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SYMMETRY AND CHIRAL RECOGNITION; SEPARATION OF ENANTIOMERS ON TRIACETYL-CELLULOSE COLUMNS

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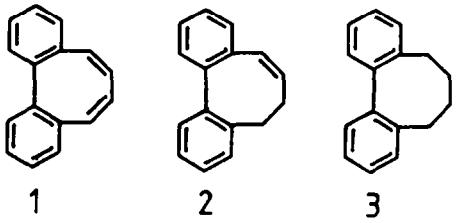
Abstract The role of molecular symmetry in chiral recognition is investigated by use of statistical methods; a theoretical expression for the difference in behaviour between C_1-symmetric and C_n-symmetric ($n>1$) chiral molecules on a chiral column being derived. The results are compared with experimental data obtained from resolutions by column chromatography on triacetylcellulose. It is shown both theoretically and experimentally that the C_n-symmetric molecules stand a better chance to be successfully resolved than C_1-symmetric species.

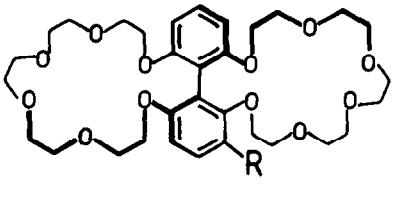
Introduction

The development over the last two decades of effective methods for the resolution of racemic mixtures on chiral columns has been a major achievement.[1] However, the understanding of the basic processes behind these remarkable results has developed more slowly. After the accumulation of such a large body of experimental results we feel that there is now a need for a closer analysis of the factors that govern chiral recognition in general and chromatographic resolution in particular.

During our work on the separation of enantiomers on triacetylcellulose (TAC) columns, we noticed that small changes in the structures of the chiral compounds often had quite unexpected effects. The series of bridged biphenyls 1-3 may serve as one striking example. The two C_2-symmetric compounds 1 and 3 afforded better separation than the C_1-symmetric 2 on a TAC-column ($\alpha^{\S}$ =2.82, 4.52, and 2.24 for 1, 3, and 2, respectively).[2] The bis-crown ether 4 (D_2-symmetry) provides a second example. It showed base-line separation whereas the mono-acetyl derivative 5 showed no separation at all under identical conditions.[3] These and similar observations have led us to consider the effect of one specific factor, the molecular symmetry, on resolution by column chromatography.



1 2 3



4 R=H
5 R=COCH$_3$

Chiral compounds are often regarded as "unsymmetrical" objects though they may well contain proper axis of symmetry (C_n-axes). In fact chiral and symmetrical compounds (e.g. a tartaric acid salt) have played an important role in the development of stereochemistry.[4]

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§We use the resolution coefficient (α) defined as the ratio of retention volumes, measured from the solvent peak, as the measure of resolution throughout this paper.

Intuitively, one would perhaps expect that a chiral resolution should be easier to achieve with an unsymmetrical and complex molecule than with a symmetrical one. However, at second thought, it is clear that for symmetrical molecules identical interactions with any one site on the chiral column occur more than once thus lending an implicit "amplification" effect to the resolution. To illustrate this effect qualitatively let us consider a hypothetical model system with a two-dimensional chiral column having two binding sites a and b in the repeating unit on the regular chiral phase as illustrated in Fig. 1. Let us compare the resolution of two enantiomeric pairs, one unsymmetrical consisting of the letter F and its mirror image form Ⅎ and one C_2-symmetric formed by the letter Z and its enantiomer Ƨ. Of the two binding sites in the repeating unit only a binds F and Ⅎ strongly. However, the binding will be different for different orientations. In one orientation, F is preferred over Ⅎ, in another the opposite is true, as illustrated in Fig. 1. Since the bindings in the two orientations are different the net effect might be sufficient for resolution but might also be too small. The letter Z and its enantiomer Ƨ are better bound in site b. In this case binding also occurs in two orientations, but due to the symmetry properties of the system the same enantiomer (Z) is better bound in both symmetry-related orientations. This will lead to an enhanced difference between the two enantiomers in interaction with the chiral phase and thus a greater possibility for a good separation.

Section of a two-dimensional chiral column with a repeating unit containing only two different active sites, a and b.

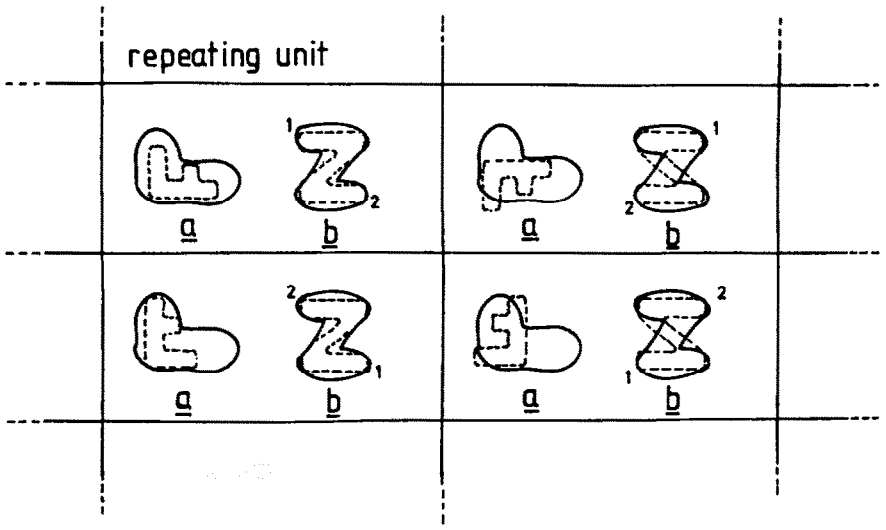

Figure 1. Schematic representation in two dimensions of the difference in binding between a chiral and unsymmetrical object (F and Ⅎ) on one hand and a chiral and symmetrical object (Z and _) on the other. The symmetrical objects (Z and Ƨ) are marked to show the symmetry-related orientations.

This simple idealized example illustrates the fact that if a chiral and symmetrical molecule is bound to a chiral stationary phase there are at least two symmetry-related orientations with identical binding conditions. This effect tends to amplify the difference in binding between the two enantiomers as compared to similar pairs of unsymmetrical molecules. In the present paper we develop this general idea and present a statistical approach to the problem of chiral recognition on chromatography columns. We then apply the results and analyse a series of previously performed separations on TAC-columns and also empirically demonstrate the importance of molecular symmetry. To our knowledge this approach is new and emphasises that separations of enantiomers on a chiral column is a chance event due to the effect of many weak interactions rather than to specific lock and key type interactions.

Theory

The behaviour of a substrate on a chromatographic column is determined by its interaction with the stationary phase. This can be quantified in terms of a substrate-surface interaction potential $\underline{V}$, which for a rigid molecule depends on the orientation $\underline{\Omega}$ and location $\underline{\bar{R}}$ of the molecule relative to the surface. Assume, for simplicity, that the latter is laterally homogeneous in the $\underline{xy}$ -plane with a characteristic repeating distance $\underline{d}$, while in the perpendicular direction we have a "bound" region for which $0 \leq \underline{z} \leq \underline{z}_0$, where a molecule for which $\underline{z} > \underline{z}_0$ is stationary relative to a moving phase (see also Fig. 2). We can then obtain a binding constant $\underline{K}$ per surface repeating unit, as

$$K = \int_0^d \int_0^d dx\,dy \int_0^{z_0} dz \int_0^{2\pi} \int_{-1}^{1} \int_0^{2\pi} d\alpha\, d\cos\beta\, d\gamma\; e^{-V(\bar{R},\Omega)/kT} \qquad (1)$$

where the orientation $\underline{\Omega}$ is specified by the Euler angles α, β and γ and $\underline{\bar{R}} = (x,y,z)$.

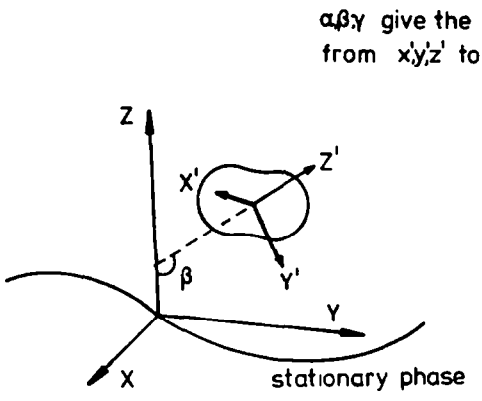

Figure 2. The orientation of a chiral compound interacting with the chiral stationary phase.

The resolution of the two enantiomers $\underline{r}$ and $\underline{s}$ on a column depends on the difference in the binding constants $\underline{K}_r$ and $\underline{K}_s$, which is the result of the difference in the interacting potentials $\underline{V}_r(\bar{R}, \Omega)$ and $\underline{V}_s(\bar{R}, \Omega)$. Equation (1) reveals an important difference between the $\underline{K}$:s and the $\underline{V}$:s in that the former are obtained as six-dimensional averages over a function of the latter. This shows that in the general case it is not trivial to extract information on $\underline{V}_r$ from $\underline{K}_r$. For the case of strong and specific interactions $\underline{V}_r$ has a marked minimum at some defined location and orientation ($\underline{\bar{R}}_r$, $\underline{\Omega}_r$) and the dominant contribution to the integral in eq. (1) will come from this point and its close surroundings. Under such circumstances $\underline{K}_r$ can be interpreted in the same terms as an ordinary solution chemical equilibrium constant. However, in the majority of cases of relevance for resolution of racemates, the chiral solutes and the stationary phase have been obtained independently from each other and there is thus no a priori reason to expect a very specific substrate stationary phase interaction. Furthermore, such strong interactions are not really necessary to obtain a good separation of enantiomers. In the normal case we are thus faced with the problem that the $\underline{K}$ in eq.(1) is a result of an average over many orientations and positions. It is a common procedure to try to discuss this $\underline{K}$ in terms of specific molecular interaction models. At the present state of knowledge we consider this to be questionable in most cases, for two reasons. Since the interactions are weak one would require a precision in the potentials $\underline{V}$ for particular values of $\underline{\bar{R}}$ and $\underline{\Omega}$ that goes beyond the present knowledge of intermolecular interaction potentials in condensed phases. Secondly, since the $\underline{K}$-value is obtained as a multidimensional average over $\underline{V}$ ($\underline{\bar{R}}$, $\underline{\Omega}$) systematic errors will be amplified.

In this paper we suggest a different approach for estimating $\underline{K}$ or, more specifically, differences in $\underline{K}$-values for chemically similar compounds such as pairs of enantiomers. Having concluded that there are little hope of obtaining sufficiently accurate quantitative estimates of the interaction

potential $\underline{V}$, we are led to a characterization of $\underline{V}$ by statistical methods. In the subsequent discussion of resolution and symmetry the orientational degrees of freedom are the most interesting ones and eq.(1) is rewritten as

$$K = \int_0^{2\pi} \int_{-1}^{+1} \int_0^{2\pi} d\alpha \, d\cos\beta \, d\gamma \, f(\alpha,\beta,\gamma) \qquad (2)$$

where

$$f(\Omega) \equiv f(\alpha,\beta,\gamma) \equiv \int_0^d \int_0^d \int_0^z dx \, dy \, dz \, e^{-V(x,y,z,\alpha,\beta,\gamma)/kT} \qquad (3)$$

A basic assumption is now that the function $\underline{f}$ can be treated using statistical methods and that its statistical characteristics are similar for chemically closely related compounds. For an enantiomeric $\underline{R},\underline{S}$-pair there is no reason to assume that $\underline{f}_r$ and $\underline{f}_s$ have different statistical properties, and thus for a particular orientation $\underline{\Omega}$ the values of $\underline{f}_r(\underline{\Omega})$ and $\underline{f}_s(\underline{\Omega})$ should then be regarded as two different samplings from the same distribution. The integral in eq.(2) represents an average over an infinite number of points, but for physical reasons we know that $\underline{V}(\underline{\Omega})$ is strongly correlated to $\underline{V}(\underline{\Omega}+\underline{\Delta\Omega})$ if $\underline{\Delta\Omega}$ is small, but uncorrelated for large $\underline{\Delta\Omega}$. For a particular class of compounds we can then associate a characteristic correlation angle

$$\Delta\Omega_{corr} = \Delta\alpha_{corr} \cdot \Delta\cos\beta_{corr} \cdot \Delta\gamma_{corr}$$

These correlations will also appear in $\underline{f}(\underline{\Omega})$, possibly somewhat modified by the spatial integration. A schematic one-dimensional representation of $\underline{f}(\underline{\alpha})$ is shown in Fig. 3a. In the interests of conceptual simplicity, the angular variation can be represented as a discrete function constant over an interval $\underline{\Delta\alpha}_{corr}$ as shown in Fig. 3b.

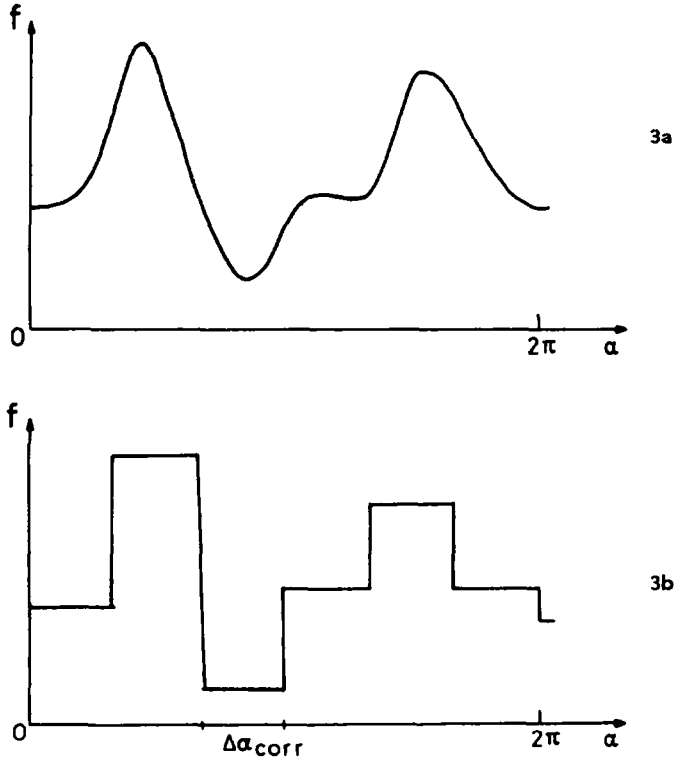

Figure 3. A one-dimensional representation of the angular dependance of $\underline{f}$ (3a); as a discrete function constant (3b).

For a particular class of compounds the statistical properties of the functions $f(\alpha,\beta,\gamma)$ can be characterised by the following five parameters;

i) the mean value $\langle f \rangle_\infty$, which is the true mean value from which the specific $f_i(\alpha,\beta,\gamma)$ are taken. The mean value $\langle f \rangle_\infty$ represents the average strength by which a particular class of compounds interacts with the stationary phase, i.e. it is a measure of the mean retention volume.

ii) the variance $v_f = \langle f^2 \rangle_\infty - \langle f \rangle^2_\infty$, which gives a measure of the fluctuations relative to the mean value. If the interaction V varies strongly with the orientation then v_f is large and this can occur if the compounds to be resolved have functional groups which interact strongly with the stationary phase.

iii-v) the three angular correlations $\Delta\alpha_{corr}$, $\Delta\beta_{corr}$, $\Delta\gamma_{corr}$. For large and flexible molecules these correlation angles are expected to be smaller than for small and/or rigid ones.

For a discrete representation of $f(\Omega)$ as in Fig. 3b, the value of K_i for a particular compound i is obtained as an average of f over a finite number of samples in the statistical distribution. The number N of independent samples is in the general case

$$N = 8\pi^2/(\Delta\alpha_{corr} \cdot \Delta\cos\beta_{corr} \cdot \Delta\gamma_{corr}) \tag{4}$$

From eq.(2) we find

$$K_i = \langle f \rangle_\infty + v_f \cdot \frac{P_i}{\sqrt{N}} \tag{5}$$

where P_i is a random number taken from a normalised Gaussian distribution

$$P(p) = \frac{1}{\sqrt{\pi}}\, e^{-p^2} \tag{6}$$

The factor $N^{-\frac{1}{2}}$ in eq.(5) arises since we take an average over N samples.

The differences between K-values for two enantiomers R and S are obtained from eq.(5)

$$K_r - K_s = v_f\,(p_r - p_s)\,/\sqrt{N} \tag{7}$$

From this equation we learn that one stands a better chance of obtaining a good resolution the larger v_f is, i.e. the larger the fluctuations in f, and the smaller the N-value is. The latter is equivalent to large correlation angles.

Consider now two chemically similar enantiomeric pairs such as the ones discussed in the introduction. Those differ basically only in their symmetry properties i.e. for one of the pairs there exists a proper axis of symmetry (C_n-axis). For the symmetric pair of enantiomers the additional information on the function $f(\Omega)$ is that $\hat{R}\, f(\Omega) = f(\Omega)$, where $\hat{R}$ is a symmetry operator. In the integral of eq.(2) the number of independent sampling points is then reduced to N/n relative to a molecule without symmetry (n is the order of the symmetry axis). The reduction of sampling points to N/n is equivalent to an increase in the difference in the binding constants for the two enantiomers by a factor of $\sqrt{n}$ relative to the expression in eq.(7) and thus for an enantiomeric pair with n-fold symmetry axes

$$K_r - K_s = v_f\,(p_r - p_s)\sqrt{n/N} \tag{8}$$

Thus we have arrived at the important conclusion that there is a higher probability of obtaining a good resolution on a chromatographic column for molecules possessing a proper axis of rotation (C_n-axis) than for unsymmetrical enantiomeric pairs. The higher order and number of symmetry axes, the better is the chance to obtain a good separation.

Results

Symmetry arguments in general do not depend on the specific theoretical model or on the level of approximation of the applied theory. To be able to test the symmetry arguments presented in this paper one would require a large body of experimental results from attempted resolutions on chiral columns of a variety of racemates selected by proper statistical methods. The resolutions should have been carried out, and the results analysed, under carefully controlled conditions. Such an ideal set of experimental results is certainly not at our disposal and is probable

non-existent. We are thus obliged to resort to a less ideal set of results obtained by one of us (R.I) from separations on a TAC-column.[5] All attempted separations, successful and unsuccessful, under near identical conditions have been collected and the results evaluated. However, the selection of compounds has not been a statistical one but rather reflects the interest of the chemical community in the possibilities afforded by the TAC column technique. Nevertheless, we consider the variation and number of compounds sufficiently large to be useful for our purpose. The types of compound range from natural products, pheromones, active pharmaceuticals, synthetic heterocycles, crown ethers, and functionalised aromatics to aromatic hydrocarbons. In total 216 chiral compounds. Thirtysix of these have at least one proper axis of symmetry (C_n-axis) and four have more than one (D_2-symmetry). The α-value for each separation was evaluated and the number of compounds within each interval of 0.2 α-units determined.* The results for the complete set are shown in Figure 4 for values of α between 1.0 and 5.0. Four of the compounds showed even better separation and are not included in Figure 4. Similarily, the results for the symmetrical compounds (C_n-axis of symmetry) are shown in Figure 5. The four compounds with D_2-symmetry have α-values between 1.95 and 2.41.

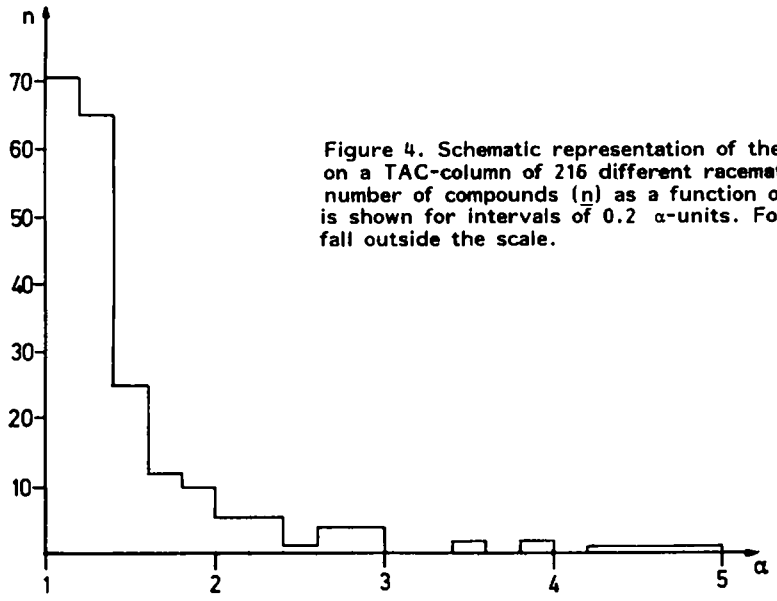

Figure 4. Schematic representation of the separation on a TAC-column of 216 different racemates. The number of compounds (n) as a function of the α-value is shown for intervals of 0.2 α-units. Four compounds fall outside the scale.

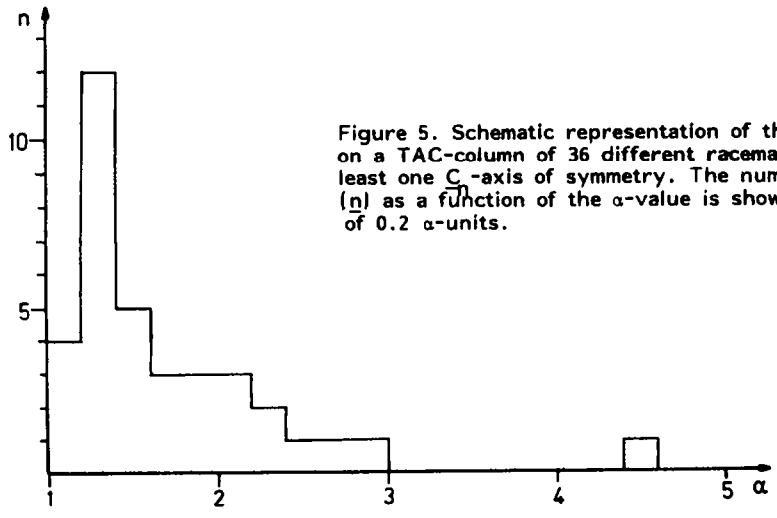

Figure 5. Schematic representation of the separation on a TAC-column of 36 different racemates with at least one C_n-axis of symmetry. The number of compounds (n) as a function of the α-value is shown for intervals of 0.2 α-units.

*In case of partial resolutions the α-values have been evaluated from the polarimeter curve rather than from the UV-absorption curve. This might have led to slightly too large α-values and an uncertainty in the assignment to the intervals α = 1.0-1.19 and α = 1.20-1.39.

The nature of the distributions shown in Figures 4 and 5 is not known to us. However, it is clear even from a brief inspection of the two distributions that they are different. The unsymmetrical compounds (Fig. 4) show, in general, low resolutions but some members of this class are remarkably well separated on the TAC-column, twelve compounds having α-values larger than 3.0! In contrast, the symmetrical compounds (Fig. 5) show quite good separation in most cases but only one compound has $\alpha > 3.0$. It is interesting to note that the $\underline{D}_2$-molecules show a much more narrow distribution although the number of compounds is too small for any significant conclusions to be drawn at present.

Although the sampling method is not a proper one statistically, we believe that the experimental results demonstrate clearly that molecular symmetry is an important factor and should be considered when resolutions on TAC-columns are attempted.

Discussions and conclusions

The arguments presented here for the importance of symmetry on chiral recognition are based on statistical properties and not on any detailed knowledge of the specific interactions between chiral phases, enantiomers and solvents. However, the nature of such specific interactions is a matter of considerable concern and has been the goal of many experimental and theoretical investigations.[6] While such work will hopefully lead to a better understanding of the factors other than molecular symmetry which govern resolutions by chromatographic methods, we would here like to make the point that when no detailed knowledge of the specific interactions is at hand (which is the most common situation) then a statistical approach is of considerable value.

Symmetry of the stationary phase. If the statistical argument that symmetrical compounds stand a better chance to be resolved than unsymmetrical ones is valid, it follows that the chiral stationary phase should be made symmetric to increase its effectiveness towards a broad spectrum of racemic mixtures. This will effectively reduce the number of sampling points $\underline{N}$ in eq.(4) and thus, indirectly, the size of the repeating unit. Then the question arises whether or not the most commonly used chiral stationary phases possess local symmetry. The chiral phases can not possibly have perfect symmetry but local $\underline{C}_n$-axis ($\underline{n} = 2$) may exist. Regions of the polymeric stationary phases with a high degree of orientation, $\underline{e.g.}$ TAC-columns, have been suggested.[7] In the helical synthetic polymers $\underline{e.g.}$ poly(trityl methacrylate) the local $\underline{C}_2$symmetry is generated by the helix,[8] while the local symmetry in chiral columns based on cyclodextrin might even be higher than $\underline{C}_2$. The symmetry around copper in ligand exchange columns is low but can approach $\underline{C}_2$.[9] However, from the still limited number of effective chiral columns for resolution of a broad spectrum of racemic mixtures, one can not yet evaluate the importance of symmetry properties of the stationary phase. Still, high local symmetry of the stationary phase for column chromatography is a desirable property and this possibility should be further explored experimentally.

The repeating unit. The number of sampling points $\underline{N}$ in eq.(4) and (7) increases with the number of different active sites or binding sites along the chiral column. To keep this number small, the repeating unit on the chiral column should also be small. Regularity is a crucial property of a stationary phase for resolution. Microcrystalline triacetylcellulose (TAC) is a useful column material, whereas the same material when dissolved and reprecipiated loses its crystallinity and most of its resolving ability, probably due to the regularity of the supporting phase.[10]

Dipole-dipole interactions. There are accumulating evidence for the importance of dipole-dipole interactions in chromatographic applications of chiral recognition $\underline{e.g.}$ on Pirkle columns.[6] In molecules with $\underline{C}_n$-axis the molecular dipole must coincide with the symmetry axis, while in molecules with $\underline{D}_n$-symmetry no overall molecular dipole is possible. Thus, there seems to be a contradiction in that both high symmetry and dipole-dipole interactions are important for chiral recognition. However, if local dipoles are considered rather than the total molecular dipole of a chiral molecule then both factors can still be important. Naturally, there must also be differences between various types of chiral columns in this respect.

Properties of the enantiomers. Is it possible from inspection of eq.(7) to derive some general conclusions about the desired properties of an enantiomeric mixture, other than symmetry, for ease of resolution on a chiral column? The number of sampling points N has already been discussed. For flexible molecules with many different conformations of similar energy N will, of necessity, be large and thus resolution low on average. However, if among all these conformations one particular conformer can interact specifically with the chiral stationary phase, then the disadvantage of flexibility can be outweighed by one specific interaction. The latter situation is equivalent to a large variance in the bindings of different conformers and orientations i.e. v_f is large in eq.(7). This occurs if a flexible or rigid molecule interacts strongly with the chiral phase for a defined geometry e.g. by a so-called three-point interaction. Thus, there seems to be no contradiction between previous suggestions regarding the factors important for chiral recognition and the present statistical approach which entails consideration of molecular symmetry as well as the specific molecular interactions. This is of considerable importance for the discussion of other aspects of chiral recognition, as presented in the subsequent part of this paper.

Of particular interest are the recent findings by Pirkle and Pochapsky of extreme selectivity in chiral recognition by joining two R- or S-forms, respectively, of readily separable leucine derivatives by long aliphatic chains.[11] The resultant functionalised diamides have C_2-symmetry but the unusually good separation is explained by simultaneous binding at two active sites on the chiral column.

Chiral recognition and symmetry. Resolution of racemates by chromatographic methods is but one of many applications of chiral recognition in chemistry. The weak interactions between the chiral phases and the passing racemates and the small differences between enantiomers have to be repeated many times over to result in good separations. Schurig and Bürkle have reported interesting results from GC-separations which support the idea presented here. Out of a series of substituted oxiranes, the C_2-symmetric species, trans-2,3-dimethyloxirane, gave the best separation on metal chelates in squalane.[12]

If symmetry is of importance in the case of weak interactions, what about other applications of chiral recognition with stronger interactions such as enzyme catalysis, certain kinetic resolutions, asymmetric synthesis, "host-guest" interactions and spontaneous resolution by crystallisation?

The stronger and more specific the interaction which results in chiral discrimination is, the less relevant are the arguments leading to eqs.(7) and (8). For the limiting case in which one expects the interaction to be dominated by one single well-defined complex, the symmetry arguments are not conclusive. The binding constant is still enhanced by a factor of two in the presence of a C_2-axis of symmetry but one can argue that the a priori probability for a certain specific complex decreases for a symmetrical species as compared to an unsymmetrical one.

Enzyme catalysis in a living system shows nearly complete chiral specificity but enzymes, esterases in particular, are also used in vitro to cleave ester bonds in general, which for C_2-symmetrical diesters can lead to an efficient kinetic resolution.[13] For this case the specificity of the enzyme is more directed towards the cleavage of the ester group (a non-chiral recognition) than to chiral recognition which is due to more specific interactions. We think, however, that the basic rationale for successful kinetic resolution of C_2-symmetrical diesters can be found in arguments analogous to those leading to eqs.(7) and (8).

Asymmetric synthesis with chiral catalysts or auxiliaries often takes advantage of chiral but symmetrical compounds. Several authors have pointed out the advantage of C_2-symmetry in asymmetric induction.[14] The examples of interesting C_n- ($n \geq 2$) and D_2-compounds in host-guest chemistry and enzyme-mimic research are also numerous.[15] From a synthetic point of view, symmetry is an advantage in many cases, and the general argument that in symmetric molecules all interactions with the surrounding molecules are repeated for each symmetry-related orientation always reduces the complexity of the problem and simplifies the analysis.

The phenomenon of spontaneous resolution by crystallisation or formation of conglomerate is of particular interest when discussing chiral recognition. Spontaneous resolution requires complete chiral recognition at all of the growing surfaces of a crystals and thus could be very

sensitive to the effect of symmetry. As early as 1972, Collet, Brienne and Jaques pointed out the most common denominator, a C_2-axis of symmetry, for 34 compounds out of 124 that up to that time had been reported to undergo spontaneous resolution by crystallisation or to form conglomerates.[16]

In conclusion, there seems to be a number of interesting applications of chiral recognition in which symmetry might be of importance and for which the statistical approach presented in this paper could prove useful to aquire a better understanding of the common factors which govern this important phenomenon.

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