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Prostereoisomerism and biological activity: possible implications for drug design

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Abstract: Prostereoisomerism (PIM), representing a subgroup within the achiral class of molecules, is manifested in a chiral environment. Although this is regardless of the orientation of the prostereoisomeric (PIC) molecule, PIM is manifested most emphatically in relation to a chiral surface ('two-dimensional chirality'). Then PIM is tantamount to 'de facto chirality' as attachment of the PIC molecule to the surface leads to diastereomeric possibilities (cf. Ogston's hypothesis). Furthermore, the formation of host–guest complexes requires a steric complementarity between the component molecules. The fact that the weak dispersive forces involved therein require an optimum distance implies a 'snugness of fit' criterion. This further implies that a chiral host prefers a chiral guest molecule, and a chiral surface prefers a PIC molecule as substrate. These indicate a general stereochemical criterion for host–guest complexation that is particularly relevant to the case of biological receptors. Indeed, a survey of several known achiral drug molecules indicates that they generally possess at least one PIC moiety, lending credence to the above arguments. Thus, it would appear that PIM represents a maximum level of molecular symmetry for biological activity to be manifested efficiently.

Key words: Host–guest, Ogston, prochiral, 2D-chirality, van der Waals

1. Introduction

The concept of prostereoisomerism (henceforth 'PIM') is well known to students of organic stereochemistry in the context of the historic Ogston hypothesis.[1–6] In the most general sense, PIM manifests itself when certain achiral (guest) molecules are placed in a chiral environment. In the archetypal case, the guest molecule possesses two identical and two nonidentical groups bonded to a tetrahedral center (**1,** Scheme 1). In an achiral environment, the two identical groups are energetically equivalent, but this degeneracy is lifted in a chiral environment (**2**). Thus, the interaction with the chiral environment renders the equivalent groups nonequivalent, and the guest molecule per se becomes chiral.

This potential for acquiring chirality in certain achiral molecules is captured by the term PIM. The above tetrahedral center was thus termed 'prochiral', although the more general term 'prostereogenic' is currently preferred. PIM may also be displayed by unsymmetrical planar molecules, the two planes (faces) of which become prostereogenic in a chiral environment (**3**). (Formally, in the context of PIM, the above terms 'identical' or 'equivalent' and 'nonidentical' or 'nonequivalent' would be termed 'homotopic' and 'heterotopic' respectively, following the original suggestion of Mislow and Raban.)[4]

The above discussion indicates that the interaction of a prostereogenic molecule with a chiral environment

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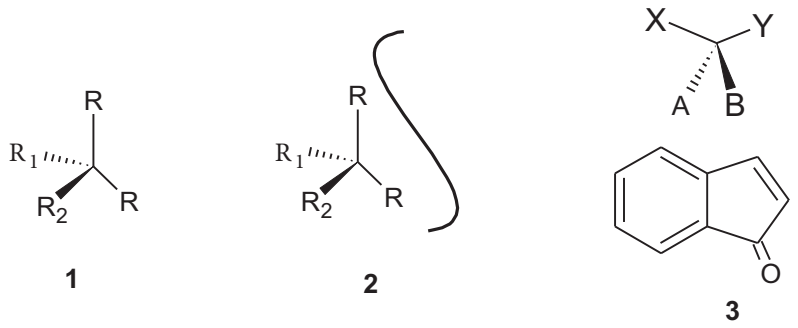
leads to unique stereochemical consequences. These, of course, derive from the definition of PIM itself. Moreover, PIM is often defined in terms of a practical act of discrimination between equivalent groups or faces, usually via a reaction leading to stereoisomeric products. However, PIM can also be discerned by a simple act of inspection—possible because the human performing it possesses a chiral sense!



Scheme 1. Molecules exhibiting prostereoisomerism: **1** possesses a tetrahedral center with two heterotopic ligands (R), **2** being a cartoon representation of **1** in a chiral environment (indicated by the 'S' shaped curved line); **3** shows a planar molecule (inden-1-one) with heterotopic faces relative to a chiral environment represented by the chiral acyclic molecule at the top (CABXY).

In the following section, various aspects of PIM, particularly vis-à-vis a chiral environment are discussed. The object of this exercise is to understand the stereochemical requirements for the interaction of biologically active molecules with their chiral receptors. The critical importance of chirality for biological activity is, of course, well recognized. However, the possible importance of PIM in biological activity has not so far been explored in any depth.

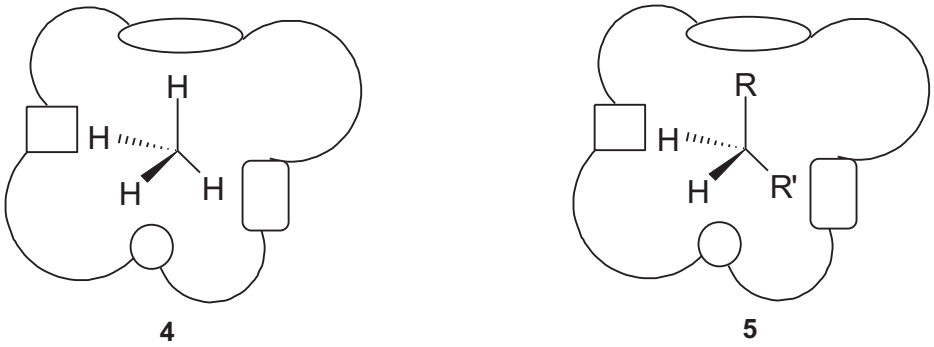
PIM is indeed well-served by authoritative reviews,[1−3] but this paper deals with PIM in the context of host–guest interactions particularly relevant to biological phenomena. Furthermore, there is controversy as to whether the term 'prostereogenic' is applicable to molecules or only to moieties (e.g., centers and faces), although there is apparently no confusion if only one of these is present.[2] In fact, 'prostereoisomeric' (PIC) seems appropriate for a whole molecule, and is thus employed henceforth in this paper.

2. Discussion

2.1. General considerations related to symmetry

PIC molecules apparently define a middle ground between 'achiral' and 'chiral'. As seen in the above case with a tetrahedral center (**1**), the presence of two nonequivalent groups is essential; these molecules still possess a plane of symmetry, although defining a subclass among achiral molecules in general. The strength of the above interaction between the guest molecule and the chiral environment would, of course, depend on various factors, but particularly on the nature of the groups and the chiral environment, the number of interactions, etc. The following 'gedanken experiments' offer interesting insights into the manifestation of PIM under various conditions.

Thus, even a highly symmetrical molecule such as methane (CH_4) may become a chiral moiety within a chiral environment (**4**, Scheme 2). This requires that the molecule be essentially restrained from tumbling, which would 'scramble' the relative positions of all the four hydrogen atoms. However, if the molecule is constrained within a chiral pocket, all the four hydrogen atoms become nonequivalent: they would then, in principle, display four distinct resonances in the proton NMR spectrum.



4 **5**

Scheme 2. Cartoon representations of a methane molecule (**4**) and a PIC molecule (**5**) in a chiral environment represented by the surrounding contour; interchange of all groups (or atoms) within any two pairs of such groups around the tetrahedral centers would correspond to the tumbling of the molecules.

In fact, this would occur even if the molecule were tumbling, but slowly on the NMR time scale. Putative attachment of the CH_4 molecule at one of its hydrogens to the chiral pocket would also lead to the nonequivalence of the remaining three hydrogens, as long as the rate of rotation of the CH_3 moiety were slow on the NMR time scale. Interestingly, this contrasts with the case of a PIC molecule (**5**), essentially because of its lower symmetry.

Thus, the equivalent groups in a PIC molecule would become nonequivalent in a chiral environment even if the included molecule were freely tumbling. This is due to the presence of the two nonequivalent groups, which provide a 'stereochemical fix' at the tetrahedral center. Thus, any tumbling event that interchanges the positions of the equivalent groups within the chiral environment also interchanges the positions of the nonequivalent groups. Since the latter interchange generates putative diastereomeric interactions (with the chiral environment), tumbling can never lead to the degeneracy of the molecule as a whole.

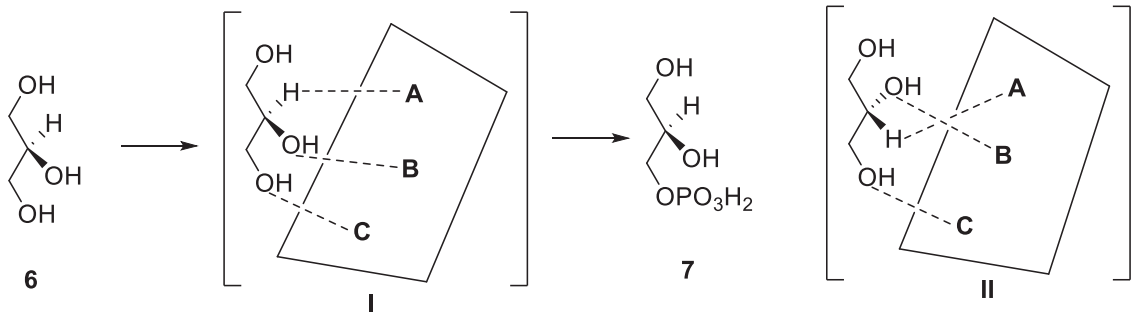
2.2. The Ogston hypothesis and two-dimensional chirality

The above discussion indicates that the interaction of an achiral molecule with a chiral environment leads to consequences that depend essentially on the symmetry level of the molecule, but also on the nature of the interaction (the molecule being constrained or not). However, it appears that the nature of the chiral environment is also significant, an insightful conclusion that was apparently presaged by the Ogston hypothesis, often considered a landmark in the history of stereochemistry.[5–8] Intriguingly, however, although the proposal led to the evolution of the idea of PIM itself, a few of its subtleties apparently remain to be elaborated. (It now appears that the idea of two-dimensional chirality is key to understanding the Ogston hypothesis, vide infra.)

The original Ogston proposal dates back to a period when modern stereochemical ideas were still evolving, and the concept of a chiral environment within a pocket of the host molecule would perhaps have been a novelty. The hypothesis is best exemplified by the enzymatic phosphorylation of glycerol (**6**, Scheme 3) to produce *R*-(-)-glycerol-1-phosphate (**7**), which involves distinguishing between the two terminal hydroxyl groups in the PIC glycerol molecule.[5,6] Although the formation of a chiral product at a chiral enzyme active site needs little agonizing, it is a testament to the insightfulness of the approach that mechanistic details were indeed pursued.

In fact, this is also an opportune juncture to refer to a remarkable early paper by Easson and Stedman, which eerily presaged many of the later developments related to the Ogston hypothesis and PIM in general.[7] These authors (although perhaps arbitrarily) assumed a three-point binding mode in order to relate the biological activity of various molecules in terms of their stereochemistry. They presciently proposed that

chirality in of itself is not a prerequisite for activity, and concluded that PIC molecules (by current terminology) would be structurally adequate for efficient binding to a chiral receptor. Experiments involving analogues of adrenaline and miotine lent impressive support to their ideas, these clearly constituting pioneering studies on the stereochemistry of drug action.

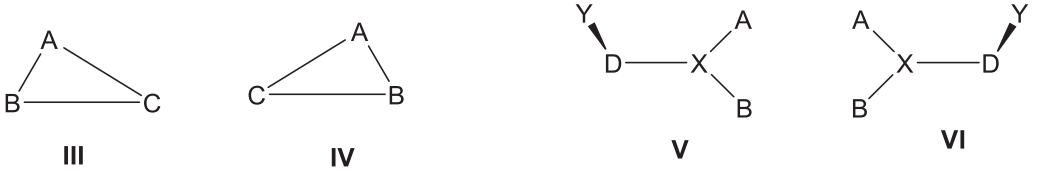


Scheme 3. The enzymatic stereoselective $O-$phosphorylation of glycerol (**6**) to form R-(-)-glycerol-1-phosphate (**7**); the Ogston three-point attachment proposal is depicted in **I** (via the dotted lines); the trapezoidal represents a chiral surface with (nonidentical) attachment sites A, B, and C; the alternative strained diastereomeric interaction is shown in **II** alongside; the reactants (ATP and glycerokinase enzyme) and byproduct ADP are not shown for simplicity.

2.3. Chiral surfaces and planar chirality

The Ogston mechanism involved a three-point attachment of a PIC molecule to, essentially, a chiral surface, i.e. a chiral pocket in which one face is shielded and hence inaccessible (cf. **I**). Then a minimum of three interactions is necessary unequivocally to exclude one of the two equivalent groups at the prostereogenic center from the reaction site. (Thus, a two-point attachment would not distinguish between the two equivalent groups, inasmuch as the unattached groups would not interact with the chiral surface. Note also that it takes a minimum of three points to define a surface!)

Therefore, the Ogston hypothesis invoked the idea of what is now understood as two-dimensional chirality.[2,3,9,10] This is possible in the case of an unsymmetrical planar object as long as the object is not moved out of the plane (Scheme 4). Thus, within the general plane occupied by it, the unsymmetrical planar object (**III**) would be nonsuperimposable on its mirror image (**IV**). This 'stereochemical parlor trick', however, acquires practical significance when a chiral pocket functions as a de facto surface (vide supra)!



Scheme 4. Two-dimensional (**III** and **IV**) and planar (**V** and **VI**) chirality; the former defines a chiral surface.

A chiral surface would be a special case of 'planar chirality', which is defined in terms of a group of four atoms in a plane, and a fifth 'pilot' atom (Y) above or below the plane (**V** and **VI**).[9,10] The difference, essentially, is that in the case of planar chirality the restriction on moving the object out of the plane is unnecessary, because of the presence of the pilot atom.

Conversely, therefore, the Ogston hypothesis implies that binding sites in biological reactions may be viewed essentially as chiral surfaces. However, in the light of current knowledge about the three-dimensional structures of biological macromolecules, the Ogston hypothesis amounts to 'overkill'! Thus, as seen above, a consideration of the overall three-dimensional space within a chiral (host) pocket indicates that the two equivalent groups at a prostereogenic center in a guest molecule may be distinguished even if the molecule were to be freely tumbling! Of course, binding interactions would (generally) increase the energy difference between the alternative bound groups at the reaction center. In principle, however, they are not necessary if the spatial environment in the chiral pocket is sufficiently demanding in terms of selectivity.

On the other hand, such an idealized view of stereoselectivity needs to be tempered by mundane considerations involving current knowledge and experience. Thus, host–guest interactions generally involve precise binding sites leading to the formation of intermediate complexes of defined structure. These may indeed represent minima along reaction contours in potential energy space. On this basis, we are now back at the Ogston hypothesis!

Thus, although the immobilization of a PIC substrate at an enzyme active site is, in principle, unnecessary in order to distinguish between the two equivalent groups (or faces), the fact is that reactions at such sites do occur via bound intermediates. In that case, the question arises as to the minimum number of interactions that are necessary to distinguish between the equivalent groups (or faces). The answer would be 'three', assuming that the binding site can be considered as a chiral surface.

The view of an enzyme active site as a chiral surface appears unexceptional, considering that the binding site somewhat resembles a mousetrap, i.e. one side is completely shielded, so the entry and exit of the substrate are restricted to the opposite side! This may seem an oversimplification, inasmuch as it ignores weak dispersive interactions (e.g., van der Waals) between the substrate and the walls of the active site cleft. However, the Ogston mechanism clearly focuses on the three strongest interactions as three functional sites in the substrate are involved!

All the same, the above mousetrap analogy needs due caution, as indicated by an intriguing paper by Mesecar and Koshland on isocitrate dehydrogenase.[8] In this enzyme, the active site is a three-dimensional cleft that is complementary to a hypothetical trigonal bipyramid. This can accommodate the same three (of the four) groups linked to the C_2 stereogenic center in the substrate enantiomers, but from opposite sides of the trigonal surface! Essentially, the binding of the fourth group at C_2 then determines stereospecificity, indicating a departure from the Ogston three-point mechanism. (Thus, the enzyme can bind either L-isocitrate or D-isocitrate, although the latter along with Mg^{2+}.)

Intriguingly, in fact, this may well indicate that three-point binding applies to PIC substrates and four-point binding to chiral substrates! Of course, a PIC substrate may lead to a chiral product (and vice versa), noting that enzymes bind both reactants and products (whatever the direction of the equilibrium). However, the enzyme could then undergo conformational changes during the reaction, and alternate between the three-point and four-point modes as appropriate. Furthermore, in fact, these preferential binding modes likely indicate that efficient binding is based on size variation between the bound groups, as argued below.

Thus, a chiral substrate possesses four different groups at a tetrahedral center (generally), and a combination of any three of these may well offer a similar degree of size variation. The three-point binding mode would not then distinguish between the two enantiomeric substrates efficiently. (Of four groups A, B, C, and D, both the combinations A, B, C and B, C, D, say, could bind with similar efficiency; in terms of size, A $<$ B $<$ C $<$ D.)

Such happenstance, however, is ruled out in the case of a PIC substrate, as two of the four groups would be identical (say A, B, C, C', with C = C'). Then only one combination would afford size variation (say A, B, C) along with stereochemical complementarity, which would also distinguish between the heterotopic groups (C and C', thus ruling out A, B, C').

Even so, the implications of the above four-point mechanism in the case of a PIC substrate are interesting. This can bind in two possible modes at the bipyramidal cleft: from both sides of the trigonal surface, but employing different heterotopic ligands in each case.

In fact, this also relates nicely to the Prelog–Helmchen nomenclature for heterotopic ligands, e.g., H_{Re} and H_{Si}, the topicity on each side of the chiral surface in the bipyramid being opposite to the other.[2,11] These modes of binding would be diastereomeric, however, as the two heterotopic ligands would experience different environments in the cleft. (These correspond to the fourth group in the isocitrate case above; the reader is referred to the original paper for the spatial representation of these ideas.)[8]

In any case, the Ogston proposal holds its ground as it defines a minimum requirement at a chiral surface (a four-point binding mechanism being not necessarily precluded)! In addition, the ability of isocitrate dehydrogenase to bind both isocitrate enantiomers as above is intriguing (in evolutionary terms), although further speculative discussion is beyond the scope of this paper.

2.4. PIM as 'de facto chirality'

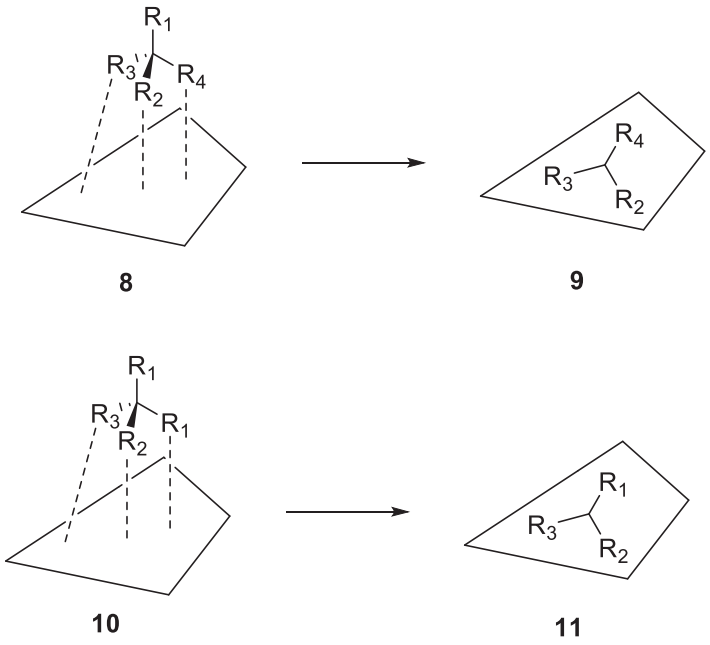
The above extended discussion leads, broadly, to the view that the interaction of a PIC molecule with a chiral environment depends crucially on the nature of the chiral environment. More pointedly, it appears that if the PIC molecule is interacting with a chiral surface, the former has all the attributes of a chiral molecule. This is because the three-point attachment of the molecule involving either of the two equivalent groups leads to the formation of diastereomeric complexes (cf. **I** and **II**, Scheme 3). On this basis, PIM should be viewed as 'de facto chirality'!

Chiral surfaces, in fact, may be viewed as resulting from the projection of three-dimensional chirality onto two dimensions (**8** → **9,** Scheme 5). Analogously, PIM can also be projected onto two dimensions (**10** → **11**), noting that two enantiomeric surfaces result as the projection can be relative to either of the two R_1 groups. Moreover, intriguingly, chirality and PIM cannot be distinguished in the resulting projections!

This is because one of the four groups around the stereogenic and prostereogenic centers is 'lost' in the projections, but this is irrelevant in the context of planar chirality. Interestingly, these arguments are practically relevant to the 'mousetrap analogy' (vide supra) of a chiral binding site: the group that is lost in the projection is the unbound group that would 'stick out' of the site.

These geometric analogies offer support to the view that PIM is de facto chirality in relation to a chiral surface. The essential difference, of course, is that chirality gives rise to two enantiomeric forms, whereas PIM does not give rise to any isomeric forms per se. Thus, the potential of PIM is only realized in the presence of external chirality; in particular, there are two distinct ways of orienting a PIC molecule vis-à-vis a chiral surface (cf. **I** and **II**, Scheme 3).

Interestingly, these arguments also apply to the above four-point model (Section 2.3). In this case, the PIC molecule fits into either side of the chiral surface in the trigonal-bipyramidal cleft. However, as noted above these binding modes would be diastereomeric, again implying that the PIC molecule is de facto chiral in the cleft. (Furthermore, these diastereomeric interactions are additional to those arising from the three-point attachment at the trigonal surface, cf. **I** and **II**.)



Scheme 5. The projection of tetrahedral chiral (**8**) and PIC (**10**) molecules onto a surface (represented by the trapezoidal); while **10** leads to an enantiomeric pair of chiral surfaces (only **11** shown), **8** leads to four distinct chiral surfaces (only **9** shown) corresponding to the faces of a tetrahedron.

2.5. Chiral binding sites and snugness of fit

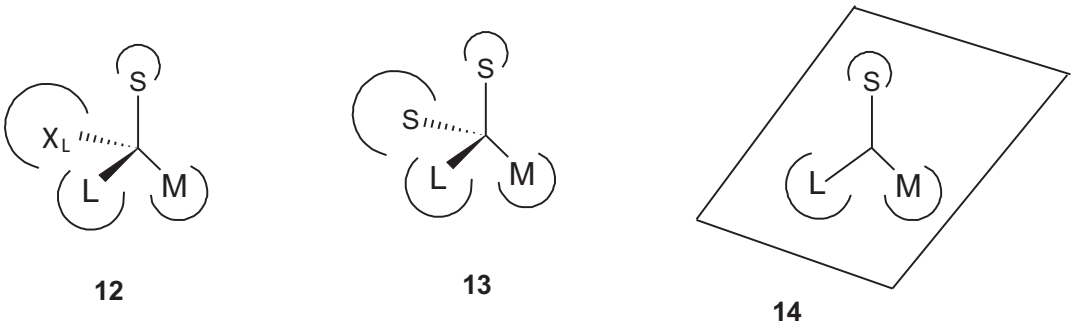
These arguments have intriguing consequences in the light of the fact that chirality plays a crucial role in biomolecular interactions. This is generally interpreted in the context of selectivity and specificity, implying that between two enantiomers of a substrate a biological binding site preferentially interacts with only one of them. However, these considerations also imply that a chiral binding site prefers to interact with a chiral rather than an achiral substrate molecule (vide infra). This is based on straightforward considerations of shape complementarity and snugness of fit.

Thus, a chiral binding site may be defined in terms of four binding pockets distributed in three-dimensional space. The pockets would be located at the corners of a tetrahedron, for shape complementarity relative to a chiral tetrahedral center. Furthermore, the pockets would all differ, in either size or the nature of binding (chelation, hydrogen bonding, etc.). Let us designate the binding pockets in terms of (say) size as S (small), M (medium), L (large), and X_L (extra large). Now a tetrahedral substrate would perforce possess four groups with the same attributes, and hence be chiral (**12**, Scheme 6).

A critical caveat in the above arguments is that they imply a close matching of steric size but also preclude a mismatch, even if it were not sterically forbidden! Thus, although it is intuitively obvious that a large group cannot fit into a small pocket (L in S), it is less obvious that a small group fitting into a large pocket may lead to an inefficient interaction (S in L). This is because the weak interactions that generally mediate the binding of substrates in hydrophobic pockets possess an optimal distance, below which steric crowding sets in, and beyond which the weak attractive forces (e.g., van der Waals) wane rapidly.[12,13]

Clearly then a chiral carbon centered molecule $CSMLX_L$ would bind more efficiently to a complementary site than would an achiral analogue (say) CSMLS (**13**). In the latter case, a small group (S) would be lodged

in a large pocket (X_L); although not sterically forbidden, it would be inefficient in terms of the minimization of the overall energy. (In other words, 'snugness of fit' is crucial for efficient binding or complexation.)



Scheme 6. Chiral (**12**) and PIC (**13**) molecules with complementary binding pockets represented by partial circles of varying size (in **13** one of the S groups is mismatched with an X_L pocket); a projection of **13** to generate a chiral surface is shown in **14**.

These arguments may now be extended to the binding of a PIC substrate to a chiral surface (**14**). The chiral surface may be analogously characterized by three binding sites S, M, and L. By arguments similar to the tetrahedral case discussed above, the chiral surface would preferentially bind molecules of the configuration CSMLY, where 'Y' designates an additional group that is not involved in the binding.

Interestingly, if Y is different from the other three groups, the molecule will be chiral; however, if Y is the same as one of the other three groups (say S), the molecule would be PIC. Clearly, this is the highest level of symmetry allowed for the substrate, for efficient binding at a chiral surface.

2.6. Planar systems

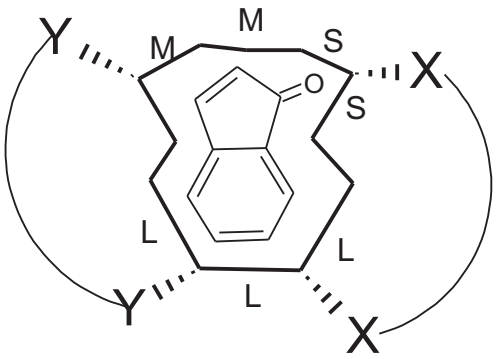
The above discussion has focused on tetrahedral substrates for convenience and ease of representation. The ideas may be extended to the case of planar molecules possessing prostereogenic faces (Scheme 7), although with additional caveats related to their symmetry characteristics. These derive from the requirement that these planar systems be complementary to a chiral surface, i.e. they essentially possess the same symmetry characteristics. As a chiral surface, by definition, cannot be dislocated from its plane ('flipped over'), this rules out the presence of a C_2 axis of symmetry, e.g., naphthalene. (In these cases, the mirror images are superimposable even without flipping over and so their contours do not define a chiral surface.)

Thus, these molecules are essentially characterized by unsymmetrical contours that give rise to edges of varying size and shape. The molecules may bind on a chiral surface that is defined by niches along the surrounding walls of a chiral cavity that are complementary to these edges. This would then render the top and bottom faces of the molecule nonequivalent or heterotopic.

As noted above, PIM can be considered as de facto chirality with reference to an external chiral surface. In the case of tetrahedral systems, the three nonequivalent groups around the prostereogenic center can be represented as S, M, and L. In the case of planar systems too, the edges along the unsymmetrical contour can be divided into sections of varying size based on approximate curvature (Scheme 7). The above mentioned snugness-of-fit criterion again indicates that a PIC molecule would be an appropriate substrate at a chiral surface. (In Scheme 7, note that the included indenone molecule will not fit efficiently into the cavity in any other orientation.)

2.7. Overall assessment and implications for drug design

The above discussion on certain stereochemical concepts and principles indicates the close analogy between chirality and PIM. Most importantly, application of the snugness-of-fit criterion indicates that chiral receptors would preferentially interact with chiral or PIC substrates for efficient binding. It was also mentioned early on that PIM forms a subclass of achiral molecules in general. Taken together, these arguments imply that PIM represents the highest level of molecular symmetry permissible for biological activity to be manifested efficiently. (In the case of planar systems, additionally, the absence of a C_2 axis is indicated, vide supra.)



Scheme 7. Cartoon representation of a planar molecule with prostereogenic planes (inden-1-one) ensconced in a chiral cavity (surrounding contour); X and Y represent points of attachment for the undefined curved bridges, and S, M, and L indicate the small, medium, and large sections (respectively) that are complementary to the edges of the cavity.

These arguments, of course, are predicated on the assumption that symmetry is the predominant criterion in determining the activity. This is clearly an oversimplification inasmuch as biological activity is determined by a whole host of properties relating to corresponding molecular features. However, the present discussion represents an attempt to disentangle stereochemical considerations, particularly concerning symmetry alone, from the skein of determining properties. (Note, also, the above requirement of efficiency; this implies that although the deduced symmetry criteria are not inviolable, following them leads to improved activity.)

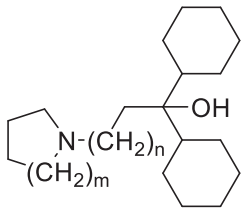
Essentially, therefore, the question being addressed is: what are the molecular symmetry criteria for biological activity to be manifested efficiently, other features being constant? Although this is a hypothetical question, if the symmetry criteria can indeed be disentangled, they can be introduced into the design of new molecules of biological interest, e.g., drugs. The resulting strategy can thus become a part of the principles of drug design in general.

2.8. PIM and known drug molecules

In view of the above considerations, it is interesting to note that a number of known achiral drug molecules display PIM. These are (inter alia):[14,15] dicyclidine (**15**, Scheme 8), dicyclidol (**16**), diphenidol (**17**), gemfibrozil (**18**), pridinol (**19**), pyrrinol (**20**), (tetrahedral systems); carbamazepine (**21**), celecoxib (celebra; **22**), diclofenac (**23**), and triclosan (**24**) (planar systems). Whilst the tetrahedral systems possess a gem-disubstituted prostereogenic center, the planar systems possess at least one moiety with a prostereogenic plane (**18** possesses both a center and a plane). Almost always, this derives from an unsymmetrically substituted aromatic ring, with meta and ortho substitution being quite common. (Several other cases have been discussed previously.)[1] Generally, it appears symmetrically disubstituted systems are unknown (they would not display PIM). Interestingly, several

commonly used drug molecules display PIM, e.g., acetaminophen (paracetamol), aspirin, and barbital (sodium salt).

The above selection of molecular structures indicates that PIM may well be one of the determining factors, generally speaking, in the occurrence of biological activity.



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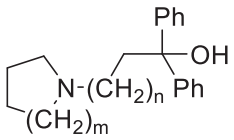

No.	m	n
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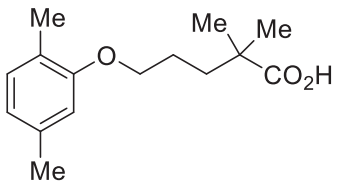
19	2	1
20	1	1



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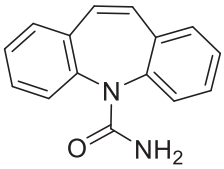

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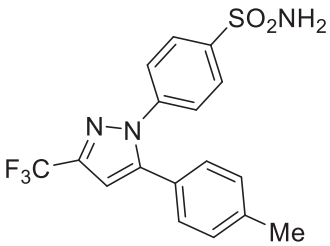

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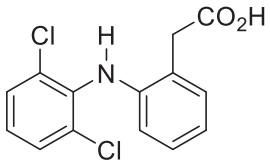
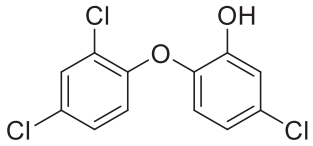


23



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Scheme 8. Known drug molecules with prostereogenic centers (**15**–**20**) and planes (**18**, **21**–**24**); note that **21** involves amide resonance at the azepine nitrogen and so lacks a C_2 axis.

2.9. Conclusions

Prostereoisomerism (PIM) defines a subclass among achiral molecules in general. By definition, PIM is manifested in the presence of an external chiral influence, which enables discrimination between the heterotopic ligands or planes. Although this is independent of orientation within a chiral environment, PIM is most palpable with reference to a chiral surface (cf. Ogston's three-point attachment hypothesis). Then PIM may be considered as de facto chirality, as its attachment to a chiral surface leads to diastereomeric adducts.

The complexation of a substrate at a chiral binding site involves, inter alia, stereochemical complementarity between the substrate molecule and the features of the binding site cavity. It is then highly likely that there is an optimum size for each of the three groups to be attached at the corresponding pockets on the surface. This is because the weak dispersive forces generally mediating these interactions require an optimum distance

for efficient complexation to occur ('snugness of fit'). This implies that a chiral cavity would prefer to bind to either a chiral or, at the very least, a PIC molecule. (The latter particularly applies if the cavity is considered as providing a chiral surface, as in the Ogston mechanism.)

These conclusions have an interesting bearing on biologically active molecules in general and the design of drugs in particular. Intriguingly, in fact, a large number of known achiral drugs display PIM, thus representing a possible vindication of the above ideas.

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