

Molecular Conformational Rigidity: An Approach to Quantification

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A method is proposed for ordering molecules on a scale of conformational rigidity on the basis of a parameter (the *F* number), which to a first approximation is evaluated with the three-states rotational isomeric-state scheme. Some particularly rigid paraffins are discussed.

In the chemical literature the terms rigidity and flexibility are often used in connection with conformational problems in solution [1–11, 18]. A large variety of more or less equivalent terms such as rotational freedom [12–14], segmental motion [15], mobility [16], chain stiffness [17], internal motions [19], fluidity [20], or motility [21] (these latter two specially in membrane chemistry) have also become popular. This variation in terminology reflects mainly the nomenclature associated with the different techniques (nuclear magnetic resonance, fluorescence polarization, transient kinetics, optical activity) and also the different backgrounds of the authors who have become involved with conformational problems.

In biological sciences, molecular rigidity is often associated with the biological function. For example, the high conformational rigidity of enzyme-active centers is the prerequisite for the very special stereochemical fit with the substrate, which in turn is the prerequisite for catalysis. The same argument can be presented for all those biopolymers that have specific binding or recognition functions. In nucleic acids, for example, the biosynthetic machinery relies heavily on the rigidity of the helical structure, and it is readily apparent that highly flexible randomly coiled biopolymers would be much less efficient as containers and transmitters of information. The fact that the conformational rigidity of biopolymers is occasionally accompanied by specific conformational changes (induced fit, allosterism, etc.) points to the

special role of dynamic factors in biology even at the level of single molecules.

As recognized by several authors [7, 9, 10, 18, 22], there are usually two different concepts associated with the term rigidity (or analogous expressions). On the one hand, this term is used to depict an equilibrium situation, i.e., to indicate that the molecule in question exists in solution in a very limited number of conformations (only one in the limit) among the very many that are a priori conceivable on the basis of its chemical structure. A large number of low- and high-molecular-weight compounds [1–6, 23, 24] have been recorded as possessing *thermodynamic conformational rigidity*, while, for example, polyethylene and several other randomly coiled chains, which are present as an equilibrium mixture of many rapidly interconvertible main-chain conformations, are considered as flexible molecules [7, 8, 10, 25].

On the other hand, the terms flexibility, rigidity, or equivalent expressions are also used in relation to kinetic problems, referring more or less implicitly to the *rate* of interconversion between the various conformers. In this case, one is dealing with *kinetic conformational flexibility/rigidity*. In polymer chemistry, the relevance of the potential energy barriers for determining the shape of a macromolecule in solution was discussed as early as 1946 when Kuhn and Kuhn [26] introduced the concept of the 'internal viscosity' of a chain. Recently, the problem of measuring the kinetic flexibility in polymers has been tackled in an elegant way by Szwarc and collaborators [9].

A difficulty in dealing with thermodynamic conformational rigidity is that there are no simple means as yet for ordering the molecules according to a quantitative scale of flexibility or rigidity. How can one assess criteria to ascribe a 'thermodynamic-flexibility number' to a given molecule? It is the aim of this paper to present an approach to the solution of this problem.

The Definition of the F -Number

A first approximation method is developed in what follows, and will be limited to hydrocarbon molecules, because their conformational properties are better understood. In this case, conformational problems can be studied within the frame of the three-states rotational isomeric-state approximation [8, 10, 25]. Accordingly, only staggered conformations of bonds are considered, each C-C bond being allowed three states: antiperiplanar (*trans*) and \pm synclinal (or \pm *gauche*) (see also Fig. 1).

On the basis of the three energy parameters illustrated in Figure 1, one can express the 'statistical weight' of each bond conformation. The first two energy parameters (ΔE_σ and ΔE_τ) are relative to three-bond interactions and are visualized with the help of Newman projections. The third energy parameter (ΔE_ω) refers to a succession of two bonds in $\pm sc \mp sc$ (*sc*=synclinal, *ap*=antiperiplanar) conformations and represents the extra energy with respect to two *gauche* interactions. We will refer to these three interactions as σ , τ and ω interactions (or conformations), respectively. When the molecule contains vicinal branching (2,3-dimethylbutane in the simplest case), one can assume, from literature data [29, 30], that the three staggered bond conformations have the same energies. The limits and validity of the rotational isomeric scheme for quantitatively expressing the conformational equilibria of paraffin-like

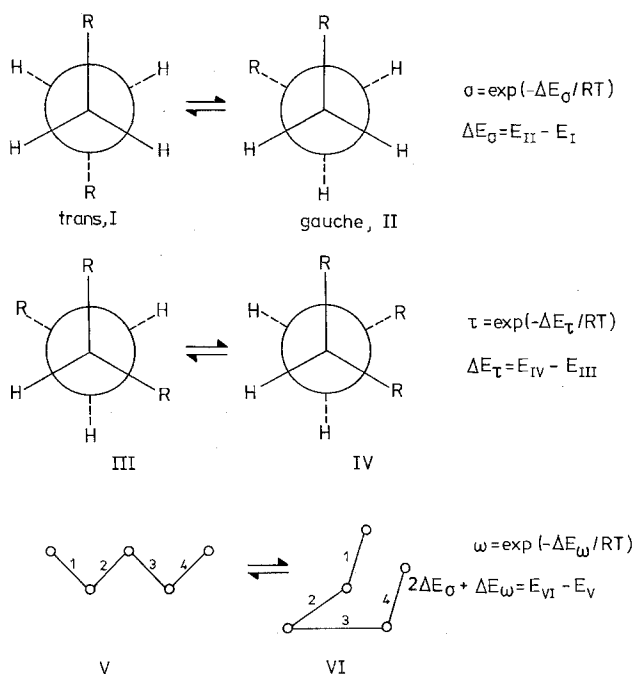


Fig. 1. The energy parameters used in the three-states conformational analysis

molecules are discussed by several authors [8, 10, 28, 31].

Once the energy of each conformation is evaluated in terms of σ , τ , and ω , the conformational partition function for the molecule, containing n nonterminal bonds, can be written in the form

$$Z = \sum_{j=1}^{3^n} \prod_{i=1}^n g_i \quad (1)$$

where g_i is the statistical weight of each *bond* conformation, the sum \sum_j being extended to all 3^n conformations of the molecule, and the \prod_j to all n bonds of the molecule around which rotation is considered.

The terms g_i are only functions of σ , τ , and ω . Clearly, Z represents a measure of the conformational space allowed to the molecule. The smaller Z is, the smaller the conformational versatility of the molecule, and vice versa. In order to compare molecules of different lengths, a normalization of some sort is needed, since the numeric value of Z is also dependent on the value of n . This can be done, for example, by introducing the parameter

$$z = \sqrt[n]{Z}$$

which represents the conformational partition function per bond, i.e., it is a measure of the conformational space allotted to the 'average bond' of the molecule. This parameter has been used by Flory to calculate the bond rotational partition function of some polymers [27].

Considering that 3^n is the maximal number of conformations allotted to each molecule (i.e., the maximal value of Z), the ratio $Z/3^n$ represents a normalized value for the molecular flexibility, and the ratio $z/3$ gives the same property referred to an average bond. A handier parameter to evaluate the molecular flexibility, and the one we propose to use, is the following F number (F from flexibility):

$$F = \frac{\ln z}{\ln 3} \quad (2)$$

According to Eq. (2), the molecules that exist in only one conformation, regardless of their actual structures, yield $F=0$ (zero flexibility, or maximum conformational rigidity). On the other hand, the molecules for which all rotamers are allowed and which possess the same energy (i.e., $Z=3^n$, or $z=3$) will be characterized, regardless of their structures, by $F=1$. This is the maximum F number, corresponding to complete thermodynamic flexibility.

In this way, each molecule can be assigned an F number on a scale from 0 to 1, which represents the

relative conformational space at the disposal of the molecule at a given temperature. Note that F is only a function of the terms $\Delta E_i/RT$, and that it is strictly a thermodynamic property (no kinetic connotations). In polymer chemistry, the function $\ln Z$ has already been used to estimate chain stiffness, and in particular the property $d\ln Z/dT$ has been used to evaluate the influence of temperature upon the conformational equilibria [10, 17, 21].

The Dependence of F on Chemical Structure

Table 1 contains the F number for a series of open-chain alkanes. Calculations have been carried out assuming $\sigma=0.43$, $\tau=0.18$, and $\omega=0.035$. This corresponds, at room temperature, to $\Delta E_\sigma=500$, $\Delta E_\omega=2000$, and $\Delta E_\tau=1000$ cal/mol (see [10, 33] and references therein). It is apparent that F varies over a wide range, depending upon chemical structure. Notice that 2,3-dimethylbutane (III) has the maximum F number, because the three possible conformations have the same zero-level energy (in this regard, bear in mind that the F number is by no means related to the *absolute* internal energy, but is only a function of the energy *difference* among rotamers).

Interestingly, 2-methylbutane (II) is more flexible than n-butane, and 3,3-dimethylpentane (VIII) is more flexible than n-pentane. The fact that the linear chain does not correspond to the higher flexibility may at first appear surprising. Certain types of branching, however, tend to equalize the *relative* energy of bond rotamers—an inspection of the Newman projections of II vis-a-vis those of I reinforces this point. In this regard, compounds X and XVIII are also of some interest, since they display a high flexibility and a high degree of branching. Notice that they are model compounds for polyisobutylene.

In several other cases, however, the presence of branching increases the conformational rigidity (as exemplified by IX vs. IV, XI vs. XIIa, see Table 2, and by XVII, XVIII, and XIX) but not in a simple and predictable way. The same conclusion can be drawn regarding the presence of asymmetric carbon atoms. In fact, the highly symmetric molecule VI is more rigid than the asymmetric molecule VII. On the other hand, XIIa, XIII, XIV, and XIX, which are asymmetric, are the most rigid of the compounds in Table 1.

Comparing now the n-alkanes I, IV, XI, XV, and XVI, we note that the flexibility number decreases monotonically. This seems to lead to the conclusion that higher oligomers of ethylene are more rigid than their low-molecular-weight analogs. This can be rationalized by noting that increasing the length also

increases the relative occurrence of conformations with ($\pm sc \mp sc$) pairs; furthermore, the statistical weight of the most stable conformation becomes less and less important relative to the Z value.

Molecules such as 2,2-dimethylbutane, or 2,2,4,4-tetramethylpentane have not been included in the scheme, since on the basis of the three-states rotational scheme they have only one possible spatial relation for atoms (as for ethane or propane). Interestingly enough, in these cases the calculation of the F number according to Eq. (2) results in an indetermination. This is not unreasonable, considering that these molecules fulfil at the same time the criteria of absolute conformational rigidity (only one conformation) and maximal flexibility (as they assume all the conformational space at their disposal). Consider also that the F number would not change by counting three rotamers instead of one around the $(CH_3)_3-C$ bond. Only the numerical value of z would be affected.

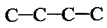
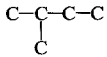
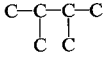
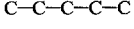
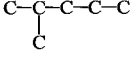
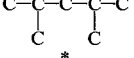
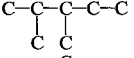
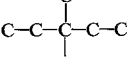
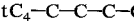
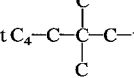
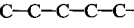
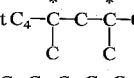
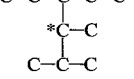
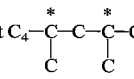
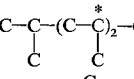
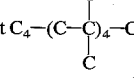
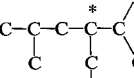
Conformationally Rigid Molecules

We will arbitrarily define a molecule as 'conformationally rigid' when $F \leq 0.1$. Some of those rigid molecules are reported in Table 2, while Figures 2 and 3 directly show the most stable conformation predicted on the basis of the three-states conformational analysis.

All of these conformationally rigid molecules possess one or two t-butyl groups. They exist in only one allowed conformation, all other rotamers being destabilized by τ or ω interactions. Compounds XX and XXIV are the only ones that do not possess asymmetric carbon atoms. Compounds XXI and XXV are the most rigid molecules designed up to now. Note that the F number of the syndiotactic form of XXV is considerably lower than that of the isotactic form, which shows the influence of diastereomerism upon molecular flexibility.

Compound XXV is a model for stereoregular polypropylene having equal chain endings. Comparison of this compound with XVII of Table 1 illustrates the effect of terminal t-C₄ groups upon flexibility. Whereas XXV is a meso structure possessing no optical activity, compound XIVb, which represents a model for isotactic polypropylene with different chain terminals, is asymmetric (see Fig. 3). Interestingly, this compound has a very high optical rotation, when this is calculated using the Brewster method [34]. The isotactic molecule assumes in fact a helical conformation, which is spiraled in the right-hand-screw sense in the case of the (3S, 5S, 7R) absolute configuration, and therefore all bonds contribute with

Table 1. The F number for some typical open-chain paraffins

Compound	n	Z^a	$F \times 100^b$
I 	1	$1+2\sigma$	56.4
II 	1	$2+\tau$	70.9
III 	1	3	100
IV 	2	$1+4\sigma+2\omega\sigma^2+2\sigma^2$	51.5
V 	2	$2+\tau+2\sigma+2\tau\omega+2\omega\sigma$	51.7
VI 	2	$2+2\omega\tau+2\omega+2\omega\sigma$	36.6
VII 	2	$3+\omega+\tau+3\tau\omega$	53.4
VIII 	2	$7+2\omega$	89.0
IX 	2	$1+2\sigma+2\omega\sigma$	28.9
X 	2	7	88.5
XI 	3	$1+6\sigma+4\omega\sigma^2+8\sigma^2+4\sigma\omega$	50.
XII a 	3	(syndio): $2+\tau+2\omega+2\omega\sigma+2\tau\omega^{e,d}$	25.6
XIII 	4	$1+2\tau+12\omega+11\omega\tau$	13.8
XIV a 	5	(syndio): $3+8\omega^{e,d}$	21.6
XV $n\text{-C}_9$	6	25.68^e	49.2
XVI $n\text{-C}_{50}$	47	6.18×10^{40e}	48.1
XVII 	6	(iso): $4+17\omega+32\omega\tau^f$ (syndio): $5+16\omega+34\tau\omega^f$	47.8 57.6
XVIII 	6	$\sim 719^e$	99.8
XIX 	6	$2+17\omega+2\tau\omega$	14.5

^a Conformations with statistical weight lower than τ have been neglected

^b Calculations have been carried out with $\sigma=0.43$, $\tau=0.18$, $\omega=0.035$

^c Iso and syndio indicate the two stereoisomers (isotactic and syndiotactic) according to the nomenclature in use in macromolecular chemistry [7]

^d For the other isomer see Table 2

^e Only the numerical value is given in this case

^f From [27]

the same sign to the molar rotation (one obtains $|\phi|_D = -300$ for the allowed conformation of the molecule assuming ± 60 as the contribution of each bond [34]).

Among the asymmetric compounds of Table 2, the two isomers XII have been synthesized, and the relation between conformation and optical activity has been investigated in some detail [6]. Originally,

Table 2. Conformationally rigid alkanes

	Compound	n	Z^a	$F \times 100^b$
XX	$tC_4-C-C-C$	1	$1+2\omega\sigma$	2.70
XXI	$tC_4-C-C-tC_4$	1	$1+2\omega^2\sigma$	0.005
XXII	$tC_4-\overset{*}{C}-C-C$ C	1	$1+\omega+\tau\omega$	3.65
XXIII	$tC_4-\overset{*}{C}-C-\overset{*}{C}-C$ C C	2	$1+2\omega+\tau\omega+\omega\sigma$	3.97
XXIV	$tC_4-C-C-C-tC_4$	2	$1+4\omega\sigma$	1.77
XII b	$tC_4-\overset{*}{C}-C-\overset{*}{C}-C-C$ C C	3	(iso): $1+\tau+2\omega\sigma+3\omega+4\omega\tau$	8.48
XXV	$tC_4-\overset{*}{C}-C-\overset{*}{C}-C-\overset{*}{C}-tC_4$ C C C	4	(syndio): $1+2\omega\sigma+2\omega\tau^c$	0.95
XIV b	$tC_4-\overset{*}{C}-C-\overset{*}{C}-C-\overset{*}{C}-C-C$ C C C	5	(iso): $1+6\omega+4\omega\tau$	3.76

^a Conformations having a statistical weight lower than $\omega\tau$ have been neglected, except for XXI

^b Calculated with σ , τ , and ω as in Table 1

^c The isotactic diastereomer has several conformations with the same zero energy

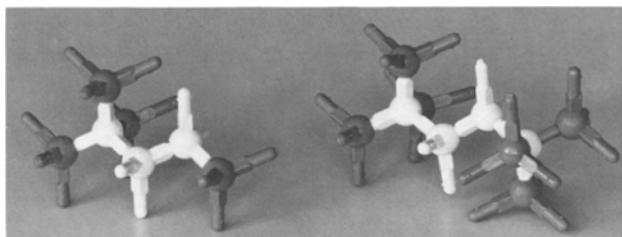


Fig. 2. The stable conformation of typical conformationally rigid molecules (for a better visualization, the methyl groups have been darkened): XX, 1,2-dimethylpentane (left) and XXI, 2,2,5,5-tetramethylhexane. Note the *all-trans* conformation of the main chain (white)

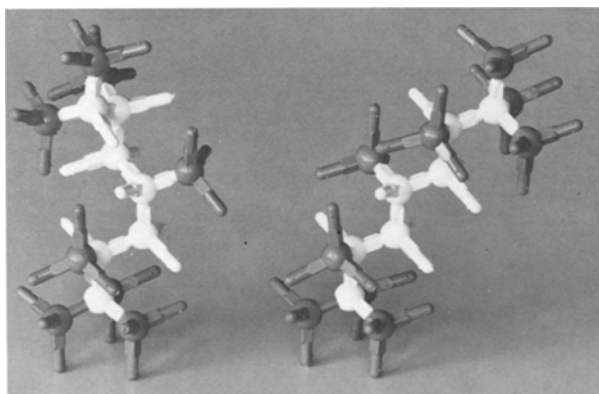


Fig. 3. Two low-molecular-weight rigid models of stereoregular polypropylene: XXV, (*meso*)-2,2,3,5,7,8-heptomethylnonane (right) and XIVb, (3*S*,5*S*,7*R*)-2,2,3,5,7,8-hexamethylnonane (left). Note the zig-zag planar conformation of the main chain in the *meso* form, and the helical conformation in the other case

they were designed as model compounds for the monomeric unit of poly(*S*)-4-methyl-1-hexene to explain the large optical rotation of this polymer [35].

Conclusions

This first-approximation procedure provides a semi-quantitative index of conformational rigidity for paraffins on the basis of the classical three-states rotational scheme. Whereas a more rigorous mathematical treatment is needed to better quantitate the relationship between structure and flexibility, the present procedure permits us to point out the basic problems and concepts in this field. It appears clear, for example, that it is not possible to rationalize in a simple way the influence of structural parameters (branching, asymmetry, length of the molecule) upon the F number. On this basis, a priori predictions of conformational rigidity appear difficult. Some semi-empirical criteria can, however, be reliably used. For example, the presence of *t*-butyl groups and asymmetric carbon atoms in general increases conformational rigidity. By carrying out the three-states conformational analysis, it is possible to single out molecules that are conformationally rigid. These molecules, owing to the simplicity of their conformational equilibria, should be the best model compounds for those physicochemical investigations in which a relationship between physical properties and molecular conformation is sought. In this respect,

compound XIVb is particularly interesting, as it represents a rigid chiral model for isotactic polypropylene. In particular, it might be useful to ask the question, until which chain length would this high conformational rigidity be maintained.

A more difficult question concerns the relationship between the F number and physical or chemical properties. In particular, which physically measurable property can be taken as an index of conformational rigidity? It does not seem possible, at this stage, to answer this question in a clear-cut way. Maybe the study of the temperature coefficient of optical activity will be of interest in this regard. In fact, the optical rotation should level off to a plateau in the lower temperature region, i.e., when the conformational equilibrium is represented by (practically) only one rotamer. In this respect, note that the temperature at which the most stable conformer represents 99 % of the conformational partition function is $T=220$ K for XXII, $T=90$ K for XII, $T=190$ K for XIVb. Reaching these temperatures while maintaining the molecule in solution does not appear impossible. For example, the two diastereomers of XII melt at around 200 K.

Still concerning the problem of the relationship between conformation rigidity and physical properties, one should recall the work by Tonelli [36]. This author has tried to correlate the conformational versatility of certain polymers with mechanical properties (e.g., the impact strength) as well as with their entropy of melting. Brant and Goebel, discussing the conformational properties of polysaccharides, employ the conformational entropy per residue as a quantity directly related to the conformational freedom of the skeletal chain segments [32]. One finds in the literature many other more or less semi-quantitative indications concerning the influence of chain stiffness or flexibility on certain polymer properties, and indeed a relationship between F number and physical data appears more feasible in macromolecules than in low-molecular-weight compounds.

Another interesting point concerns the relationship between the F number and chemical reactivity. For example, it is known that certain cyclic structures are less reactive because they are frozen in a 'wrong' conformation. To attempt such correlation, the present F number scheme should first be extended to include compounds with functional groups: this appears today to be within the realm of possibility.

The criticism of Prof. H. Morawetz (Brooklyn, USA) and Dr. U. Suter (ETH, Zürich) has been highly appreciated.

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Received February 7, 1977