Struct Chem (2006) 17:347–350
DOI 10.1007/s11224-006-9008-2

BRIEF COMMUNICATION

Paradigms and paradoxes: Mechanisms for possible enhanced biological activity of bilaterally symmetrical chemicals

Alexander Greer · Orrette R. Wauchope · Nicola S. Farina · Paul Haberfield · Joel F. Liebman

Received: 30 November 2005 / Accepted: 7 December 2005 / Published online: 1 August 2006

Abstract We propose a mechanism that bilateral symmetry yields an entropic advantage for enzyme recognition. We suggest that bilateral symmetry may be a guiding principle used by nature to produce some particularly effective receptor–ligand interactions. An essential result is that bilateral symmetry is common among enzyme inhibitors, which coupled with an enhanced bond energy that connects dimer molecules compared to a reduced bond energy profile for higher oligomers provides a clue to explain the abundance of bilaterally symmetrical molecules found in Nature.

Keywords Molecular bilateral symmetry · Enzyme recognition · Receptor–ligand interactions

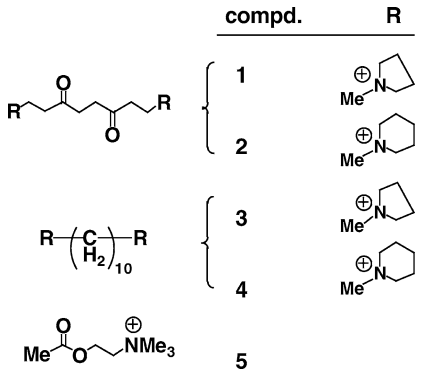
Recent interest has focused on natural product bilateral symmetry and the prediction of selectivity of dimeric molecules by density functional theory (DFT) and semiempirical calculations [1]. It has been shown that bilateral symmetry [defined as including C_2 (sigma mirror or rotation axis), C_s, and C_{2v} point groups in molecules] is present in a number of natural product structures. Dimeric natural products were found to evolve more energy per connection than the corresponding trimers or tetramers. The assumption of maximization of interaction energy suggests the corollary conjecture about the apparent absence of natural products possessing higher symmetry.

The biological activity and associated physical processes of dimeric natural product molecules may emerge as an area for development. The work that is described here includes a literature analysis aimed at uncovering differences in biochemical data of bilaterally symmetrical molecules with those that lack this symmetry. A question we seek to address is: "Are there any biological advantages when bilaterally symmetrical molecules interact with enzymes or other receptors?"

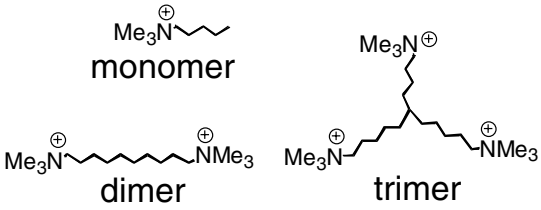
A literature search of biological activity was used to distinguish between trends among molecules that possess C_1, C_2 (sigma plane or axis) or C_{2v} point groups in molecules to determine whether molecular bilateral symmetry may influence biological activity. Data was collected from reports on the biological properties of 90 bilaterally symmetrical natural products possessing C_2 or C_{2v} point groups and 275 randomly selected C_1-symmetry natural products that do not possess bilateral symmetry. The literature analysis revealed that natural products possessing bilateral symmetry more frequently produce enzyme inhibition (22%) in comparison to the natural products, which do not possess bilateral symmetry (8%). It is evident that some protein active sites bind bilaterally symmetrical molecules, but do not possess apparent "bivalent complementary cavities. For instance, the neuromuscular blocking properties of bisquaternary pyrrolidine (**1**, **3**) and piperidine derivatives (**2**, **4**) represent competitive inhibitors of acetylcholine esterase (Scheme 1) [2, 3]. The effectiveness of these agents is related to the disparity between compounds possessing one vs two quaternary nitrogens. Inhibitors possessing bilateral symmetry are composed of two like parts and may have an entropic advantage over acetylcholine (**5**) in their interaction with the receptor site. Such structures clearly

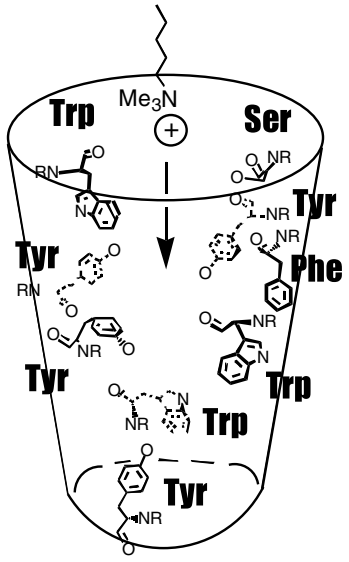
A. Greer (✉) · O. R. Wauchope · N. S. Farina · P. Haberfield
Department of Chemistry, Graduate Center and The City University of New York (CUNY), Brooklyn College, Brooklyn, 2900 Bedford Avenue, NY 11210–2889, USA
e-mail: agreer@brooklyn.cuny.edu

O. R. Wauchope · J. F. Liebman
Department of Chemistry and Biochemistry, University of Maryland, Baltimore County, Baltimore, Maryland 21250, USA



Scheme 1

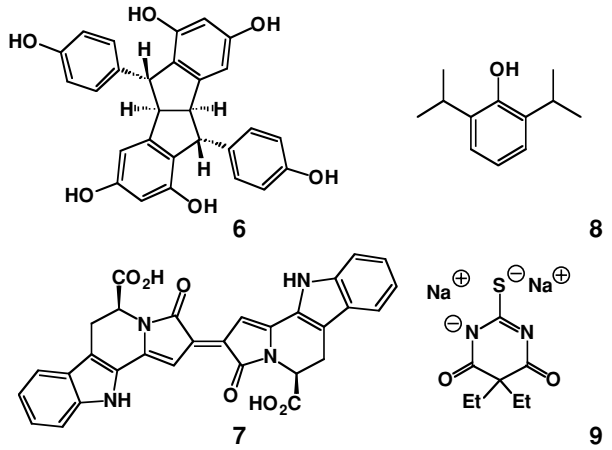




Scheme 2

evolved, since proteins are specialized for structure-based stability relationships with natural molecules [4]. Scheme 2 shows the amino acid residues located in acetylcholine esterase. Preliminary calculations at the HF/STO-3G level predict a lower energy for the dimer in the complexation reaction compared to the monomer and trimer.

Compounds with C_2 or C_{2v} symmetry possess a symmetry number of 2. C_2 (sigma plane or axis) or C_{2v} point groups are common among barbituates (5,5-diethyl barbituric acid, 5-ethyl-5-isopentylbarbituric acid, brevital, phenobarbital), anesthetics (ether, sevoflurane, propofol, 1,2-dichloro-1,2,3,3,4,4-hexafluorocyclobutane), and narcotics (pethidine, meprobamate, ethinamate), which also



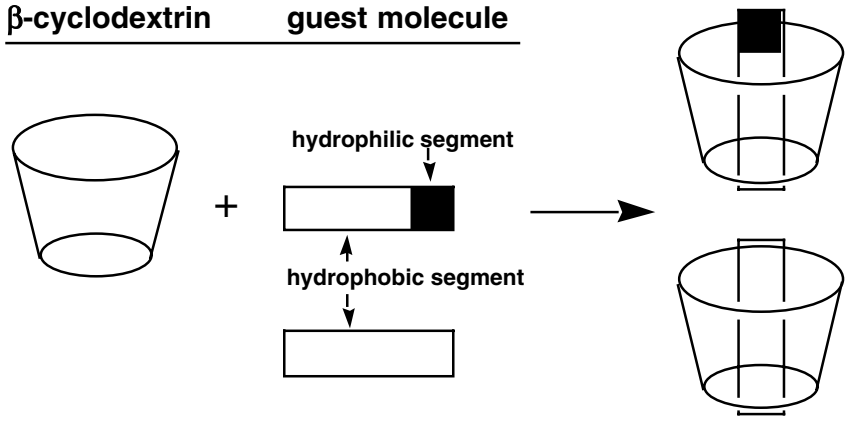
Scheme 3

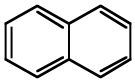
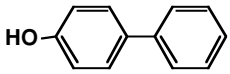
tend to occupy sites on protein targets, although many of these compounds are not natural products. This leads us to propose that molecular bilateral symmetry is a variable common among enzyme inhibitors. The difference between uni- and bilaterally symmetrical natural products recorded in the literature may be accounted based upon an enhancement of the effect with enzyme receptors. We include structures here of some natural products [e.g., 5,10-*bis*- (4-hydroxy-phenyl) -4b,5,9b,10-tetrahydro-indeno[2,1-*a*]indene-1,3,6,8-tetraol (**6**) and 5′-hydroxy-3,3′-dioxo-6,11,6′,11′-tetrahydro-5*H*,5′*H*-[2,2′]bi[indolizino[8,7-*b*]indolylidene]-5-carboxylic acid (**7**)] and some non-natural products [e.g., 2,6-diisopropylphenol (**8**) and sodium 5,5-diethyl-2-thiobarbiturate (**9**)] that have the two-fold symmetry (Scheme 3).

One may view β-cyclodextrin chemistry in a similar light for a model system that mimics the substrate interactions of enzymes. Complexation of bilaterally symmetrical hydrophobic guests may cause entropy to increase given two preferred directions for inclusion (Scheme 4). β-Cyclodextrin is an enzyme "mimic" that recognizes guest molecules based on hydrophobicity for the direction of inclusion. Entropy appears to be favored for C_2 and C_{2v} symmetric molecules compared to C_1 symmetric molecules (Scheme 5) [6]. Extra contacts can increase the binding strength if this overcomes the entropy loss. The capture of molecules by β-cyclodextrin seems to occur with different ease. Recognition frequency may be favored for molecules possessing bilateral vs unilateral symmetry, with a special entropic advantage to the former.

Experimental studies have previously revealed the origins of the dependence of melting point on molecular symmetry. The effect of the symmetry number on the melting point is recognized because of the increase in the chance of the molecule attaching. For example, a C_2 symmetric molecule can attach to the crystal in two ways. Literature values for the melting points of CF_4 (–191°C), CF_3Cl

Scheme 4



	ΔG°	ΔH°	TΔS°
	-4.59	0.19	4.78
	-3.18	0.10	3.27
	-3.87	-2.72	1.12
	-0.98	-0.31	0.67

Scheme 5 Energies of association (kcal/mol)

(–189°C), CF_2Cl_2 (–158°C), $CFCl_3$ (–111°C), and CCl_4 (–23°C) show a deviation from linearity [5]. The binding of CF_4 to the crystal is influenced by the symmetry number, but also the molecular weight to determine its rate of release from the crystal, determined by melting points. This is interpreted in terms of a symmetry dependent structure in relation to the solid surface, in which lower symmetry is hindered by restriction in the addition to the solid complex. Higher symmetry molecules recognize the surface of the crystal more readily. A higher symmetry number contribution leads to an increased chance for interaction between the molecule and the face of the crystal. The higher symmetry in a natural product leads to a more favorable connection to the crystal since more orientations can fit properly onto the crystal. It is also noted that plastic crystals in which the molecule behaves like it is more spherical and of higher symmetry in which the condensed phase molecule rotates, librates and wiggles on a lattice site and so the crystal does not melt (lose its long-range order) until some higher temperature is achieved.

Another reason based on geometric proximity may also be offered. Suppose the macromolecule, here denoted by M, has but one active site and the interacting small molecule has two equivalent active sites, here denoted by m–m. To first approximation the strength of binding in the complex M m–m should not be that different from that in M m–r where m–r denotes a related small molecule with but one active site m and r is the rest of the species. As the bond between M and m–r bond is stretched (with or without solvent separation) it is weakened. Eventually it breaks and the two resultant molecules separate, they diffuse away. However, let us allow for r to be now m, we now consider a small molecule with two active sites. As the M m–m bond is broken involving the first active site m, the second active site m remains relatively nearby. It is ready to react with the M just formed. From the vantage point of the chemist who is observing the reaction, i.e., is outside of the molecule, the resulting product is the same as the reactant. The bond between M and m–m has not been broken. It appears stronger than between M and m–r. Much the same applies to the case where M has two sites for binding, we have M–M except in this case depending on geometric constraints of the macromolecule and small molecule alike, the two M's in M–M can interact with the two m's in m–m. We recognize this as analogous to the binding of a metal ion with a bidentate ligand, and the increased stabilization related to the increased strength and stability of chelates over corresponding complexes formed by monodentate ligands. If M has two active sites but m but one, we have the same behavior as first enunciated — perhaps that is a reason for why so many enzymes have multiple identical subunits?

In conclusion, we have shown that natural products are abundant as dimers and many are used in enzymatic processes based on data from the literature. In the case of an acetylcholine esterase model, a compound possessing two quaternary nitrogens binds more effectively compared to compounds with one or three quaternary nitrogens. We suggest that the driving force for recognition via equilibrium favoring the crystal to the liquid is amplified for binding between bilaterally symmetrical natural products and its crystalline receptor. Bilaterally symmetrical structures may have

evolved since proteins are specialized for structure-function stability relationships with natural molecules. It is of significance that bilateral symmetry is common among enzyme inhibitors. An experimentally tested result which supports the conclusions presented here may be found in the principle of "multivalent" drug design. The design of small molecule ligands have been conducted in this fashion to enhance receptor/ligand interactions and affinity of binding.

Acknowledgements This research was supported in part by PSC-CUNY. O.R.W. is the recipient of the David Davidson Memorial Summer Research Award donated by Herbert and Estelle Meislich.

References

1. Voloshchuk T, Farina NS, Wauchope OR, Kiprowska M, Haberfield P, Greer A (2004) J Nat Prod 67:1141
2. Bellarosa L, Zerbetto F (2003) J Am Chem Soc 125: 1975
3. Bamford DG, Biggs DF, Chaplen P, Davis M, Maconochie JG (1971) Can J Pharm Sci 6:17
4. Descamps-François C, Yous S, Chavatte P, Audinot V, Bonnaud A, Boutin JA, Delagrange P, Bennejean C, Renard P, Lesieur D. (2003) J Med Chem 46:1127
5. Pauling L (1970) General Chemistry; W. H. Freeman Publishing Co., San Francisco, CA, p 398
6. Rekharsky MV, Inoue Y (1998) Chem Rev 98:1875