frame must necessarily be reflected in the conformational energy map. Thus (Fig. 3) the energy maps of 2,2,3-trimethylpentane and 2,2-dimethylpentane have a 3-fold symmetry arising from rotation around ϕ_1, whereas the maps of n-pentane and 3,3-dimethylpentane are centrosymmetric.

From the comparison of 2,2,3-trimethylpentane and 2,2-dimethylpentane one may notice the decrease of $z/2\pi$ brought about in the former case by vicinal methyl groups: the conformational space around the negative values of ϕ_2 becomes inaccessible for the more branched compound, and $z/2\pi$ drops from 0.098 to 0.073. Another example in this regard is given by the comparison between 2,2-dimethylbutane and 2,2,3-trimethylbutane, where the smaller value of $z/2\pi$ corresponds again to the compound having vicinal methyl groups.

In n-pentane and 3,3-dimethylpentane, the position of the energy minima corresponds to the angles expected on the basis of the 3-state scheme, whereas rather large deviations are present for the other two compounds. We will discuss the question of the most probable values of the torsion angle in the next section.

From Table 3 note also that the compounds which have the greatest conformational rigidity are also compounds which were predicted to be rigid according to the 3-state scheme.[1] However, the $z/2\pi$ values are spread in a relatively small range. The maximal flexibility among the compounds investigated pertains to n-pentane, the maximal rigidity to compound **22b**. Thus, the conformational space allotted in average to a bond of a paraffine at room temperature is only 5-13% of the total. This already modest conformational versatility further decreases by decreasing temperature: thus, for n-pentane, 3,3-dimethylpentane and 2,2,3-trimethylpentane the value of $z/2\pi$ is between 2.8 and 3.1% at 50 K (reflecting a significantly different temperature coefficient of z in the various cases).

This evaluation of the conformational flexibility is at variance with the results obtained in the previous paper[1] with the 3-state scheme. In fact, the flexibility number F defined there varies in a much larger range, for example $F = 100\%$ for 2,3-dimethylpentane, $F = 51.5\%$ for n-pentane, $F = 0.95\%$ for XXV(meso). The reasons for this difference are obvious from the premises of the calculations in the two cases. The classical 3-state scheme emphasized the *number* of actual conformations with respect to the possible total number (which is 3 per bond), the present calculation procedure estimates the conformational *space*, with respect to the total allotted space (which is 2π per bond).

A particularly interesting case to consider in this regard is the comparison between 3,3-dimethyl pentane (which according to the 3-state scheme is extremely flexible, having 7 conformers with the same zero energy) and 2,2-dimethylpentane, which is rigid according to the 3-state scheme, having only one zero energy conformation (or 3 equivalent conformations considering the degeneracy arising from rotation around the $C-C(CH_3)_3$ bond). As apparent from Table 3, both compounds are rather flexible with the new calculation scheme, and actually 2,2-dimethylpentane is the more flexible.

A rationalization of this feature can be offered on the basis of Fig. 3 which shows energy maps of n-pentane and 3 other methyl substituted pentanes. Inspections of the two maps shows that indeed 2,2-dimethylpentane has only three energy minima, whereas the 3,3-dimethylpentane has 7 approximately equivalent energy minima. However, the space allowed to the latter around the minima is very small, so that the numerical value of z is larger in the former case. This argument can be presented for introducing the importance of the width of the energy minima in conformational energy calculations.

It is clear from these considerations that the expression "conformational flexibility" (or rigidity) is intrinsically ambiguous. It may in fact be used to indicate the number of accessible conformational energy minima, or the overall conformational space, and the two criteria may not be in mutual agreement. In fact, they convey two different concepts. It may then be useful to better qualify the term "conformational flexibility" by discriminating between these two concepts, i.e. by defining a "space-conformational flexibility", F_s, and a "number-conformational fiexibility", F_n. F_s can be evaluated as we have done in this paper, namely $F_s = Z^{1/n}/2\pi$, where Z is the conformational partition function obtained by computing the potential energy hypersurface of the entire molecule. The pure F_n, i.e. the relative number of conformational throughes populated to more than an (arbitrary) critical value, depends on the model used. With a 3-state scheme and a limit of ca 1.5 kcal mol^{-1} bond^{-1} (reasonable for ca 300 K), an estimate of F_n could be calculated by setting $\sigma = 1$ and $\omega = \tau = 0$ in the simple conformational partition functions evaluated in the previous paper,[1] and normalizing to 3^n (the maximal number of allowed molecular conformational states in the 3-state scheme), namely $F_n = \ln Z^*/n \ln 3$ where Z^* is the simplified rotational-isomeric conformational partition function (this can also be obtained on the basis of the original scheme of Brewster[10]). According to the above definition, F_n varies between 0 (maximal rigidity, when only one geometrical state is allowed) and 1 (all theoretical 3^n states allowed). Thus, for n-pentane $F_n = 0.89$, for 2,3-dimethylpentane $F_n = 0.50$, for **12b** $F_n = 0.25$. The parameter F as defined in the previous paper[1] is a less primitive flexibility number as it takes into account the relative energy of the various conformational states, but does not take into consideration the width of the energy minima and conformation space occupied overall.

CONFORMATIONAL VERSATILITY OF INDIVIDUAL BONDS

The parameter $z/2\pi$ is a property mediated over all bonds of the molecules. It may also be of interest to analyze for the conformational behavior of the individual bonds. This can be done by expressing the *a priori* probability density of the torsion angle of each bond, namely ψ_i, as defined above. This function permits to graphically display detailed information on the population of various rotation angles regardless of how many different angles are present in the molecule. Of course, the interrelation among the different angles are not visible. Curves can be obtained as shown in Figs. 4-6. For each bond, the number of peaks reflects the number-flexibility F_n, whereas the width of the peak(s) reflects its space-flexibility F_s.

Obviously, for n-pentane and 3,3-dimethyl pentane $\psi_1 = \psi_2$. Notice, in both cases, the expected symmetric distribution around $\phi = 0$, and that the maxima around

the gauche position deviates slightly from the ideal gauche values (± 120). In Fig. 4(b), notice that, contrary to the case of n-pentane, the more populated positions of the ϕ values are around the gauche position. These features (difference between n-pentane and 3,3-dimethylpentane, and asymmetry of the density distribution curves) are enhanced by decreasing temperature. Note also that at room temperature, oscillations around the most probable value of ϕ are as large as 20–25°.

From Fig. 5 it is apparent, in another graphical form, what we have already discussed in the previous section on the basis of the energy maps: the symmetric form of ψ_1 and ψ_2 in the case of 2,2-dimethylpentane 5a, the distortion of the distribution in the other compound 5b, and that only one set of values is allowed to ϕ_2. Notice also that for 2,2,3-trimethyl pentane at 500 K the density distribution function ψ_2 assumes a rather different form, with a secondary region centered at around 90°.

This kind of bond analysis is particularly useful for compounds having more than two torsion angles, for which energy maps of the type of Fig. 3 cannot be drawn. Figure 6 shows the case of compound 12, iso-12 (Fig. 6(a)) and syndio-12 (Fig. 6(b)). In both cases, the

molecules are conformationally rigid (in terms of number-flexibility) around ϕ_1, since this angle has only one maximum in population in the trans position. In the syndiotactic case, the molecule is also rigid around ϕ_2, but at room temperature it has a small secondary energy minimum around the trans position.

The position of the energy minimum is quite different in the two cases, being in the trans position in the syndiotactic and in the gauche (+) position in the isotactic form. The terminal torsion angle is the most flexible, and more so in the syndiotactic than in the isotactic form. In general, the symmetry of the individual peaks in ψ_1 increases with decreasing temperature.

OPTICAL ACTIVITY

Optical rotations at $\lambda = 589.3$ nm were computed according to the relations described above. Table 4 reports the calculated optical rotations of some alkanes containing t-butyl groups. Experimental values have been published for compounds 12a and 12b; they were the first "conformationally rigid" open chain paraffins, and were synthetized and investigated as model compounds for poly[(S)-4-methyl-1-hexene].[16,17] The observed high values of the optical rotation of the compounds (and the
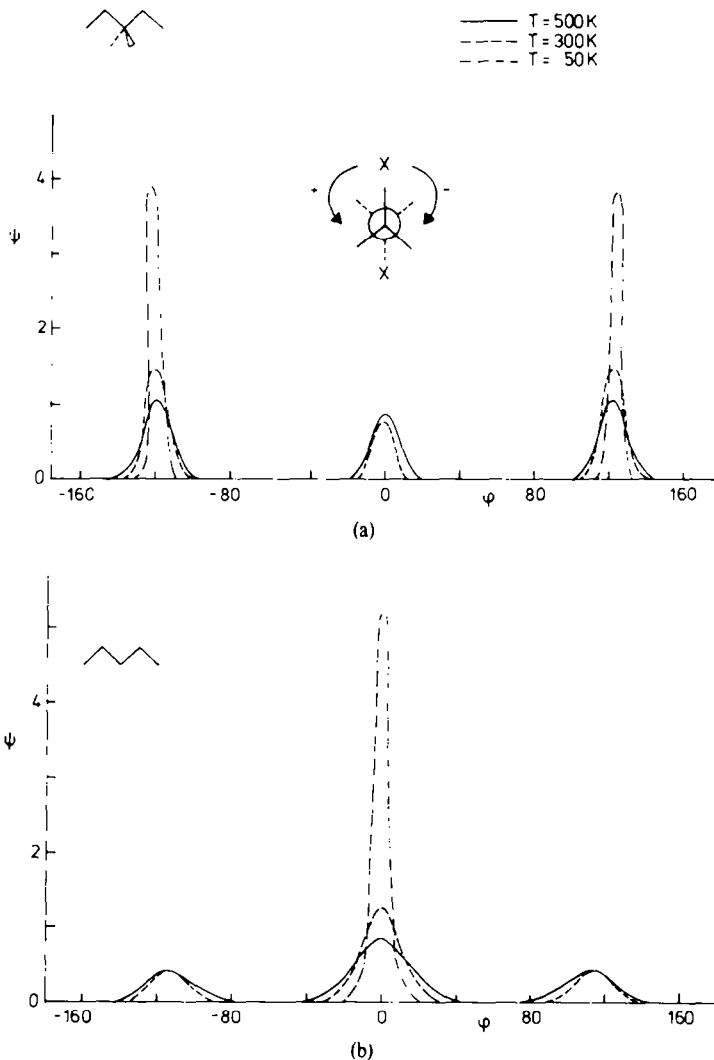

Fig. 4. The *a priori* probability density function of the torsion angles of 3,3-dimethylpentane (a) and n-pentane (b) at different temperatures.
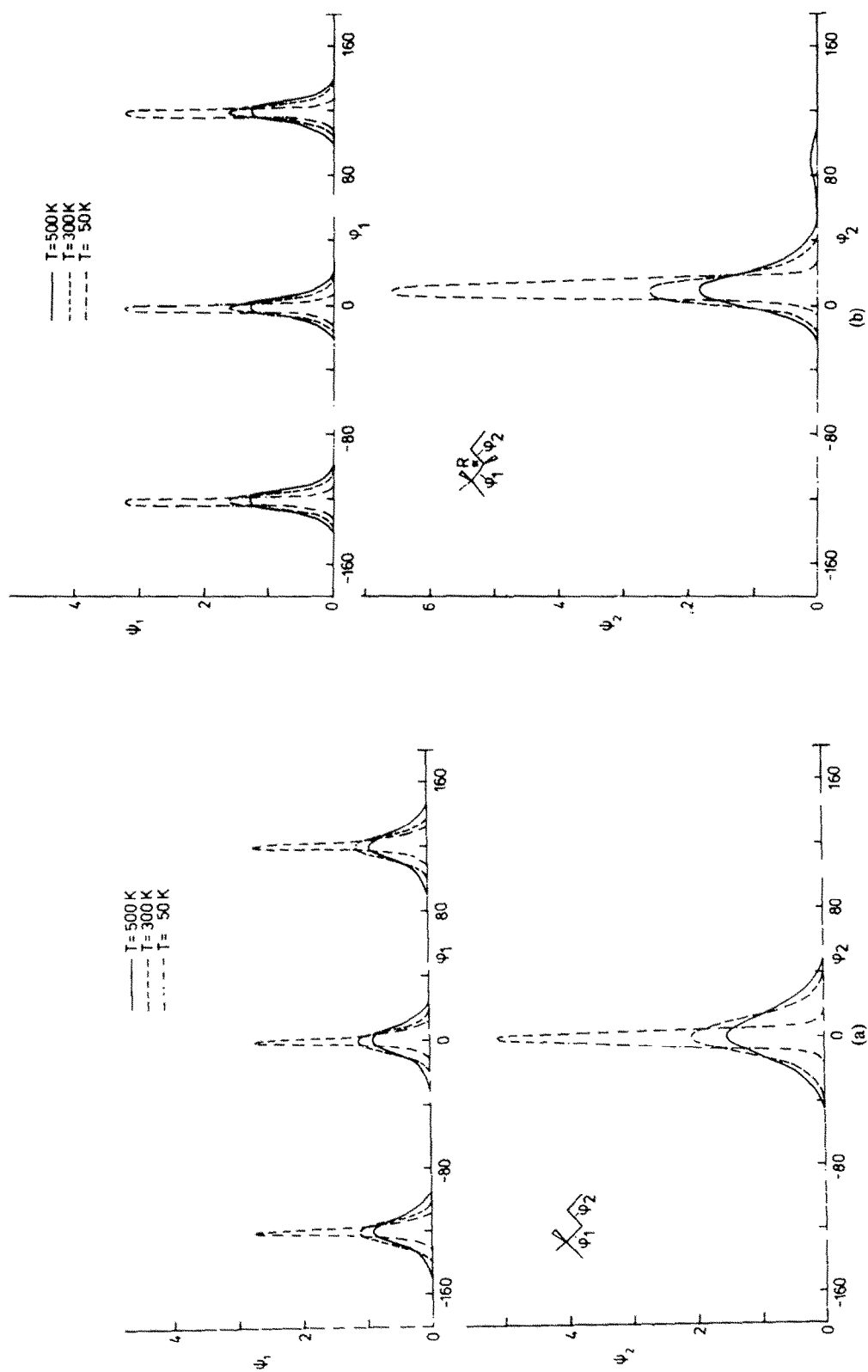
Fig. 5. The *a priori* probability density function of the two torsion angles at different temperatures for 2,2-dimethylpentane (a) and (*R*)-2,2,3-trimethylpentane (b).
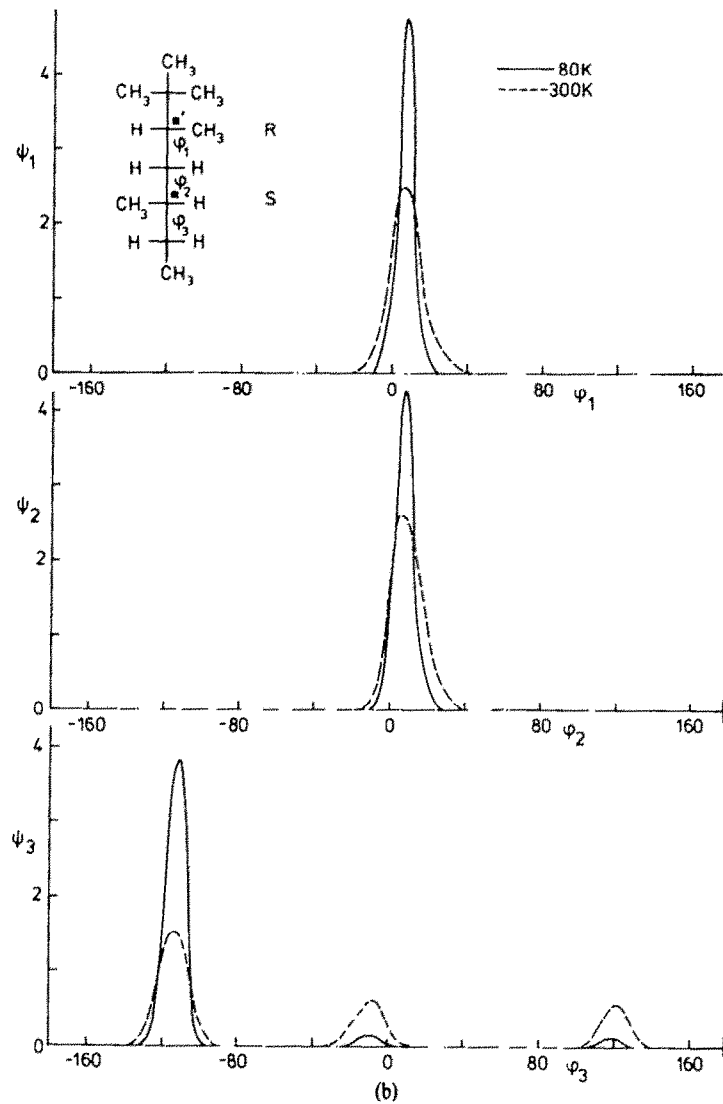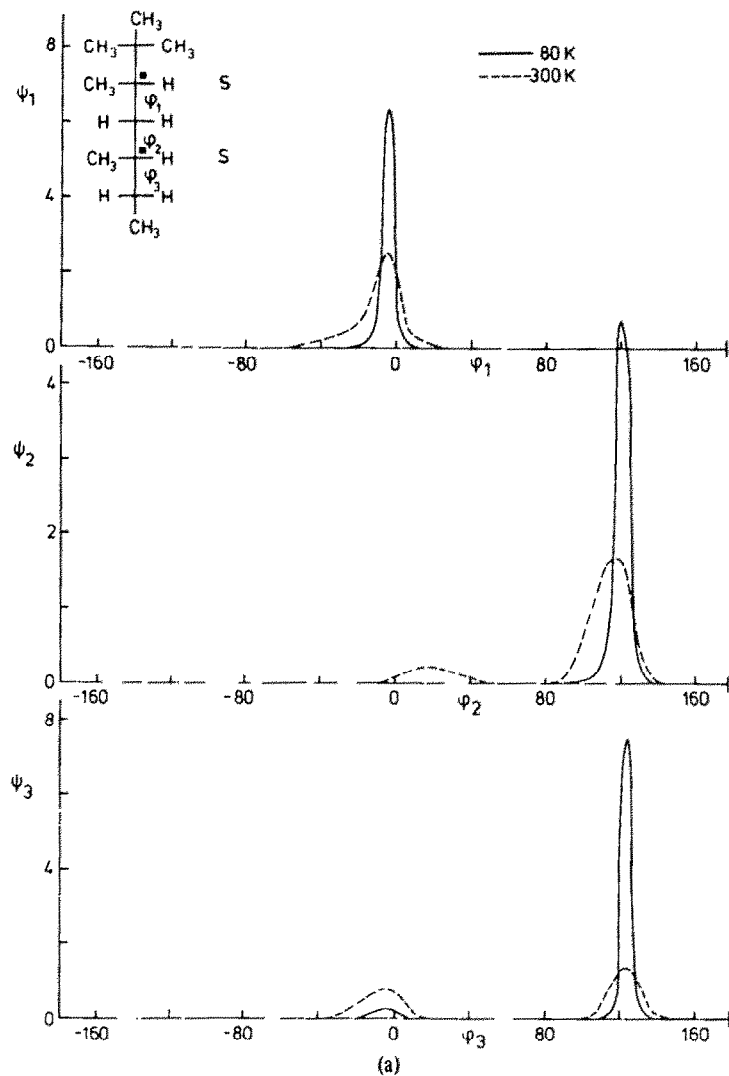
Fig. 6. The *a priori* probability density function of the three torsion angles at different temperatures for (3S,5S)-2,2,3,5-tetramethylheptane (a) and (3R,5S)-2,2,3,5-tetramethylheptane (b).

Table 4. Optical activity properties of some alkanes containing t-butyl groups[a]

Compound	$\langle[\Delta M_1]\rangle^b$	$\langle[\Delta M_2]\rangle$	$\langle[\Delta M_3]\rangle$	$\langle[\Delta M_4]\rangle$	$\langle[\Delta M_5]\rangle$	$\langle[M]\rangle$	$\dfrac{d\langle[M]\rangle}{dT}$
22 (R)-2,2,3-trimethylpentane	+63.6	—				+63.6	-0.025
21a (3R,5S)-2,2,3,5-tetramethylheptane	+60.1	+57.7	25.0			+142.8(+137.8)	-0.15(-0.13)
12b (3S,5S)-2,2,3,5-tetramethylheptane	-58.4	-43.4	-15.6			-117.0(-97.5)	-0.20(-0.15)
26 (3S,5R)-2,2,3,5,6-pentamethylheptane[c]	-43.2	+31.8	-68.4	+52.6		-79.9	-0.016
14b (3S,5S,7R)-2,2,3,5,7,8-hexamethylnonane	-51.8	-5.6	+19.0		-68.7	-54.5	+0.061

[a] Calculated at 300 K in units of degrees cm² dmole⁻¹. In parenthesis the experimental values, from Ref. 10, at λ = 589 nm.

[b] The first contribution is relative to the bond after the t-butyl group, i.e. C–C–C–C.

[c] A paper describing the synthesis and the conformational properties of this compound and its diastereomer (3S,5S) will appear soon (Ref. 15).

fact that they were of opposite sign) supported the concept of Pino and co-workers[16–18] that the high optical rotation of poly[(S-4-methyl-hexene] in solution was due to the strong preference of these chains to assume left handed helical conformations in the backbone. Our calculated values for the optical rotation and its temperature coefficient are in agreement with the experimental values.

The calculated contribution of individual bonds to the total optical rotation are of the same sign for all bonds in compounds 12a and 12b. This is no longer true for compounds 14b and 26, and this mutual "internal" compensation results in lower molar rotations. The latter two compounds are especially interesting, since their only difference is an additional –CH₂–CH(CH₃)– unit inserted in the middle of 26; they both have some features in common with poly(propylene). The first bond and the last two bonds of both show very similar $\langle[\Delta M_i]\rangle$, but the two additional bonds in 14b exhibit smaller values and decrease the total effect. All $\langle[\Delta M_i]\rangle$ in 14b decrease in magnitude with increasing temperature, as we expect (and observe) for all cases in Table 4, but the temperature gradients are of different magnitude $(d\langle[\Delta M_i]\rangle/dT$ is +0.011, +0.014, -0.061, -0.027 and +0.003 for bonds 1, 2, 3, 4 and 5, respectively) and the result is an overall increase of optical rotation with an increase in temperature.

In contrast with the molecules 12a and 12b, where the method used in this paper yields values in rough agreement with those calculated earlier[16,17] on the basis of the original Brewster method,[10] the compounds 14b and 26 are assigned quite different estimates with new and old methods. With the original scheme values of -300 for 14b and -180 for 26 can in fact be calculated.

CONCLUSIONS

The detailed investigation of the conformational characteristics of the alkane has shown an agreement between the calculated and the experimental values for the optically active alkanes where experimental values were available. This fact lends support to the many conjectures deduced from the calculations that have until now no immediate experimental verification.

An entity that until now lacks experimental support is the *a priori* probability density function ψ_1 of each bond. This function correlates with any quantity which is dependent on one torsion angle only, e.g. vicinal NMR coupling constants. This function is also very helpful in representing conformational characteristics of complex molecules, and can be used to describe much of the information contained in the potential energy surface.

The necessity to distinguish between the number of troughes in the potential surface and the fraction of this surface that is populated to more than a marginal degree, led to the differentiation between *number*-flexibility and *space*-flexibility. The space-flexibility F_s determines the "conformational free energy"; it is a clear physicochemical concept, and some experimental validation could be obtained, for instance from melt-entropy data.[19] The number-flexibility F_n, although a less clearly definable concept, is also rather important: correlation between conformational factors and chemical reactivity, for instance, promise to be much higher for number than for space-flexibility. The main chain of a typical globular protein in solution will have only a very small F_n (approaching zero), while a typical random coil, such as poly(ethylene) will be characterized by $F_n \sim 0.5$. F_n is

expected to be much more sensitive to structural features than F_s; however quantitative relationships between chemical structure and F_n or F_s are not yet available.

REFERENCES

[1] P. L. Luisi, *Naturwissenschaften* **64**, 569 (1977).
[2] P. J. Flory, *Statistical Mechanics of Chain Molecules*. Interscience, New York (1969).
[3] P. J. Flory, *Pure Appl. Chem.* **26**, 309 (1971).
[4] J. H. Brewster, *Tetrahedron* **30**, 1807 (1974).
[5] P. L. Luisi and F. Ciardelli, *Structure and Properties in Polymer Chemistry* (Edited by A. D. Jenkins and A. Ledwith). Wiley, London (1974).
[6] R. H. Boyd and S. M. Breitling, *Macromolecules* **5**, 279 (1972).
[7] S. Tanaka and H. A. Scheraga, *Ibid.* **9**, 142 (1976).
[8] U. W. Suter and P. J. Flory, *Ibid.* **8**, 765 (1975).
[9] N. L. Allinger, *Adv. Phys. Org. Chem.* **13**, 1 (1976).
[10] J. H. Brewster, *J. Am. Chem. Soc.* **81**, 5475 (1959).
[11] J. H. Brewster, *Topics in Stereochemistry* (Edited by N. L. Allinger and E. Eliel), Vol. 2, p. 1 (1967).
[12] J. H. Brewster, *Topics in Current Chemistry*, **47**, 29 (1974).
[13] D. H. Whiffen, *Chem. Ind.* 964 (1956).
[14] A. I. Vogel, W. T. Cresswell, G. H. Jeffrey and J. Leicester, *J. Chem. Soc.* 514 (1952).
[15] U. Azzena, U. W. Suter and P. L. Luisi, submitted to *Helv. Chim. Acta.*
[15] U. W. Suter, *Habilitationschrift*. ETH Zürich (1979).
[16] S. Pucci, M. Aglietto, P. L. Luisi and P. Pino, *Conformational Analysis* (Edited by G. Chiurdoglu). Academic Press, New York (1971).
[17] S. Pucci, M. Aglietto, P. L. Luisi and P. Pino, *J. Am. Chem. Soc.* **89**, 2787 (1967).
[18] P. Pino, *Adv. Polym. Sci.* **4**, 393 (1965).
[19] A. E. Tonelli, *Macromolecules* **6**, 558, 563 (1962).