ISOMERISM AND TOPICITY IN THREE- AND FOUR-DIMENSIONAL SPACE*: A REVIEW

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Dedicated to the memory of Dr Karel Bláha.

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Isomerism is a notion of a considerably broad meaning. Not only chemists but also physicists, biologists and philosophers come across it. In the sequel, some basic problems of the contemporary understanding of the phenomenon of isomerism of molecular structures and related problems of topic relationships between homomorphic ligands and faces are dealt with. Illustrating factual material is selected within the domain of organic chemistry. With the rapid development of nomenclature in this area in mind, the issues are presented from a point of view stressing the unity of historical and logical moments. Problems arising when moving from the analysis of molecular structure models towards the analysis of real sets of molecules are highlighted. Differences between the analysis of static molecular structures in three-dimensional space and the analysis of real dynamic molecular structures in four-dimensional space are dealt with in greater detail. The method of NMR spectroscopy is discussed from this standpoint as an example of the most widespread research tool for investigating intramolecular dynamism at present. Stereo--differentiating reactions are also treated briefly and a suggestion is made to introduce into the teaching of isomerism and topicity a classification of differentiating interactions. The relationships discussed are demonstrated comprehensively using the chemical behaviour of an optically active trisubstituted cycloheptatriene-norcaradiene system as an example and, are also discussed in connection with some new findings concerning actual chiral geometries in some conventionally achiral systems. Attention is paid to didactic presentation of the topic and an attempt is made to show probable trends in future development in this domain.

1. INTRODUCTION

Two young chemists, Friedrich Wöhler and Justus von Liebig whose later friendship and cooperation had become an example to others[1], blamed each other for inac-

* A slightly modified version of this article appeared in Chem. Listy *81*, 146 (1987) (in Czech).

curacies in elemental analyses. The object of their disagreement were two substances of identical atomic composition but different properties: silver cyanate (AgNCO) prepared by Wöhler[2] and silver fulminate (AgCNO) prepared by Liebig[3–5]. Repeated analyses had proved the accuracy of work of both[6]. Gay-Lussac who had gained some experience with a similar phenomenon before[7,8] equipped Wöhler's paper[2] with a footnote[9]: "to explain these differences, it is necessary to postulate a different mode of combination among the elements". Wöhler's famous experiment, transformation of ammonium cyanate into urea[10], has been another example of the phenomenon that was foreseen by Alexander von Humboldt[11] in 1797 and for which Berzelius, after finding that natural tartaric acid ((+)-tartaric acid) and *meso*-tartaric acid had identical molecular formulas, introduced the notion "isomerism"[12,13]. Pasteur's[14] and Wislicenus'[15] work then led directly to van't Hoff[16] and Le Bel[17] who endowed also this notion with a clear three-dimensional content.

Let the following facts testify to the significance of the notion isomerism in contemporary chemistry: (*a*) A structure with the geometry of a trigonal bipyramid, formed by five different ligands bonded to one centre, is theoretically capable of twenty different structural arragements[18,19]. (*b*) The number of isomeric structures grows rapidly with increasing number of atoms in a molecule (Table I) so that, out of

TABLE I

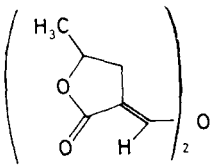
The total number of isomeric alkanes C_nH_{2n+2} and isomeric monosubstituted alkanes $C_nH_{2n+1}X$ (adapted from ref.[20])

	C_nH_{2n+2}	n	$C_nH_{2n+1}X$
	1	1	1
	1	2	1
	1	3	2
	2	4	5
	3	5	11
	5	6	28
	11	7	74
	24	8	199
	55	9	551
	136	10	1 553
	345	11	4 436
	900	12	12 832
	4 412	13	37 496
	6 563	14	110 500
Total	12 459	1 to 14	167 689

the total set of 167 689 possible monofluoroalkanes with C_1 to C_{14}, 110 500 are isomers with molecular formula $C_{14}H_{29}F$. It could be said, from this point of view, that chemistry, and organic chemistry especially, is, to a considerable extent, chemistry of isomeric molecules.

2. ISOMERISM AND TOPICITY IN THREE-DIMENSIONAL SPACE

Isomers are generally non-identical structures of identical atomic composition (the generalized notion chemical isomerism is comprehensively dealt with by Slanina[21]); this definition implies that isomers differ in their properties. If two chemical structures-geometrical models of real molecules-are found to be non-identical, it is expected, provided that the models correspond to reality, that there exists a way of differentiating between real sets of these molecules. This jump from the world of geometrical constructs-models of molecules-into the world of real molecules is not without problems if it were only for the fact that it is a jump from the world of models of the substantial into the phenomenal world. Moreover, limits of differentiation are conditioned historically. It must be, therefore, allowed for the possibility that, in a given historical moment, differences in behaviour of real sets of isomeric molecules lie below the attained limits of observability (with equimolar mixture of (±)- and *meso*-isomers of ether *I* neither column chromatography and HPLC nor ^1H (100 MHz) and ^{13}C (25 and 100 MHz) NMR spectra are able to differentiate between diastereomers. Differentiation is possible in ^1H (400 MHz) NMR spectra.[22]). Not every necessary condition (here a structural difference) is a condition sufficient for differentiation; the dialectical unity and difference between the substantial and the phenomenal has not only been a source of further development in particular scientific disciplines; it has often led to misunderstanding, too. For that matter, "... alle Wissen-



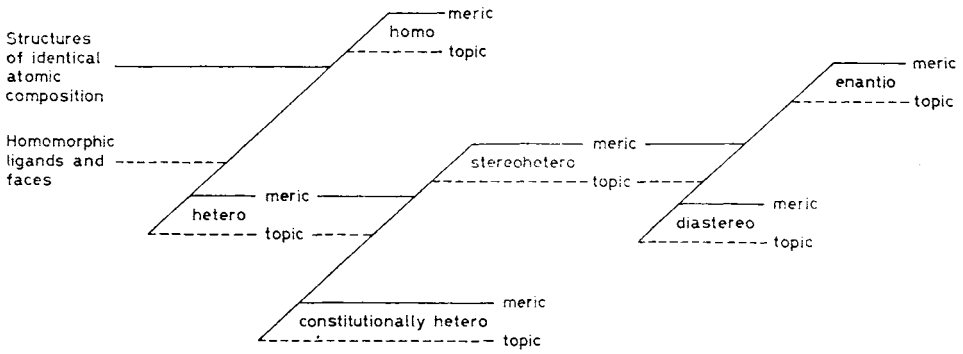
I

schaft wäre überflüssig, wenn die Erscheinungsform und das Wesen der Dinge unmittelbar zussamenfielen[23]". However, mistaking the substantial for the phenomenal or vice versa, a necessary condition for a sufficient one, has been a constant source of problems in chemistry as well. Thus, e.g., in the domian directly related to our topic, the IUPAC nomenclature rule[24] (rule E-4.1. (note (2)) states that "All chiral molecules are molecules of optically active compounds... There is a 1 : 1 correspondence between chirality and optical activity.", while enantiomers of 5-ethyl-5-propylundecane

prepared by Wynberg[25] are optically inactive within the whole range of 280 – 580 nm (measured with a spectropolarimeter with experimental error of 0·0008°). Thus the existence of mixtures composed of x kinds of isomeric molecules which, under certain circumstances, reveal the presence of y kinds of isomeric molecules (where $x > y$) is feasible and the notion residual stereoisomerism, introduced by Mislow[26] and broadened by Eliel[27] to the notion residual isomerism, is justifiable and useful even under conditions (cf. compound *I*) when all isomerizations are frozen out, i.e., in three-dimensional space.

Isomerism is a notion resulting from comparison within a set of at least two structures; a single structure, therefore, is not an isomer and when $y = 1$ one can speak only about residual structure or residual species[27].

The contemporary common classification of structures of identical atomic composition, part of the existing nomenclature[24], is dichotomic and based on comparison in pairs. Two structures of identical atomic composition are either homomeric[28] (identical) or heteromeric[29] (isomeric). If they are heteromeric, the criterion for further differentiation is constitution. Heteromeric structures are either constitutionally heteromeric or stereoheteromeric. While a satisfactory classification of constitutionally heteromeric structures has not yet been carried out[21], stereoheteromeric structures are either enantiomeric or diastereomeric*, as shown in Scheme 1. The mutual relationship of two structures of identical atomic composition is always characterized by a single characteristic term of the classification scheme, i.e., the two structures can be, e.g., either enantiomers or constitutional isomers but not both at the same time. Only a set of enantiomeric structures may consist of just two elements. The notion enantiomerism is the only one of the characteristic terms of the classification scheme that is necessarily connected with the notion chirality (an evidence of the fact that chirality and stereoisomerism are notions originating in



SCHEME 1

* Ref.[24], rule E-4.6.

conceptually different views; differences between them are beginning to be understood only now[30]), i.e., only enantiomeric structures are necessarily chiral. Enantiomeric structures, as well as homomeric structures, have always the same symmetry point group. However, point groups which characterize enantiomeric structures, unlike point groups characterizing homomeric structures, may not contain, as their element, any symmetry operation of the second kind (symmetry operation including reflexion). As properties of any system are invariant with respect to its symmetry operations[31], all properties of homomeric structures are identical. By the same token, enantiomeric structures have identical scalar but different pseudoscalar* properties[32]. Diastereomeric and constitutionally heteromeric structures do not necessarily have identical symmetry point groups; their properties are different whether scalar or pseudoscalar. This general expression includes an old chemical experience that enantiomeric structures have identical while diastereomeric and constitutionally heteromeric structures have different inner energy contents. Exactly, the first half of this statement holds for isolated enantiomeric structures without the presence of outer fields; in such a situation, their total hamiltonians are identical except for the sign. In real world, their inner energy contents could differ[33] but, the magnitude of the difference prognosticated (relatively 10^{-15} to 10^{-18}) is beyond the range of contemporary possibilities of experimental verification and, it has not yet been proven[34].

We learn about the structure of compounds by observing and measuring their behaviour, properties. Each measurement leads to an energy interaction and measurements with identical interaction energy values do not differentiate between the objects measured. Thus, generally, constitutionally heteromeric and diastereomeric structures are distinguishable by any of their properties (in a real situation, there is the complication of too small differences, accidental identity of properties under certain conditions or time-scale dependent phenomena), enantiomeric structures only by differences of their pseudoscalar properties. As shown in Fig. 1, differentiation of enantiomeric structures is possible only under conditions where the energetic degeneracy is broken down, i.e., in the presence of a chiral agent (be it environment, effect or reagent); only under these conditions a diastereomeric relationship is formed between the agent and each of the enantiomers, characterized by different inner energy of the new forms (e.g., transition states) or different and thus distinguishable interaction energy. With diastereomeric or constitutionally heteromeric structures differentiation is possible using both chiral or achiral agents.

Thus, the common classification of structures of identical atomic composition given in Scheme 1 has a certain logical and noetical shortcoming in that there are more fundamental differences between the subgroups of the main classification

* Pseudoscalar properties are (unlike scalar ones) characterized by reversal of the sign of their numerical value if the observed object is replaced by its nonsuperimposable mirror image.

groups than there are between these main groups themselves; diastereomeric structures are more similar, in their behaviour, to constitutionally heteromeric structures* and enantiomeric structures are more similar to homomeric structures. This shortcoming is conditioned historically by the importance of localized bonds in chemistry (a bond between two atoms in a molecule either exists or does not exist) and the importance of the notion constitution derived from that. At the present stage of development, it is obvious that the issue of bond relation between two atoms in a molecule is rather a question of extent and, a localized bond is only one of the extremes. However, formalization of the electron-pair bond in the valency dash of a chemical formula is illustrative and still has an important message to convey. Thus, it is not surprising that a new proposal for classifying structures of identical atomic composition appeared[35], based on geometrical rather than topological properties of the molecular model (Scheme 2). In this classification, all pair-wise bond relationships among all atoms in a molecule are taken into consideration and, geometric models of structures of identical atomic composition are classified on the basis of feasibility or unfeasibility of an isometric transformation** between them. If an isometric transformation exists in three-dimensional space, it is either an isometry of the first kind (I_1), transforming the geometric model of a molecule into itself (proper congruence, e.g., homomeric structures), or an isometry of the second

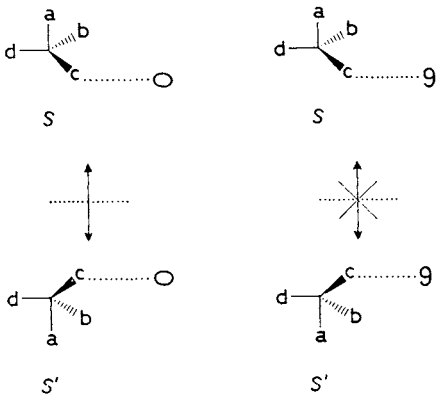


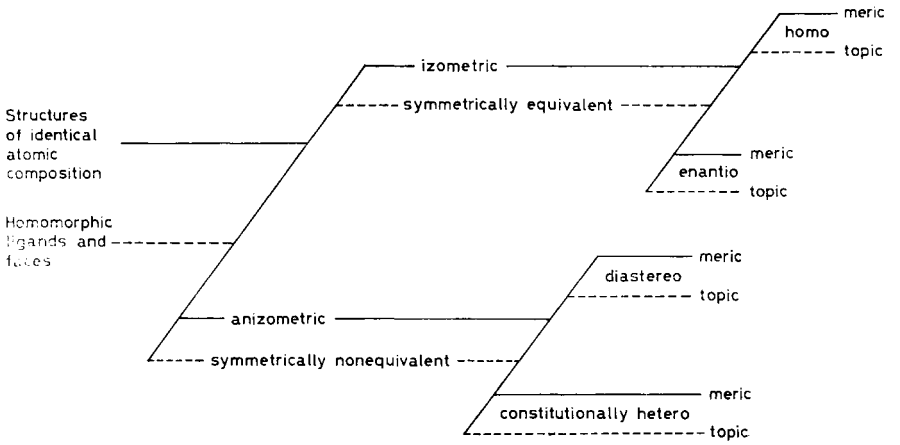
FIG. 1

Enantiomeric ⟷ and diastereomeric ⟷ relationships in an interaction of enantiomeric structures (S) and (S') ($a \neq b \neq c \neq d$) with an achiral (O) and a chiral (9) agent

* Diastereomeric structures differ often in their physical and chemical properties more than do constitutionally heteromeric structures. Thus, e.g., *trans*-4-bromo-4-octene gives 4-octyne upon treatment with sodium methoxide in methanol, whereas *cis*-4-bromo-4-octene gives 3,4-octadiene under the same conditions[36], or fumaric acid, unlike maleic acid, does not form cyclic anhydride.

** An isometry is a transformation which preserves the lengths of all line segments between pairs of points, i.e., which preserves the shape and size of the figure — here the geometric model of a molecule.

kind (I_2), transforming the geometric model into its nonsuperimposable mirror image (improper congruence, e.g., enantiomeric structures). In classification Scheme 2, an isometric transformation is applied as the main criterion and, structures o identical atomic composition are divided into isometric (according to the transformation I_1 or I_2 homomeric or enantiomeric, respectively) and anisometric (diastereomeric or constitutionally heteromeric from the constitution viewpoint).



SCHEME 2

Although its adequacy to a substantial feature of chemical reality is beyond dispute, the proposal of a new classification of structures of identical atomic composition seems not to have become very widespread. Out of possible reasons for this situation, the most significant seems the one resting on considerable inertia of habitual thinking. The new classification gives no space to such deep-rooted notions as stereoisomerism and stereoisomer and, even the notion isomerism itself has in it lost its central position.* However, its indisputable usefulness lies at least in that it has clarified important problems; near future will obviously appreciate it as the one of a greater carrying capacity.

From the historical point of view, the first observation that two homomorphic**

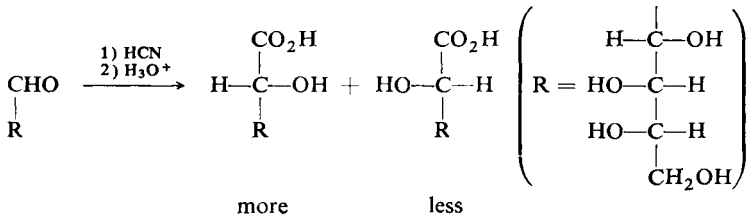
* Differences between both approaches to classification are discussed in detail in ref.[30]. It is shown that Scheme 1, where primacy is given to constitution, follows in the tradition of van't Hoff and Le Bel, whereas Scheme 2, where primacy is given to symmetry, follows in the tradition of Pasteur.

** Homomorphic[37] ligands are atoms or groups of atoms which, considered in isolation, i.e., separated from the rest(s) of a molecule(s) of which they are a part, are identical (properly congruent); in case the ligands are nonsuperimposable mirror images (are improperly congruent), they are called enantiomorphic[37].

ligands bonded to the same atom can behave differently has been decarboxylation of ethylmethylmalonic acid in the presence of brucine[38] (*A*).

$$C_2H_5(CH_3)C(CO_2H)_2 \xrightarrow[t]{\text{brucine}, -CO_2} \begin{matrix} 55\%(S)\text{-}(+) + 45\%(R)\text{-}(-) \\ C_2H_5CH(CH_3)CO_2H \end{matrix} \qquad (A)$$

Ten years earlier, it was found that addition of hydrogen cyanide to L-arabinose gave, after hydrolysis of the cyanohydrins formed, a mixture of L-mannonic and L-gluconic acids (*B*), where the L-mannonic acid prevailed[39]. It can be said, in view of the

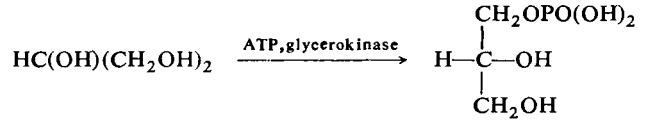


(*B*)

contemporary knowledge, that this has been the first observed case of a reaction wherein there have been non-equivalent manifestations of two molecular environs of the carbonyl group corresponding to two half-spaces separated by the molecular plane – to two corresponding faces of an aldehydic functional group. Similarly, addition of hydrogen cyanide to benzaldehyde in the presence of emulsine[40] or quinine[41] gave an optically active product (*C*), i.e., in the resulting mixture of cyanohydrins, one prevailed.

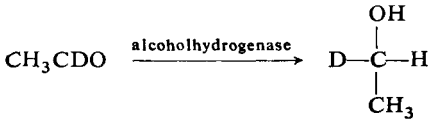
$$C_6H_5CHO + HCN \xrightarrow{\text{quinine}} \text{opt. active } C_6H_5CHCN(OH) \qquad (C)$$

Out of abundant similar reactions described up to now, let us only give two classical examples from biochemistry. Phosphorylation of glycerol with ATP in the presence of glycerokinase gave (*R*)-(−)-glycerol-1-phosphate[42] exclusively (*D*) and, reduction



(*D*)

of acetaldehyde-1-d with yeast alcoholdehydrogenase yielded only (*S*)-(−)-ethanol-1-d[43–45] (*E*).



(*E*)

From another area, let it finally be shown that, with molecules $CF_2BrCHBrC_6H_5$ (*II*) and $CH_2BrC(CH_3)BrCO_2CH_3$ (*III*), NMR spectra display distinctly different signals for fluorines[46] and methylene hydrogens[47], respectively.

A clear understanding of these facts was setting in rather slowly. In the domain of reactivity, a rational explanation based on mechanism[48,49] fell into oblivion and only Ogston's[50] hypothesis (a three-point contact model) brought about an explanation again. That the reason for all these phenomena was the symmetry of the reacting structures and that this behaviour was independent of the mechanism of the process, was obviously discovered[51], for the first time, in 1954. In the domain of NMR, an explanation was presented[52,53] in the early sixties. Exact analysis, however, was carried out in complex only in the paper by Mislow and Raban[54], who had dealt with the so-called topic* relationships in detail and who, in their classification, had introduced the notions homotopicity and heterotopicity.

From the contemporary viewpoint, homomorphic ligands and faces can be classified as either homotopic or heterotopic. Heterotopic ligands and faces are then either constitutionally heterotopic or stereoheterotopic. Stereoheterotopic ligands and faces are either enantiotopic or diastereotopic. This classification is thus completely analogical to that of structures of identical atomic composition according to Scheme 1 and is a part of it as well. This classification, too, is dichotomic and based on a comparison, in this case a comparison between two (at least) homomorphic substructures (ligands or faces). The comparison may be either internal (a comparison between homomorphic substructures within a single structure) or external (a comparison between corresponding substructures in different structures).

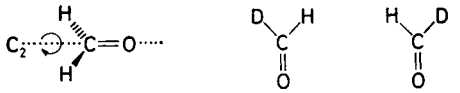
Ligands are homotopic by internal comparison if their interchange leading to a homomeric structure can be carried out by rotation about an axis of rotation, C_n ($\infty > n > 1$),** which is a symmetry element of the structure. Faces are homotopic by internal comparison if their interchange leading to a homomeric structure can be carried out by rotation about a two-fold axis of rotation, C_2.** Evaluating in this way the hydrogen atoms and the faces of the carbonyl group in formaldehyde, (*Fa*), we find them both homotopic.

Instead of the above mentioned symmetry criterion, advantage can be taken, for identifying topic relationships of homomorphic ligands, of a substitution criterion and, for identifying topic relationships of homomorphic faces, of an addition criterion. Applying the substitution criterion, we gradually substitute each of the compared ligands for another ligand, different from all ligands bonded to the atom or atoms to which the original ligands are bonded. In a great majority of cases, a substitution of compared ligands for ligands formed by, or containing another isotope, will suffice. If the ligands are homotopic, we must obtain, by their gradual substitu-

* From Greek topos = place.

** Asymmetry (C_1) excludes homotopicity by internal comparison.

tion, homomeric structures, as shown in (*Fb*) for the hydrogens in formaldehyde. Applying the addition criterion, we compare structures formed by an addition of the same achiral reagent to each of the compared faces. If the faces are homotopic, the products are homomeric, as shown in (*Fc*) with formaldehyde and hydrogen cyanide as addens. In some cases, the addition criterion meets with problems[55]; then, the symmetry criterion will solve the question[56].

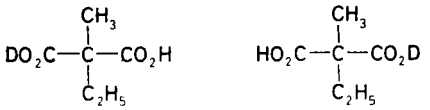


a *b*

(*F*)

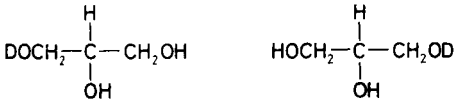
c

If the substitution or addition criterion leads to heteromeric structures, the compared ligands or faces are heterotopic. Identifying constitutional heterotopicity is usually an unambiguous matter that does not need deeper inquiry.



a

(*G*)



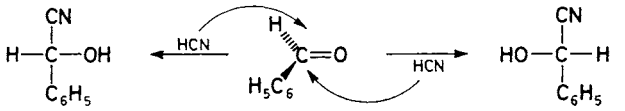
b

Ligands are enantiotopic by internal comparison if their interchange, leading to a structure homomeric with the original one, can be effected only by a rotation-reflection operation (S_n).* Faces are enantiotopic by internal comparison if there exists a S_n axis perpendicular to the plane and no C_2 axis exists in the plane of the faces.* From the viewpoint of the substitution criterion, ligands are enantiotopic by

* Chirality excludes enantiotopicity by internal comparison.

internal comparison if gradual substitution of each of them leads to enantiomeric structures. Thus, according to (*G*), carboxyl groups in ethylmethylmalonic acid, (*Ga*), and hydroxymethylene groups in glycerol, (*Gb*), are enantiotopic.

From the viewpoint of the addition criterion, faces are enantiotopic by internal comparison if gradual addition to each of them leads to enantiomeric products. Thus, according to (*H*), the faces of the carbonyl group of benzaldehyde are enantiotopic.

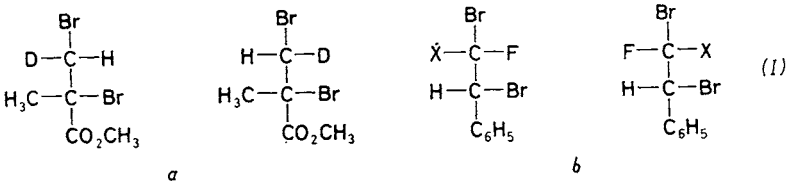


(*H*)

The same conclusion will be arrived at when analyzing the mutual relationship of the faces of acetaldehyde, (*E*), whether deuterated or not.

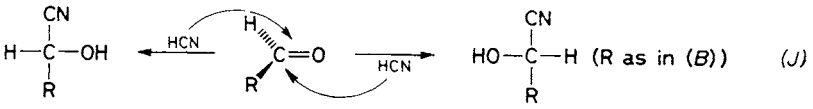
When comparing externally between homomeric structures, all corresponding ligands and faces are homotopic. When comparing externally between enantiomeric structures, all corresponding ligands and faces are enantiotopic.

Ligands and faces are diastereotopic by internal comparison if they are not constitutionally heterotopic and cannot be interchanged by any symmetry operation. From the standpoint of the substitution criterion, ligands are diastereotopic by internal comparison if gradual substitution of each of them leads to diastereomeric structures. Thus, the methylene hydrogens in the compound *III* are diastereotopic, according to (*Ia*), and the same holds for the fluorines in the compound *II*, as follows from (*Ib*).



a *b* (*I*)

From the standpoint of the addition criterion, faces are diastereotopic by internal comparison if gradual addition to each of them leads to diastereomeric structures. Thus, according to (*J*), the faces of the carbonyl group in L-arabinose are diastereotopic.



(*J*)

When comparing externally between diastereomeric structures, all corresponding ligands and faces are diastereotopic.

Let us now consider in greater detail the general consequences of the analysis of homomorphic ligands and faces. The total hamiltonian of an isolated molecule and the corresponding wave-functions reflect the symmetry of the molecule. If two ligands or two faces are homotopic, the electron distribution around them is identical (properly congruent); let them be enantiotopic, and the electron distribution around one of them is a nonsuperimposable mirror image of the electron distribution around the other. With ligands and faces which are diastereotopic or constitutionally heterotopic, the electron distributions are different. In other words, properties of ligands and faces are always identical when they are homotopic and, always different when they are constitutionally heterotopic or diastereotopic. Ligands and faces which are enantiotopic differ in properties only in the presence of a chiral agent (reagent, environment or effect), under all other circumstances their properties are identical, as follows from Fig. 2.

It is obvious, on the basis of these considerations, why diastereotopic hydrogens or fluorines give rise to distinct signals in NMR, why achiral hydrogen cyanide is sufficient for differentiation of diastereotopic faces in L-arabinose and why, for differentiation of enantiotopic carboxyl groups in ethylmethylmalonic acid, enantiotopic hydroxymethylene groups in glycerol and enantiotopic faces of the carbonyl group in acetaldehyde-1-d the presence of a chiral agent is absolutely necessary.

Especially the widespread use of NMR spectroscopy which enables us to follow localized properties of atoms in a molecule directly, makes clear understanding of the relationships between homomorphic ligands necessary. Fig. 3 shows the consequence of these relationships in practice on a schematic cut-out of ^{1}H NMR spectra of analogous compounds of γ-butyrolactone and γ-valerolactone series. In the butyro-

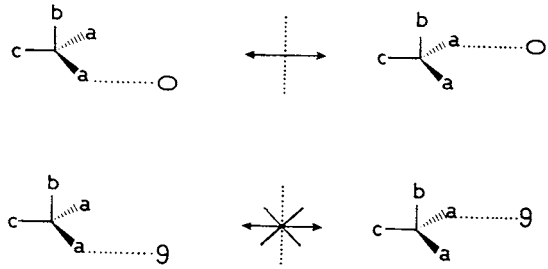
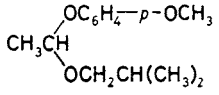


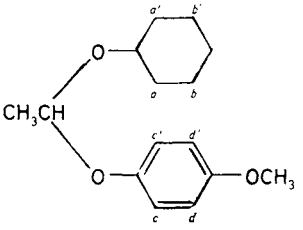
FIG. 2

Enantiomeric ←┼→ and diastereomeric ←╳→ relationships in an interaction of enantiotopic ligands a (a, b, c are achiral; $a \neq b \neq c$) with an achiral (○) and a chiral (9) agent

lactone compound, the given protons are enantiotopic and therefore isochronous* under the conditions of NMR measurement in achiral solvent, whereas the given protons in the valerolactone compound are diastereotopic, anisochronous* and, in the spectrum, not only their spin–spin interactions with the surrounding protons but also their mutual interaction is manifestly shown. Thus, in achiral NMR, the cause, the necessary condition for anisochrony of homomorphic ligands is their diastereotopicity or their constitutional heterotopicity. That this is not a sufficient condition follows from the following fact. In acetaldehyde isobutyl *p*-methoxyphenyl acetal (*IV*), the geminal methyl groups are diastereotopic. In ^{1}H NMR, their aniso-



IV



V

chrony shows clearly even at 60 MHz, whereas, in ^{13}C NMR at 25 MHz, they remain isochronous[59]. On the other hand, in ^{13}C NMR of acetaldehyde cyclohexyl *p*-methoxyphenyl acetal (*V*), diastereotopic carbons *a*, *a'* and *b*, *b'* give distinctly

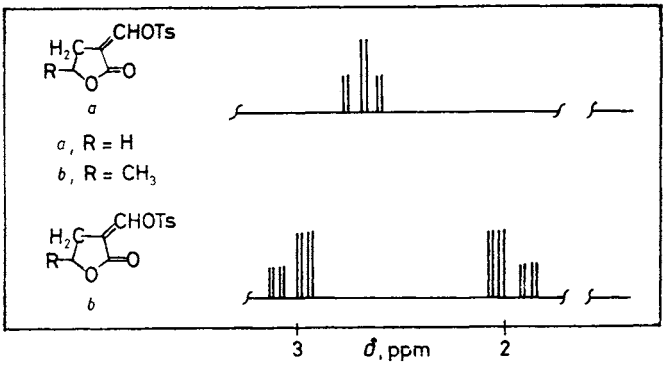


FIG. 3

A schematic cut-out of ^{1}H NMR of given methylene protons of (*E*)-3-(*p*-toluenesulfonyloxymethylene)dihydro-2(3*H*)-furanone[57] (*a*), and (*E*)-3-(*p*-toluenesulfonyloxymethylene)-5-methyldihydro-2(3*H*)furanone[58] (*b*).

* Isochronous nuclei have the same chemical shift, anisochronous nuclei differ in chemical shift.

different signals at 25 MHz, whereas diastereotopic carbons *c*, *c'* and *d*, *d'* remain isochronous under these conditions[59]. The anisochrony of carbons a, a' and b, b' in compound *V* suggests the importance of the notion external comparison. Regarding the small natural occurence of ^{13}C (1·108%), the probability is negligible that the signals of the diastereotopic carbons in question are being measured within one molecule. In fact, their signals originate in the corresponding atoms in different homomeric molecules. As shown[60] in detail, however, substructures corresponding in external comparison are not necessarily comparable by internal comparison (when present in a molecule only in one specimen, e.g., methoxy group in the compound *V*) but, substructures corresponding in internal comparison are always comparable by external comparison. In homomeric molecules, "the geminal anisochrony is precisely the same whether reference is made to diastereotopism by internal or external comparison[60]".* The term "chemically equivalent nuclei[61]", often used by NMR spectroscopists, is now seen to denote, under achiral conditions, nuclei homotopic and enantiotopic or, under chiral conditions, only homotopic nuclei.**

The classification of homomorphic ligands and faces in Scheme 1 has the same shortcoming as the analogical classification of structures of identical atomic composition. Introduction of a new classification, analogical to the classification of structures of identical atomic composition given in Scheme 2, in which these shortcomings are removed, presents no problems[35]. Let us quote: "Since a symmetry operation is an isometry which preserves the initial position of the figure in space, the parallel classification scheme for topic relationships is logically obtained by replacement of I_1 and I_2 with symmetry operations of the first and second kind, respectively. Groups of atoms in a molecule are either related by a symmetry operation of the molecule, or they are not. If they are, they are either homotopic or enantiotopic, according as to whether the symmetry operation is of the first kind or only of the second. If the groups are not related by a symmetry operation of the molecule, they are diastereotopic or constitutionally heterotopic, according as to whether they have the same constitution or not (ref.[35])".

---

* Generally, however, a difference can show in behaviour of ligands diastereotopic by internal comparison and ligands diastereotopic by external comparison. For instance, mutual spin-spin interactions between the former can show in NMR, whereas no such interaction exists between the latter. There should be a difference in ^{13}C NMR spectrum of a hypothetical modification of the compound *IV* with the geminal methyl groups composed of ^{13}C and H and the ^{13}C NMR spectrum of the compound *IV*.

** That it all sounds a little bit complicated is mainly due to the fact that chemists, for simplicity, are still used to consider an object under scrutiny isolated from its surroundings and from the means they use for scrutiny. The physically sound way, however, would be to consider the object, its surroundings and the method used as a whole. Considering any achiral solute in a chiral solvent in such a way would show, in principle, that there are no enantiotopic ligands in the solute molecules.

Thus, two groups arise, as shown in Scheme 2. The group of symmetry equivalent ligands and faces which are interchangeable under the symmetry operations of the structure and the group of symmetry nonequivalent ligands and faces which are not. Unlike the isometric classification of structures of identical atomic composition, this symmetry-based classification of homomorphic ligands and faces has become quite common, especially in the domain of NMR spectroscopy.

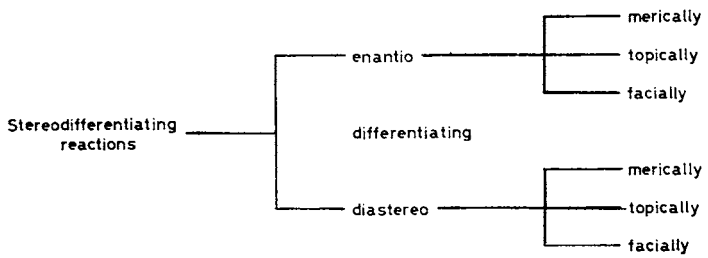
3. DIVERTIMENTO – DIFFERENTIATING REACTIONS AND INTERACTIONS

One of the basic problems of chemistry, the one of the greatest practical and general significance, has been the problem of reactivity in the broadest sense of the word. From the point of view of methodology as well as of the information content, it has often been more advantageous to treat this problem by comparison, to proceed towards solving the problem of reactivity by way of investigating relative reactivities. Relative reactivities of isomeric compounds, especialy of those that are not constitutional isomers, have been an important part of the whole issue; in the domain of stereoisomeric compounds, many problems are more subtle and, at present, in many respects more vital for the future development of chemistry and its impact on the practical life of mankind. A state of knowledge attained should always be adequately represented in systemization – classification. Let us therefore consider, in connection with the previous section of the article and in general terms, classification problems of reactions of stereoheteromeric structures and of localized reactivity of stereoheterotopic ligands and faces. The most important group of such reactions has still been widely known as asymmetric*, the first published example there of being the reaction (*B*). Let us briefly deal with this group of reactions from a standpoint closely related to the contents of the previous chapter, a standpoint first used by Izumi[63]. Izumi's classification has been based on the notion differentiation; in connection with a differentiation of stereoheteromeric structures or, as the case may be, stereoheterotopic ligands and faces under chiral conditions, the term stereodifferentiation has been used.

Unlike earlier conceptions, Izumi's classification has formulated unambiguously principal general conditions for the course of individual types of stereodifferentiating reactions, thus giving a clear clue for the direction of their further investigation. As mentioned before, enantiomers as well as enantiotopic ligands and faces can only be differentiated on the basis of chiral effects. Limiting ourselves to differentiating reactions, we will understand under a chiral effect a "nonflexible" action of a chiral agent (be it reagent, catalyst, environment or simply a physical influence) causing a permanent change in the original state of the system and not just fluctuations

* In current literature[62], as the phenomenon of chirality accompanying them is not always asymmetry, these reactions have often been called enantioselective.

from equilibrium. Reactions of this type where in the differentiation process chirality originates in the reagent, have been called enantiodifferentiating reactions by Izumi[63] (Scheme 3); products of these reactions are usually enantiomers.



SCHEME 3

As already noted, diastereomers and diastereotopic ligands and faces are, in principle, distinguishable by any method. Reactions in which these are differentiated are included in the group of diastereodifferentiating reactions as far as chirality, conditioning differentiation, is present in the substrate, i.e., the diastereomers under differentiation are chiral or, as the case may be, the diastereotopic ligands and faces are parts of a chiral structure.*

Within each main classification group of Scheme 3, subgroups are then distinguished according as to whether the differentiation achieved in the reaction is connected with differentiation of whole structures (-meric-differentiating), of homomorphic ligands (-topic-differentiating), or of homomorphic faces (-facial-differentiating reaction).** Thus, those reactions are not included in Izumi's classification where achiral diastereomers, or diastereotopic ligands and faces incorporated in achiral structures, are differentiated; so-called asymmetric transformations of the first and second kind[64] are, according to Izumi[63], not included in the stereodifferentiating reactions either.

This classification could be broadened in this respect as, in principle, there cannot be any difference between differentiation of diastereotopic hydrogens in achiral vinyl chloride and differentiation of diastereotopic hydrogens in the chiral substrate of reaction (*K*), as there cannot be, in principle, any difference between differentiation of diastereotopic faces of chiral L-arabinose (*B*) and diastereotopic faces of achiral 4-tert-butylcyclohexanone. If a racemic modification is seen as a stochastically achiral system according to Mislow and Bickart[65], i.e., chirality of real

* The conceptual difference between stereoisomerism and chirality[30] leads to the fact that diastereomers can be chiral as well as achiral and diastereotopic ligands and faces can be parts of chiral as well as achiral structures[54].

** Izumi[63] has classified stereodifferentiating reactions into -meric-, -topic-, or -facial-differentiating, according as to whether the differentiation is taking place "at a chiral, prochiral, or sp^2-prochiral center...".

molecular systems is seen phenomenologically, there is no reason to exclude asymmetric transformations of the first kind (a transformation of a labile racemic substrate under the action of an optically active reagent in solution) and asymmetric transformations of the second kind (a transformation of a labile racemic modification under the action of an optically active reagent, leading to an excess of one diastereomer in the solid state) from enantiomeric-differentiating reactions. In both cases enantiomers are differentiated and chirality originates in the reagent, which is in accordance with Izumi's[63] definition. The asymmetric transformations of the first and second kind have been excluded from the classification by Izumi on the grounds that both are thermodynamically controlled processes. So, however, are other reactions included in the classification, e.g., Meerwein–Ponndorf–Oppenauer equilibria[66]. A differentiation, whether kinetic or thermodynamic, is a function of the whole system–substrate, reagent, solvent, etc.

Although actual mechanisms of stereodifferentiating reactions are not considered in this classification, some mechanistic requirements can be inferred from its basic tenets. Obviously, intermediates or transition states have to be formed between which diastereomeric relationships* exist. Within such generally formulated necessary conditions, it is possible to solve more rationally also possibilities of intended creation of higher intensity of diastereomeric relationships between the transient structures (greater energy differences) with the aim of achieving a higher degree of differentiation in reactions. If chiral effects in the reactions are conceived in such a broad sense that would include even, e.g., effects of polarized radiation, then, the so-called absolute asymmetric synthesis could be included in the classification of stereodifferentiating reactions as well. It can be derived, as a necessary condition, that the "nonflexible" effects of the chiral physical influence must be, according to the type of differentiation, aimed at either the whole structure (such enantiomeric-differentiating absolute asymmetric syntheses are known, cf. e.g., refs[63,64]), or at the ligands or faces under differentiation.

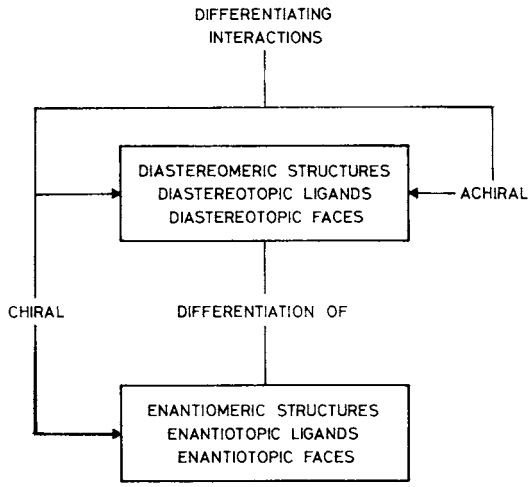
Reactions (*A*) and (*D*) are then classified as enantiotopic-differentiating, reactions (*C*) and (*E*) as enantiofacial-differentiating and, all three classical Pasteur's methods for separation of enantiomers as enantiomeric-differentiating reactions; with mechanical separation of hemihedral crystals, the chiral agent is man. Reaction (*B*) is diastereofacial-differentiating and reaction (*K*), where one of the two diastereomeric products is formed in excess[68], is diastereotopic-differentiating.

$$(S)\text{-}(-)\text{-}C_6H_5CH_2S(O)CH_3 \xrightarrow{CH_3I,\ C_4H_9Li} C_6H_5CH(CH_3)S(O)CH_3 \qquad (K)$$

It would be useful, especially from the didactic point of view, to make use of an analogical classification of stereodifferentiating interactions ("flexible" effects which lead only to a short-term, although repeated, fluctuations from equilibrium) which make it possible to differentiate stereoheteromeric structures or, as the case may be,

* A theory of diastereomeric transition states was published by Salem[67].

stereoheterotopic ligands and faces. The classification could be similar to the one suggested in Scheme 4. It would show clearly the conditio sine qua non for differen-



SCHEME 4

tiation of enantiomeric structures and enantiotopic ligands or faces, i.e., the necessity of using a chiral effect. It would also show the general differentiability of diastereomeric structures and diastereotopic ligands or faces by, in principle, any effect. In connection with a survey of currently used kinds of "flexible" chiral and achiral effects (Table II), including the possibilities of modification by which the individual effects can be transformed from achiral to chiral (e.g., NMR using chiral shift reagents or in chiral solvents, X-ray using the anomalous X-ray scattering, recent methods of enantioselective ionization in mass-spectrometry[69], infrared circular dichroism[70], and Raman circular intensity differential spectroscopy[70,71]), such a classification could serve better realization of what is, in principle, feasible and what not, as well as a realization of modifications necessary for transforming a problem from the category of impossible into the category of possible.

4. ISOMERISM AND TOPICITY IN FOUR-DIMENSIONAL SPACE

To define a molecule, besides a definition of geometry, a definition of time[72] is required. (Perhaps, the main reason for repressing this fact so often into the subconscious lies in that its clear realization so intrusively reminds us of our own mortality).

The time factor invaded the static conception of isomerism as late as 1885 with

the work by Laar[73,74]; there it was denoted a special space under the notion tautomerism. That isomerism itself is indivisibly connected with the time-dimension has been stressed, e.g., in ref.[26].

Let us now consider the problems discussed in the second section from the point of view that includes the time dimension as well and that only now treats the issues at the level of current knowledge. Let us do so with some selected examples, first for pairs of structures of identical atomic composition, then for homomorphic ligands and faces. In Fig. 4, examples are given of homomeric and heteromeric structures. Let them first be evaluated according to the position of individual structures in pairs on the vertical y where, for this purpose, let the difference Δy for compared structures in a pair be proportional to ΔG_0. A transformation of one structure into the another one (whether practically realizable or not) represents a reaction in accord with the mass-conservation law for which, therefore, an equilibrium constant can be defined. With pairs of homomeric and enantiomeric structures $\delta \Delta G_0 = 0$ and thus $K = 1$, with pairs of diastereomeric and constitutionally heteromeric structures $\delta \Delta G_0 \neq 0$ and thus $K \neq 1$. The fact already discussed is thus expressed in another – thermodynamic and, perhaps, more illustrative – way. Let us now devote our attention to kinetic characteristics of the above mentioned equilibria which, if known, are given in Fig. 4. Let us consider relative positions of the compared pairs of structures of the same type (e.g., homomeric) on the vertical which, for this purpose, be the axis of ΔG^* or, (as we are concerned with monomolecular reactions) the axis of mean life-times, τ, of the given structures. The mean

TABLE II

A survey of commonly used "flexible" chiral (A) and achiral (B) effects

"Flexible" effect	A	B	Transformation from B to A is possible (+)
Visible and ultraviolet spectroscopy	–	+	–
Infrared spectroscopy	–	+	+
Raman spectroscopy	–	+	+
Optical rotatory dispersion	+	–	–
Circular dichroism	+	–	–
Polarimetry	+	–	–
NMR spectroscopy	–	+	+
EPR spectroscopy	–	+	–
X-Ray analysis	–	+	+
Mass spectrometry[a]	–	+	+

[a] Mass spectrometry is a "nonflexible" effect. It has been included in the Table because of its capability of differentiation.

HOMOMERS
CONSTITUTIONAL HETEROMERS
DIASTEREOMERS
ENANTIOMERS
Kinetically stable
Kinetically labile
ΔG*, kJ mol⁻¹ or τ, s (300 K)
≈270
≈1·6.10³³ *
115·9
(ref.75)
2·4.10⁵
81·2
(ref.76)
2·2
42·7
(ref.77)
4.10⁻⁷
≈400
≈7·1.10⁵⁵ *
>140
(ref.78)
3·8.10¹⁰
113·4
(ref.81)
8·9.10⁵
~90
(refs79,80)
7·5
18
(ref.82)
2·2.10⁻¹¹
77·5
(ref.83)
5.10⁻¹
~20
(ref.84)
~4·9.10⁻¹¹
R = CO2CH3

life-times given best show directly that, at the lower edge of Fig. 4, there are kinetically labile structures and, at its upper edge, there are kinetically stable structures. While kinetically stable stereoheteromeric structures are commonly known under the name configurational isomers and kinetically labile stereoheteromeric structures under the name conformational isomers (conformers), for kinetically labile constitutionally heteromeric structures the term tautomers has become common. Mutual transformations of homomeric structures are known as topomerizations[85], mutual transformations of heteromeric structures as isomerizations. A difference between conformers and configurational isomers is thus the difference in a height of the energy barrier separating them and thus a difference in the interconversion rate under defined physical conditions. Restricting the notion configurational isomers to stereoisomers the interconversion of which requires bond breaking (i.e., multiple bonds isomerism) and, the notion conformers to stereoisomers interconverted by rotation about single bonds, is then artificial,* since it does not express the heart of the matter; all the same, it has been commonly handed down from one textbook to another. Similarly, the term atropoisomerism is only of historical significance and otherwise it has only complicated an understanding of the problem itself; among atropoisomers, both kinetically stable (e.g., 2,2'-dicarboxamido-6,6'-dimethoxybiphenyl with a barrier[86] of 105 kJ mole^{-1}) and kinetically labile (e.g., 2,2'-dimethoxybiphenyl with a barrier[87] of 57·4 kJ mole^{-1}) pairs can be found. The question is rather the boundary between configuration and conformation; a rigorous dividing line would always be artificial and is obviously useless. As an orientation boundary for man's practical needs, the useful height of the barrier of 100 kJ mole^{-1} (1 hour mean life-time under ambient conditions, cf. Table III) will do good service.

Mislow[29] stated that the conception of isomerism had a practical sense only if an experimental method existed, capable of differentiation between isomers. Apparently, it is necessary to ask where a boundary of the energy barrier is to be placed, above which structures expressed by different models could yet be practically differentiated and, which structures it is then sensible to regard as isomeric. Eliel[27] has proposed a solution to this problem; two different structures of identical atomic composition

←

FIG. 4

A comparison of thermodynamic and kinetic stability of pairs of structures of identical atomic composition. Values of $\Delta G^{\neq}$ and τ designated by $\sim$ are approximate, estimated from date in the literature, values $\Delta G^{\neq}$ and τ designated by $\approx$ are rough approimations.
Numbers indicated by asterisk, (*), though correctly arrived at from the corresponding energy barrier values, seem to loose some sense when compared to the estimated "age" of the universe ($\approx 10^2$ s). A verbal statement, e.g., limitless, would, perhaps, be more appropriate.

* Such problems apparently stem from the importance given to localized bonds; different viewpoint are useful when "the time does not seem ripe to legislate...[24]".

are considered isomeric if they are at, or very near, a minimum on a potential energy hypersurface and the energy barrier between them is equal to, or higher than, kT, or RT mole^{-1} (where k is the Boltzmann constant and R is the gas constant). For better evaluation of this problem, several relevant data, calculated for a simplified system with two degenerate potential energy minima divided by a barrier of $\Delta G^{\neq}$ (representing topomerizations or enantiomerizations, from our point of view), are given in Table III. Let it be added to the data in Table III that a molecular vibration half-time is approximately 10^{-13} and an electron excitation half-time approximately 10^{-15} seconds. Thus, the boundary suggested by Eliel[27], dependent only on temperature, is truly an extreme limit from the viewpoint of chemistry; it will satisfy both the preparative chemist and the spectroscopist.* Electronic excited states have long been considered, by quiet agreement among chemists, to be an altogether special category.

On the basis of this proposal, conformationally diastereomeric *gauche*- and *anti*-forms of 1,2-dichloroethane, with a barrier[27] of approximately 13 kJ mole^{-1}, are regarded as isomers; their kinetic lability is expressed in the term conformational, their mutual relationship in the term diastereomers. Both possible pyramidal forms of asymmetric amines $R^1R^2R^3N$ (conformational enantiomers) are regarded as isomers as well, since the barrier dividing them is greater[27] than 24 kJ mole^{-1}. By

TABLE III

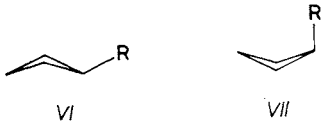
Mean life-time, τ, dependence on $\Delta G^{\#}$ for a degenerate system with two potential energy minima (calculated according to Eyring's equation[88]).

$\Delta G^{\#}$ kJ mole^{-1}	τ, s, at temperature, K		
	200	300	400
5	$4{\cdot}8 \cdot 10^{-13}$	$1{\cdot}2 \cdot 10^{-13}$	$5{\cdot}4 \cdot 10^{-14}$
10	$9{\cdot}8 \cdot 10^{-12}$	$8{\cdot}9 \cdot 10^{-13}$	$2{\cdot}4 \cdot 10^{-13}$
20	$4{\cdot}0 \cdot 10^{-9}$	$4{\cdot}9 \cdot 10^{-11}$	$4{\cdot}9 \cdot 10^{-12}$
50	$2{\cdot}7 \cdot 10^{-1}$	$8{\cdot}1 \cdot 10^{-6}$	$4{\cdot}0 \cdot 10^{-8}$
100	$3{\cdot}1 \cdot 10^{12}$	$4{\cdot}1 \cdot 10^{3}$	$1{\cdot}4 \cdot 10^{-1}$
RT mole^{-1}	$6{\cdot}5 \cdot 10^{-14}$ ($1{\cdot}7$)[a]	$4{\cdot}4 \cdot 10^{-14}$ ($2{\cdot}5$)[a]	$3{\cdot}2 \cdot 10^{-14}$ ($3{\cdot}3$)[a]

[a] The height of the barrier RT mole^{-1} at the temperature given.

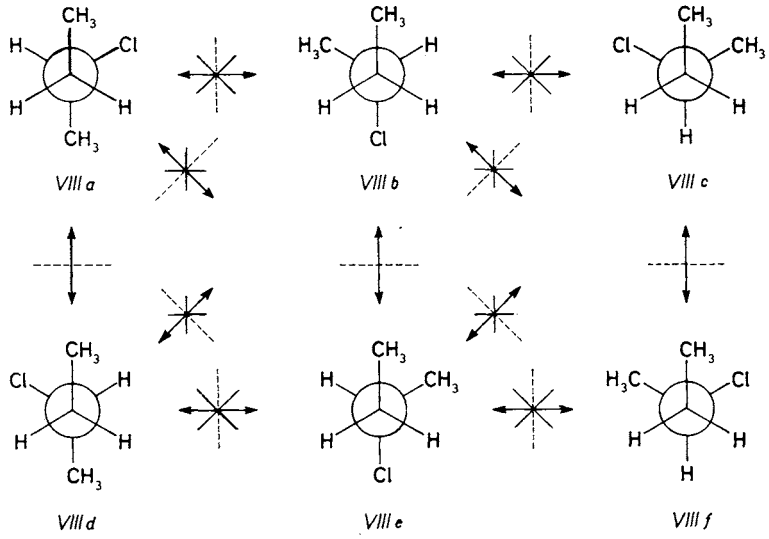
* RT mole^{-1} is still great enough, compared to the barrier above which two different structures can be distinguished in principle. According to ref.[89], height of this barrier is minimally $2h\nu/\pi$, where ν is the vibration frequency at a minimum of a potential energy hypersurface. Using mean molecular vibration frequency (10^{13} s^{-1}), 35 J mole^{-1} is obtained.

the same token, the both forms (*VI*) and (*VII*) of monosubstituted cyclobutanes, with a barrier[27] greater than 6 kJ mole^{-1}, are isomers (conformational diastereomers). However, oxetanes corresponding to *VI* and *VII* are regarded as a single molecular



VI *VII*

structure, since these are divided by a barrier[90] of only 420 J mole^{-1}. Thus, the total number of possible isomeric structures in a sample of racemic 2-chlorobutane is six (*VIIIa – VIIIf*) (Scheme 5), with the pair-wise enantiomeric or diastereomeric relationships as shown. As stated by Eliel[27], this maximum number has never yet been observed simultaneously. In principle, it would be possible by low-temperature NMR in a chiral solvent. Generally, however, also in this case, using different methods leads to experimental observation of different number of residual stereoisomers.



SCHEME 5

In this context, a question is significant, concerning the capability of various methods to differentiate between structures with limited lifetime, i.e. the question concerning the so-called "time scale" of experimental methods. Little explanation is needed for a statement that the time scale of preparative chemistry is limited from

below by life half-times in minutes. But what is the time scale in, e.g., NMR or infrared spectroscopy and, what is it like? Often, a NMR spectrometer is compared to a quickly shooting film camera capable of differentiating only a certain number of snaps within a time unit. Since this comparison, though ilustrative, is fundamentally incorrect, let us recall, in a greater detail, the correct answer[91,92].

It has been said already that each measurement is an interaction, characterized by a certain interaction energy. In our case, an interaction energy is measured in interactions of electromagnetic radiation with matter; interaction energies are measured, characterising two different interconverting structures or substructures. Whether these interactions are localized or not, they supply information about the change under way. But, differences in interaction energy and mean life-times of the individual interconverting structures or substructures are tied together according to the uncertainty principle by the equation (*1*).

$$\Delta v = \boldsymbol{h}/2\pi\tau \qquad (1)$$

It follows that the energy difference is accurately measurable only if the mean life--time is long enough. The shorter the mean life-time, the greater the measured energy difference must be in order to be measurable with sufficient accuracy.From this standpoint, time-scales of some instrumental methods are given in Table IV,

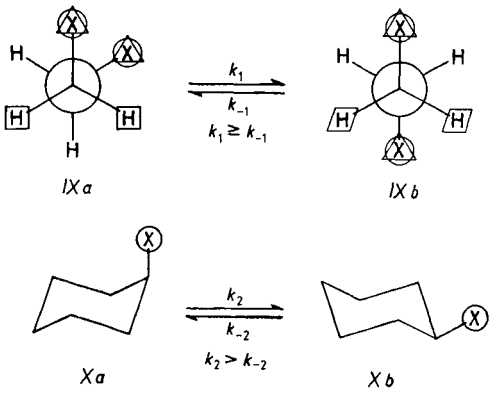
TABLE IV
Time scales of selected spectral methods (adapted from ref.[93])

Spectral method	Approximate time scale, s
Electron diffraction[a]	10^{-20}
Neutron diffraction	10^{-18}
X-Ray diffraction	10^{-18}
Photoelectron spectroscopy (ESCA)[b]	10^{-16}
Ultraviolet spectroscopy	10^{-15}
Visible spectroscopy	10^{-14}
Infrared and Raman spectroscopy	10^{-13}
ESR	10^{-4} to 10^{-8}
NMR	10^{-1} to 10^{-9}
NQR	10^{-1} to 10^{-8}
Mössbauer spectroscopy (Fe)	10^{-7}
Molecular beams	10^{-6}
Preparative separation	$>10^{3}$

[a] Time scale of 10^{-18} is given in ref.[94]. [b] According to ref.[95].

i.e., minimum mean life-times for which it is possible to differentiate, by the method given, between interconverting structures or substructures.

It is then only natural that by infrared spectroscopy, but not by NMR, hydrogen bonds are normally studied and forms —X—H...Y are differentiated from forms —X—H, that *gauche*- and *anti*- forms of 1,2-dihalogenoethanes were differentiated by Mizushima[96] by means of ir spectroscopy and, that electron difraction was successfully used by Hassel[97] to differentiate axial and equatorial forms of halogenocyclohexanes for the first time. These differentiations would not be possible by a NMR spectrometer at ambient temperature; on the other hand, rapid formation and disintegration of collision complexes between a lanthanide shift reagent and a NMR sample, leading to signal averaging on the "slow" NMR time-scale, does not complicate but mostly simplifies the shifted spectra, making lanthanide shift reagents an useful "poor man's alternative to a superconducting magnet[98]". The conformational diastereomers (*IXa,b* as well a *Xa,b* in Scheme 6) were, in the above examples,



SCHEME 6

The rate constants k_1, k_{-1} as well as k_2, k_{-2} are of comparable magnitude. If the structures *IXa,b* and *Xa,b* are considered in three-dimensional space then, ligands ○ are diastereotopic by external comparison, ligands △ are homotopic by internal comparison, ligands □ are diastereotopic by internal comparison, and ligands ⍁ are enantiotopic by internal comparison. In four-dimensional space, whereas the ligands △ remain as labeled under all conditions, the other ligands remain as labeled only provided τ_{IX} and τ_X are long enough with respect to the time scale of the method used for observation. With the compound *IX* (X = Br), $k_1 = 5 \cdot 10^{12}\ s^{-1}$ and so $\tau_{IX} = 2 \cdot 10^{-13}$ s in the gas phase[99]; with the compound *X* (X = Br), $k_2 = 7{\cdot}7 \cdot 10^5\ s^{-1}$ and so $\tau_X = 1{\cdot}2 \cdot 10^{-6}$ s in the liquid state[100].

differentiated on the basis of different localized behaviour of characteristic diastereotopic ligands. So, let us further consider heterotopic ligands and faces in the time dimension. At the same time, let us treat in greater detail the NMR time-scale as

of a method which is of the greatest importance for differentiation of heterotopic ligands and which has made detailed investigations possible not only of equilibria but also of their dynamics.

More attention than before has to be devoted to problems between the substantial and the phenomenal. As mentioned already, symmetry equivalent ligands (Scheme 2) manifest themselves identically under achiral conditions. In NMR spectroscopy, they are isochronous. This isochrony is inherent and necessarily manifested under all achiral conditions provided its cause is preserved, i.e., the symmetry equivalence. Symmetry criteria, however, must always be applied correctly with regard to the time-scale of observation. From this point of view, cyclohexane appears in ^{1}H NMR spectrum at room temperature as if it had the symmetry of point group D_{6h} and not of D_{3d}, i.e., axial and equatorial hydrogens appear as symmetry equivalent ligands due to chair–chair inversions, fast with regard to the NMR time scale. Cyclopentane behaves, in ^{1}H NMR, as if it had the symmetry point group D_{5h} which does not correspond to the fact observed by electron diffraction that cyclopentane is best represented by a set of homomeric structures with the symmetry point group C_s (envelope) and a set of homomeric structures with the symmetry point group C_2 (half-chair) (the C_s and C_2 structures being conformational diastereomers), interconverting[101] over a barrier[102] of 16·7–33·5 kJ mole^{-1} (experiment) or 16·7 kJ . . mole^{-1} (calculation)[103]. Similarly, a proton-decoupled ^{19}F NMR spectrum of *cis*-1,2-diflurocyclohexane measured at ambient temperature corresponds to a structure with the symmetry point group C_s and not to the fact that the compound observed is an equimolar mixture of enantiomers with the symmetry point group C_1; only when the temperature is lowered enough, two symmetry nonequivalent fluorines are seen in the spectrum, with all accompanying features[65].

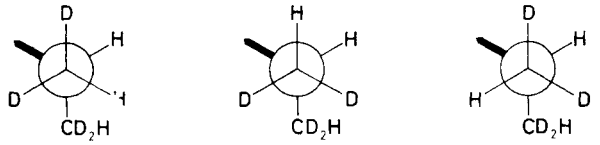
Substantial stereochemical features of any static (considered in three-dimensional space) system can be exactly expressed in terms of symmetry point groups. However, substantial stereochemical features of a dynamic (considered in four-dimensional space) system can only be expressed in terms of permutation groups[104].

Thus, the statement about identical properties of symmetry equivalent ligands under achiral conditions must be refined into an universally valid form: ligands that are symmetry equivalent with regard to the time scale of observation have, under achiral conditions, identical properties.

The situation is a little more complicated with ligands that are symmetry nonequivalent (Scheme 2) with respect to the time scale of observation; their symmetry nonequivalence is a necessary but not a sufficient condition for their different behaviour. Although the necessary condition is met, under certain rigorously defined measurement conditions, their manifestation can be accidentally identical. This phenomenon of accidental identity of properties[105] was observed, e.g., for chemical shift of diastereotopic protons in 1,2,3-triphenyl-2-propanol under changing con-

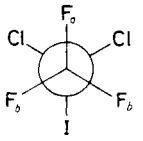
centration of shift reagent[106] and, for ^{1}H NMR signals of two methoxy groups in 1-(2-methoxynaphthyl)-1-(2-methylnaphthyl)-1-(2,4,6-trimethoxyphenyl)methane under changing temperature[105]. It is important to note that, if the conditions are changed, the accidental identity of behaviour disappears. (After all, anomalous ORD curves of enantiomers also cross at the point of zero optical rotation, so that at this wavelength each of the enantiomers simulates an achiral compound.)

Our analysis has shown so far that different behaviour of homomorphic ligands and faces is caused by their symmetry nonequivalence under conditions and time scale of observation; in NMR, this is usually manifested by anisochrony. The origin of anisochrony is still, however, being discussed in terms of an intrinsic and a so-called population-dependent anisochrony. The idea is still considered to be at least useful[55] although it has been pointed out[107] that it is logically impossible to construct molecules which would manifest only population-dependent but not intrinsic anisochrony of geminal groups and, it has been conclusively proved[60] that anisochrony of homomorphic ligands stems from a single cause – their symmetry nonequivalence under conditions and time scale of the experiment. Let the previous discussion be supplemented with a few selected examples. The infrared spectrum of gaseous di(dideuteriomethyl)amine (*XI*) shows[108] three different C—H bonds, i.e., three diastereotopic hydrogens, as befits the conformational diastereomers *XIa*–*XIc*. ^{1}H NMR spectrum of the compound *XI* shows only one C—H bond



XI a *XI b* *XI c*

(only one kind of hydrogen bound to carbon). The reason for differentiation in the infrared is the much shorter time scale, against which the rotational interconversion of conformers *XIa*–*XIc* is slow. Even in a simple compound, rotation about a formally single bond can be slowed down so much as to make homomorphic ligands bonded to the same atom diastereotopic on the time scale of low-temperature NMR. For all examples, let us take 1,1,1-trifluoro-2,2-dichloro-2-iodoethane (*XII*), where



XII

two kinds of fluorine (F_a and F_b) show[109] in low-temperature ^{19}F NMR. Finally, let us return to the ^{13}C NMR spectrum of the acetal *V*. The observed isochrony of carbons c, c′ and d, d′ is the result of rotation about the phenyl–acetal oxygen bond, fast with respect to the time scale of ^{13}C NMR experiment at ambient temperature. There is one remarkable feature, concerning the structure *V*, that should not escape our attention. Carbons a, a′ and b, b′, unlike carbons c, c′ and d, d′, are noninterchangeable by intramolecular dynamics of the structure; they remain so as long as the structure *V* exists as such and, their nonequivalence should be, in principle, discernible regardless of the time scale of observation. On the other hand, carbons c, c′ and d, d′ are interchangeable within the structure *V* by intramolecular dynamics and their discernibility is time scale sensitive.

TABLE V

Representative chemical shifts ranges and time scales (adapted from ref.[92])

Nucleus	Approximate shift range ppm	Shifts, kHz, at a field of		Time scale, s, for a maximum shift at a field of[a]	
		1·4 T	7 T	1·4 T	7 T
^{1}H	0—10	0—0·6	0—3	$2{\cdot}7 \cdot 10^{-4}$	$5{\cdot}3 \cdot 10^{-5}$
^{13}C	0—200	0—3	0—15	$5{\cdot}3 \cdot 10^{-5}$	$1{\cdot}0 \cdot 10^{-5}$
^{19}F	0—300	0—17	0—85	$9{\cdot}0 \cdot 10^{-6}$	$1{\cdot}8 \cdot 10^{-6}$
^{31}P	0—700	0—17	0—85	$9{\cdot}0 \cdot 10^{-6}$	$1{\cdot}8 \cdot 10^{-6}$
^{59}Co	0—15 000	0—214	0—1 070	$7{\cdot}0 \cdot 10^{-7}$	$1{\cdot}0 \cdot 10^{-7}$
^{205}Tl	0—34 000	0—1 177	0—5 886	$1{\cdot}0 \cdot 10^{-7}$	$2{\cdot}7 \cdot 10^{-8}$

[a] For a minimum resolvable shift of 1 Hz, time scale = $1{\cdot}6 \cdot 10^{-1}$ s.

TABLE VI

Representative scalar coupling constants and time scales in NMR (adapted from ref.[92])

Scalar coupling constants	Corresponding average values, Hz	Corresponding time scales, s
$^{2}J(H, H)$	10	$1{\cdot}6 \cdot 10^{-2}$
$^{1}J(^{13}C, H)$	150	$1{\cdot}0 \cdot 10^{-3}$
$^{2}J(H, F)$	50	$3{\cdot}2 \cdot 10^{-3}$
$^{1}J(^{13}C, ^{199}Hg)$	2 500	$6{\cdot}4 \cdot 10^{-5}$

Let us summarize by quoting: "A segment has no identity outside of its identity as a part of the molecule and the symmetry of such a segment is inseparable from that of its environment[30,110]" and, let us add, from the influence acting upon it.

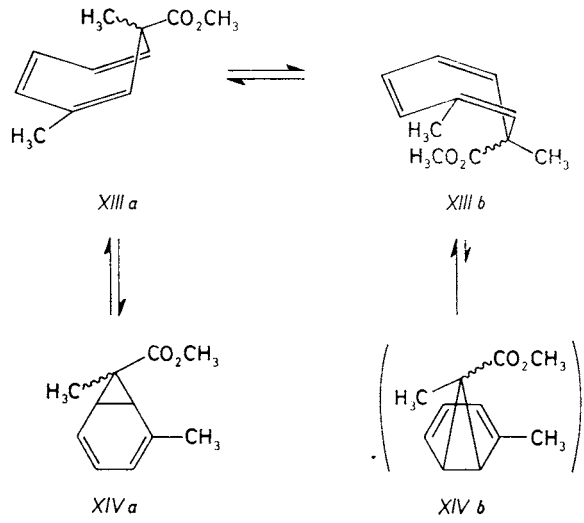
Let us now turn our attention to the question why has the time scale of NMR spectroscopy (Table IV) such a wide range. For our discussion, it will suffice to realize that in NMR spectroscopy three quantities can be measured, directly related to the time scale of the method: chemical shifts, coupling constants and relaxation times. The first two are the basis of the common use of the method. Chemical shift differences (in Hz, for our purpose) as well as interaction constants are immediately usable in the equation (*1*), the former being, among other things, directly dependent on the magnetic field intensity. Tables V and VI reveal that the time scale of NMR must be considered in connection with the nucleus measured, the frequency of the spectrometer used as well as with the anticipated difference of chemical shifts or the magnitude of the measured interaction constant. Relaxation times can be entered into relations with various interconversion rates at the molecular level and, as shown, e.g., in ref.[92], their use often shifts the NMR time scale down into the picosecond region. These facts, together with the possibility of observing the system measured in a relatively wide temperature interval, make dynamic NMR spectroscopy an indispensable tool for studying interconversions with barriers between 20 and 150 kJ mole^{-1} (cf. Table IV).

5. COMPREHENSIVE APPLICATION IN AN EXAMPLE

"Now give me the food for which you have given me appetite" Dante asked of Vergil. As a similar demand from at last some readers is anticipated by the guide to this area, let us confront the preceding conclusions with reality and let us try to find out to what extent they correspond to it and how fruitful they are. Optically active 2,7-dimethyl-7-methoxycarbonylcycloheptatriene[111] (*XIII*) or optically active 2,7--dimethyl-7-methoxycarbonylnorcaradiene[111] (*XIV*) seems a suitable system for our intellectual analysis and, the stereochemical course of a 1,5-sigmatropic migration in *XIV*[112] seems a suitable problem.

The compounds *XIII* and *XIV* are kinetically labile constitutional heteromers, their kinetic lability being connected, under ambient conditions, to two different isomerization processes passing over two energy barriers differing only little in height. One of the isomerizations is an inversion of the cycloheptatriene diastereomers *XIIIa* and *XIIIb* with a barrier around 30 kJ mole^{-1}, the other is an electrocyclic isomerization of *exo-* and *endo-* norcaradiene diastereomers *XIVa* and *XIVb*, respectively, via *XIIIa* and *XIIIb* with a barrier[113] around 40 kJ mole^{-1}. These processes are shown in Scheme 7; the compound *XIVb* (in parentheses) is present, at equilibrium, in an undetectable amount[111], by which the situation is simplified for further

consideration. These isomerizations are then supplemented (from the practical viewpoint at temperatures above 100°C) by our problem of the 1,5-sigmatropic isomerization of the norcaradiene derivative *XIVa* with a barrier[112] around 150 kJ . . mole^{-1}. Besides a 1,5-sigmatropic C—C bond migration[114] leading first to the constitutional heteromers (*XV*) and (*XVI*), a 1,5-sigmatropic C—H bond migration[113]

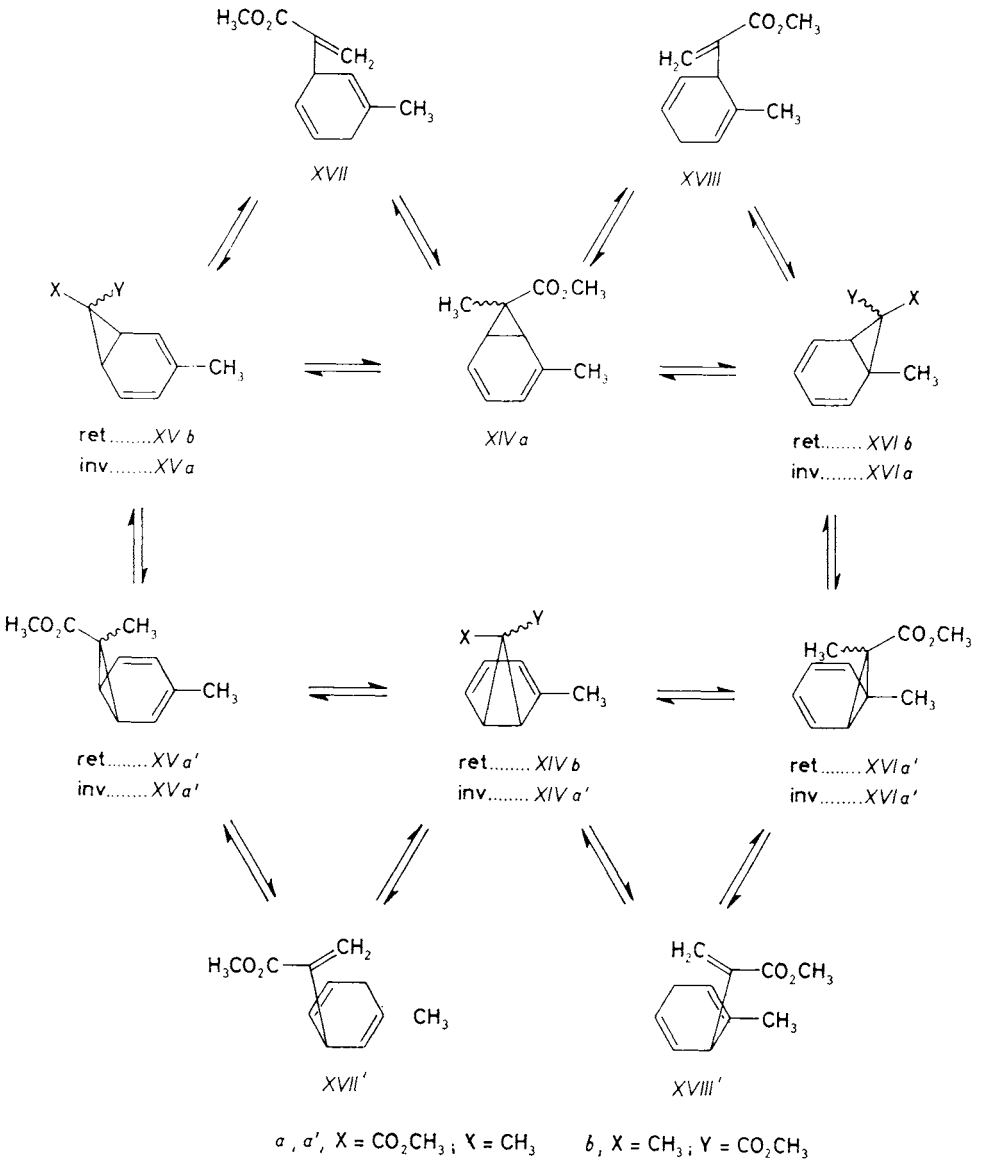


SCHEME 7

In Schemes 7, 8 and 9, an *endo*-substituent in bicyclic structures and a pseudoaxial substituent in monocyclic structures is indicated by a wavy line

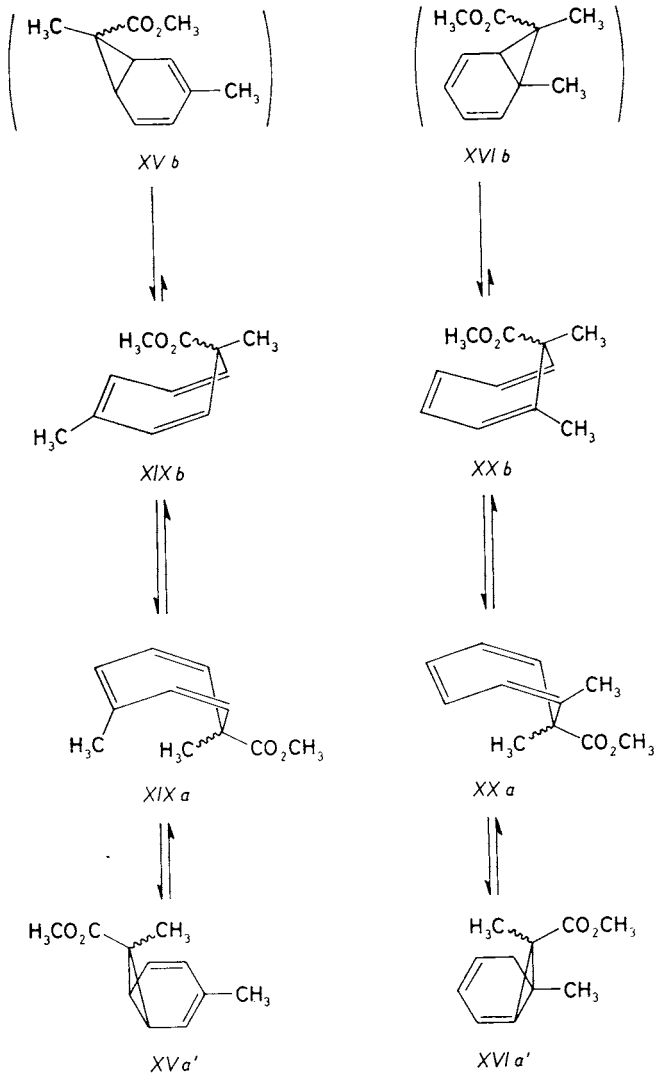
leading first to the constitutional heteromers (*XVII*) and (*XVIII*) must be taken into account as a competing process, as shown in Scheme 8. Our problem now is to evaluate the possibilities of proving whether, in the norcaradiene skeleton isomerization (the so-called walk around rearrangement), the configuration of the C-7 carbon is retained or inverted. Scheme 8 shows that while configuration retention leads, after the first step from the starting compound *XIVa*, to constitutional heteromers *XVb* and *XVIb*, configuration inversion leads to constitutional heteromers *XVa* and *XVIa*. In further steps, configuration retention leads gradually to constitutional heteromers *XVa'* and *XVIa'*, enantiomers of the compounds *XVa* and *XVIa* and, the circle is closed by formation of the compound *XIVb* which, as shown in Scheme 7, does practically exist only as the more stable diastereomer *XIVa*, our original starting compound. Configuration inversion leads, in further stages, gradually to the constitutional heteromers *XVa'* and *XVIa'* (enantiomers of *XVa* and *XVIa*) and, finally to

the compound *XIVa'*, the enantiomer of the original starting compound. The compounds *XVb* and *XVIb*, formed in the first step of the reaction where configuration is retained at carbon C-7, are thermodynamically less stable than the corresponding



SCHEME 8

diastereomers *XVa* and *XVIa*. According to Scheme 9, an analogy to Scheme 7, these compounds will isomerize, in a rapidly established equilibrium, into the more



SCHEME 9

stable *XVa* and *XVIa* via the corresponding cyclohexatriene structures (*XIX*) and (*XX*), respectively. Making an overall evaluation of our analysis we find that, after equilibrium has been established, the reaction mixture should (disregarding the

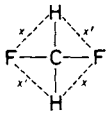
enantiomeric pairs *XVII*, *XVII'* and *XVIII*, *XVIII'* formed in both branches of the reaction) contain a mixture of the compounds *XVa'*, *XVIa'* and *XIVa* if the configuration was retained and a mixture of the compounds *XIVa*, *XIVa'*, *XVa*, *XVa'*, *XVIa* and *XVIa'* if the configuration was inverted. With configuration retention, optical activity should be preserved in the reaction mixture while, configuration inversion should lead to complete racemization. Although this conclusion has nothing new to say as it was foreseen by Berson[114] nearly twenty years ago, the fact that we have arrived at it independently will partly make up for the dissapointment of not having been the first. Let us add that experimental results[112] are in accordance with configuration inversion in the reaction.

Quam quisque norit artem in ea se exerceat (let everybody who has acquired some art, excercise it) goes an old well-tried motto. It is left to the reader, therefore, to carry out a no less interesting analysis of topic relationships (e.g., among methyl groups) in the above system. Such analysis, including necessarily the time factor, will logically take the reader to selecting methods and experimental conditions by and under which these transformations could be, in principle, studied.

6. INDICATIONS OF FUTURE DEVELOPMENT

In the aforementioned, some problems have been deliberately simplified, other have not been even touched upon. In the final phase, complications cannot be evaded but, some preparations have to be done first.

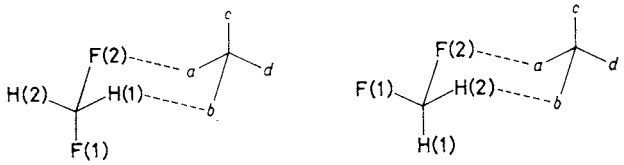
So far, relationships between identical pairs of nonhomomorphic ligands have not been considered, e.g., relationships between pairs *a*, *b* in a general structure Ca_2b_2. In such a structure, both ligands *a* as well as both ligands *b* are homotopic but, not all relationships *a*...*b* are. Mislow and Raban[54] have already noted that the structure Ca_2b_2 can be viewed as if it were composed of four *aCb* subunits belonging to two enantiotopic sets, containing two homotopic *aCb* subunits each. An example of difluoromethane illustrates homotopic relationships x, x and x', x' as well as enantiotopic relationships x, x' between the pairs of hydrogen and fluorine. For



these reasons, difluoromethane should, in principle, show two $^2J_{H,F}$ coupling constants in a chiral solvent, as suggested in ref.[54] Under such conditions, the two hydrogens and the two fluorines should be anisogamous*. Mislow is cited in ref.[55]

* Isochronous nuclei having different spin–spin interactions with another nucleus; often called magnetically nonequivalent. A symmetry criterion for isogamy (or anisogamy), originating with Mislow, is given in ref.[55]

(loc. cit.[106]) as stating that all efforts to prove this anisogamy have, so far, failed. By way of exercise in the previous deductions a condition can be derived for diastereotopicity of the hydrogens and the fluorines in difluoromethane, i.e., for their anisochrony in NMR. The condition would be the presence of a chiral solvent, simultaneously interacting with the hydrogens and with the fluorines; such interaction would lead, with enantiotopic pairs of H...F relationships (H(2)...F(1), H(1)...F(1) and H(2)...F(2), H(1)...F(2)), to diastereomeric associates with diastereotopic hydrogens and fluorines.



Our analysis of structures of identical atomic composition and homomorphic ligands and faces considered in a simplified way structures of isolated molecules, especially their geometrical properties*, disregarding intra – or intermolecular interactions. All our chemical experience, however, suggests that, the real physical situation, where we are faced with statistical sets of interacting molecules, is so represented only to a certain approximation. Even the idea of molecular structure itself has been taken, by some chemists at least, for only a comfortable fiction for an isolated molecule and it has been advocated that it can be spoken about only in connection with a set of molecules[115-118].** (As for the degree of heresy, these ideas can well be compared to those for which Giordano Bruno was once burnt at the stake.)

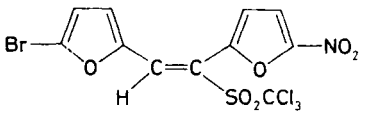
If now we take into account not an isolated molecule but a set of homomeric mutually interacting molecules of the general type Ca_3b, it may be possible that in consequence of mutual interactions, the molecules are transformed into the type $Caa'a''b$ (desymmetrized[30]), best stabilized by the intermolecular interactions.***

* In considering model molecular geometries, advantage has been taken here of a so-called polyhedral model[30], where nuclear positions are idealized to the corners of regular bodies. The use of the model is not without restrictions, however, and the interested reader is well advised to consult ref.[30] where also other models of the molecule are introduced and discussed.

** The problems stem from the fact that one of the central ideas of chemistry, the idea of molecular structure, has caused remarkable difficulties to quantum mechanics. Only when the nuclear and electron movements are separated (in Born–Oppenheimer approximation), the idea of a potential energy hypersurface can be arrived at. From the standpoint of a practicing chemist, these are problems in quantum mechanics and not in objective reality. It would be difficult in the extreme to form an idea of intermolecular forces which could, knowing the magnitude of internuclear forces, be responsible for the formation of the molecular structure.

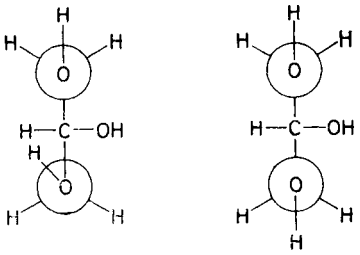
*** For want of a better formulation, let us quote from ref.[30] (loc. cit.[10,11]): "This is an expression of Curie's principle of superposition of symmetry groups: in a composite system, only those symmetry elements remain that are common to the component subsystems."

The crystal structure of the compound (*XXI*), with all three C—Cl bonds differing in lenght[119], can serve as an example. Thus, in the crystalline state of the compound *XXI*, the carbon atom of the trichloromethyl group has C_1 local (site) symmetry[30], even though it is not a stereogenic atom.*



XXI

Similar behaviour has been predicted theoretically (with the highest accuracy currently attainable) also for sets of molecules in the liquid state. E.g., with glycerol (*D*), where the hydroxymethylene groups have been pronounced enantiotopic (*G*) (*b*), calculations at a high reliability level[122] show the basic conformational state (*XXIIa*) to be asymmetric and more stable than the symmetric conformational state (*XXIIb*) by about 40 kJ mole^{-1}. More such examples have been published[108,123].



XXII a *XXII b*

What is the impact going to be of this and similar findings on the way our subject has been treated? In the basic conformer of glycerol *XXIIa* which is, considering its thermodynamic preference, practically the only representative of glycerol under real conditions, the hydroxymethylene groups are diastereotopic. It can be stated that the aforementioned symmetry-based classification need not undergo any change, it is and is going to be capable of incorporating and meaninfully systematically

* According to McCasland[120] a stereogenic atom is: "(*a*) An atom (usually carbon) of such nature and bearing groups of such nature that it can have two nonequivalent configurations. (*b*) An atom bearing several groups of such nature that an interchange of any two groups will produce an isomer (stereoisomer)." According to ref.[121], stereogenic atom is one of stereogenic units. Convincing argument are given in ref.[30] to abandon expressions like "asymmetric atom", "center of chirality", and the like.

classify all the new development. It is necessary, however, that facts entered into the classification process be adequate to questions asked; moreover, consequences following from the classification should be stressed and acted upon.

A shift in the classification, similar to that encountered with glycerol, should stimulate our further interest in studying reactivity; the shift of the reaction (*D*) from enantiodifferentiating to diastereodifferentiating reactions, as befits the exclusive presence of the conformer *XXIIa*, will require further intensive reserach. Its direction, however, is outlined.

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