for carrying out the preparation of the compounds presented in this paper. We thank also Richard S. Ware for providing high-resolution mass spectra and Dr. Earl B. Whipple for NMR studies.

Registry No. 1 (n = 4), 55440-84-1; **2** (X = t-oct, Y = CH_3), 2563-08-8; **2** (X = Y = H), 120-80-9; **3**, 54533-84-5; **4f**, 119319-62-9; **6b**, 119319-00-5; **6c**, 124175-43-5; **6d**, 124175-44-6; **7f**, 119318-69-3; **7f** (Y = CH_2OCOCH_3), 119271-39-5; **7f** (Y = CH_2OH), 119271-40-8; **9a**, 124175-32-2; **9b**, 119362-70-8; **9c**, 119362-73-1; **9d**, 119362-75-3; **9e**, 124175-33-3; **9f**, 119362-79-7; **9f·K**, 124175-45-7; **9g**, 124175-34-4; **9h**, 124175-35-5; **9i**, 124175-36-6; **9j**, 124175-37-7; **9k**, 124175-38-8; **9l**, 124175-39-9; **10a**, 124175-40-2; **10b**, 124175-41-3; 11, 1139-46-4; **12** (Y = CH_2 morpholino), 119319-02-7; **13** (Y = CH_3), 488-17-5; **16**, 119271-46-4; **17**, 119271-41-9; **18**, 65659-36-1; **19a**, 122-60-1; **19b**, 3101-60-8; **20a**, 119318-91-1; **20b**, 119319-37-8; **21**, 124175-42-4; **22**, 124199-83-3; CH_2=$C(CH_3)C$-$H_2C(CH_3)_3$, 107-39-1; 4-*tert*-butyl-2,6-dimethylbenzoic acid, 58537-98-7; morpholine, 110-91-8; 2-[2-[2-(2-chloroethoxy)ethoxy]ethoxy]tetrahydropyran, 85539-28-2.

Voronoi Binding Site Model of a Polycyclic Aromatic Hydrocarbon Binding Protein

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A three-dimensional Voronoi binding site model has been formulated from a series of competitors for the binding site on a recently isolated polycyclic aromatic hydrocarbon binding protein (PBP) from mouse liver. The PBP binds polycyclic aromatic hydrocarbons, such as benzo[a]pyrene (B[a]P), with high affinity and shows other characteristics associated with receptor–ligand complexes. Altogether, the in vitro binding constant of seven molecules were used to deduce the geometry and the energetics of a possible site model consisting of five regions: one tetrahedron-shaped finite central hydrophobic pocket, one infinite region representing access to the solvent, and three strongly repulsive regions representing the sterically forbidden walls of the pocket. The model then predicted the binding energies correctly for nine additional competitors and suggests that competition of monoaromatic (benzene) derivatives with B[a]P would be weak.

In order to understand the specific binding of small molecules to biological receptors, we have recently devised a novel approach to objectively deduce the structure and energetics of a binding site, given the observed binding energies for a series of ligands.[1-4] For example, what can we say about the shape and intermolecular forces governing the binding of competitive inhibitors of an enzyme, given their binding constants, but without knowing the enzyme's X-ray crystal structure? The algorithm for deducing this should be as little influenced as possible by the preconceptions of the investigator and should yield a vague result when given insufficient data. The technique is to construct a simplified picture of the site which still allows the ligands to explore their full range of energetically allowed conformations and alternate orientations within the site. Binding energies are modeled as a sum of interactions between ligand atoms and the regions of the site they occupy. The method we have used to achieve this is based on modeling the site as Voronoi polyhedra, and its main features have already been described.[2,4]

As a challenging test of the method, we selected a data set consisting of the binding constants of a series of competitors for a recently isolated protein, polycyclic aromatic hydrocarbon binding protein (PBP),[5] from mouse liver which binds polycyclic aromatic hydrocarbons (PAHs) with high affinity.[6-8] This protein is relatively small (31 000 Da) and binds PAHs with receptor-like properties, that is, not only with high affinity, but also in a saturable and specific manner. Benzo[a]pyrene (B[a]P) is the best characterized ligand, and other ligands have been studied as competitors for [^{3}H]B[a]P. Results with a specific binding photoaffinity label suggest that PBP has one binding site for this class of ligands.[7] The on- and off-rate binding kinetics are also consistent with a receptor function for this protein. As can be seen in Chart I, the ligands in this study are not members of any homologous series and differ widely in shape. Most methods for developing quantitative structure–activity relationships (QSAR) deal with sets of compounds which are structurally so closely related that one generally assumes they may be unam-

Table I. Observed and Calculated Binding of the Compounds of Chart I for the Five-Region Site Shown in Figure 1

compound	ΔG^a_{m-}	ΔG^a_{m+}	$\Delta G^a_{m,calc}$	optimal mode[b]
1, benzo[a]pyrene	17.7	19.0	19.0	15 C, 8 H
2, dibenzo[a,c]anthracene	17.3	18.6	18.6	14 C, 8 H
3, chrysene	16.7	18.0	17.9	14 C, 8 H
4, pyrene	16.3	17.6	16.3	13 C, 7 H
5, cyclopenta[c,d]pyrene	15.6	17.6	15.8	13 C, 6 H
6, fluoranthrene	16.7	18.0	17.8	14 C, 8 H
7, 3-methylcholanthrene	16.1	17.4	17.4	13 C, 8 H
8, 1-aminonaphthalene	10.6	11.9	11.9	10 C, 6 H (NH_2 in r_1)
			11.9	9 C, 6 H (NH_2 in r_2)
9, 2-aminofluorene	13.8	15.1	14.4	11 C, 7 H (NH_2 in r_2)
10, 1-aminoanthracene	14.9	16.2	15.2	12 C, 7 H (NH_2 in r_2)
11, 9-aminophenanthrene	14.9	16.2	15.2	13 C, 7 H (NH_2 in r_1)
			15.2	12 C, 7 H (NH_2 in r_2)
12, 9-hydroxybenzo[a]-pyrene	18.2	19.5	18.3	15 C, 7 H (OH in r_1)
13, 7α,8β-dihydroxy-7,8-dihydrobenzo[a]pyrene	17.3	18.6	18.4	12 C, 7 H (OHs in r_2)
14, 9β,10α-dihydroxy-9,10-dihydrobenzo[a]pyrene	17.6	18.9	18.9	13 C, 7 H (OHs in r_2)
15, 4α,5β-dihydroxy-4,5-dihydrobenzo[a]pyrene	17.4	18.7	17.4	10 C, 7 H (OHs in r_2)
16, 2α,3β-dihydroxy-2,3-dihydrofluoranthene	16.5	17.8	17.7	12 C, 7 H (OHs in r_2)

[a] The ΔG are given as $-\ln K_i$ where K_i is the association constant of the competitor with the receptor. [b] The optimal modes are given as the number of C and H atoms lying in r_1, the rest being in r_2.

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(1) Crippen, G. M. *Ann. N. Y. Acad. Sci.* 1984, *439*, 1.
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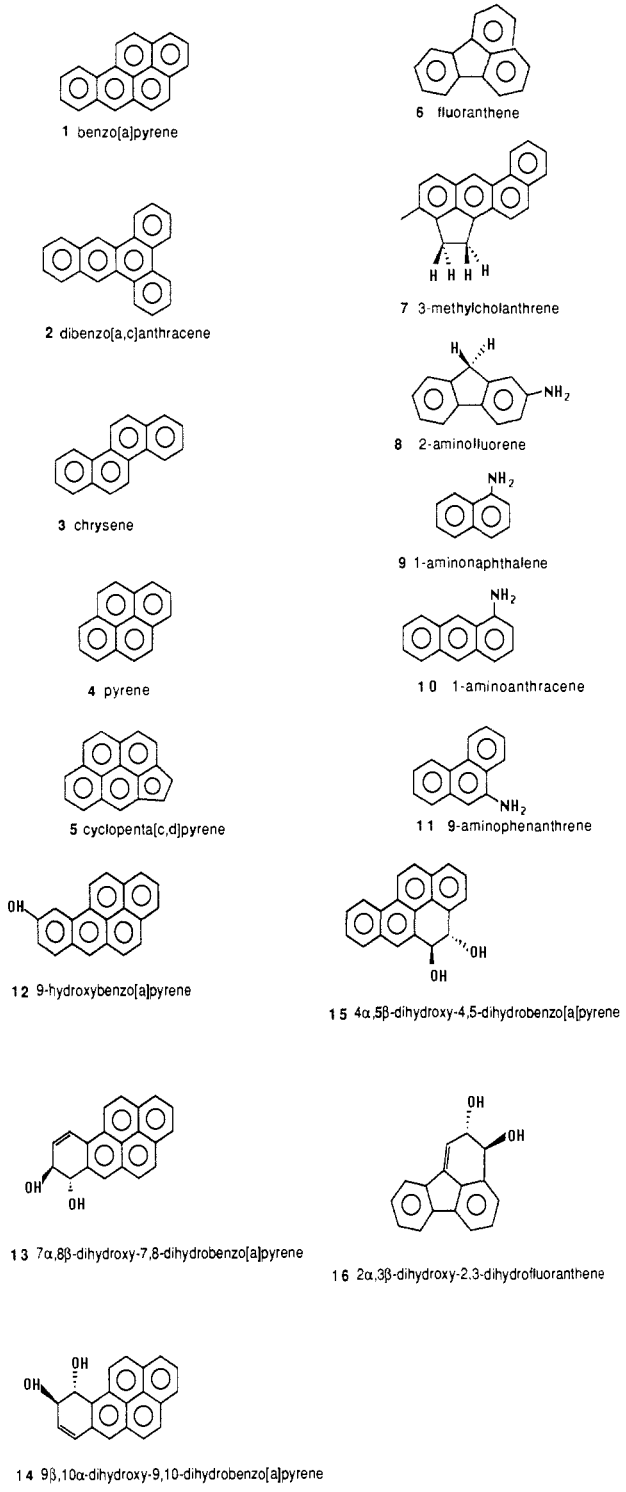
0022-2623/90/1833-0771$02.50/0 © 1990 American Chemical Society

Chart I. Competitive Inhibitors of [^{3}H]Benzo[*a*]pyrene Binding



biguously superimposed and they indeed bind in analogous orientations at the receptor site. Clearly, these methods would not be able to deal with the set of ligands of Chart I. Since our Voronoi approach does not make any assumptions about the orientation of the ligand molecule in the binding site and its conformation upon binding, the choice of this data set is appropriate and critical in evaluating this new method.

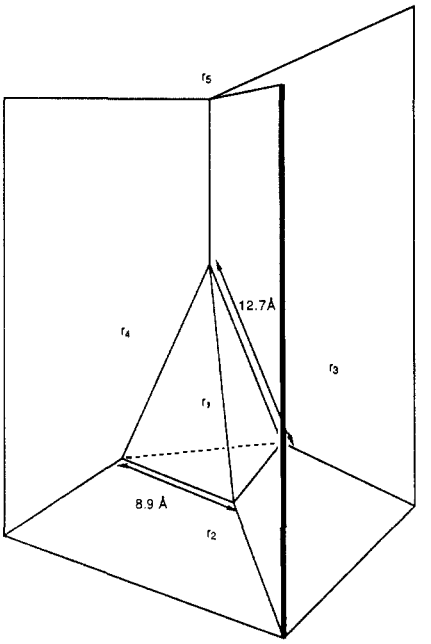


Figure 1. Five-region Voronoi site obtained for the compounds of Chart I. Region r_1 is the trigonal pyramid in the center, while the other regions have infinite volume and therefore are indicated by portions of their boundary planes. Region r_2 starts at the base of the pyramid and extends downward; r_3 opens out toward the right; r_4 opens out toward the left; and r_5 opens out toward the background. Regions r_3–r_5 are blocked for binding.

Results and Discussion

Going from the simplest Voronoi site geometry to the more complex, we found that the observed binding energies of compounds **2** and **6** could not be fitted within experimental error ranges to a one-region or a two-region site (see the lower and upper experimental bounds ΔG_{m-} and ΔG_{m+} in Table I). Close examination of the binding data shows that the affinity of a ligand increases roughly with the number of carbons and hydrogens until a critical molecular size is reached and then remains constant for molecules bigger than pyrene. Hence, a correlation between, say, the logarithm of the octanol/water partition coefficient and binding is impossible. In fact, as already noted, most methods of QSAR would have difficulty in the initial step of superimposing these compounds to find a pharmacophore, because they do not form a congeneric series. Apparently there must be a hydrophobic-preferring binding pocket of some limited size, large enough to contain ligands about the size of pyrene (or smaller), but not much bigger. Since most of the molecules are planar, this fact naturally leads to the idea that this pocket should have at least two finite dimensions in order to only accommodate the smaller molecules of the set. Such a Voronoi site can be obtained by having four coplanar generating points and is thus made of four regions (one central region made of two finite dimensions and three infinite regions). Even so, it was found very hard to fit the data set, as extended molecules like chrysene or dibenzo[*a*,*c*]anthracene can easily place themselves along the infinite dimension of the central region and bind better than others molecules of similar number of atoms. To reduce as much as possible this discrimination between large molecules, the hydrophobic pocket must be completely finite and of specific size. Note

(4) Boulu, L. G.; Crippen, G. M. *J. Comput. Chem.* **1989**, *10*, 673–682.
(5) Abbreviations used: B[*a*]P, benzo[*a*]pyrene; Hepes, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; EDTA, ethylenediaminetetraacetic acid; PBP, polycyclic binding protein; PAH, polycyclic aromatic hydrocarbon.
(6) Collins, S.; Marletta, M. A. *Mol. Pharmacol.* **1984**, *26*, 353–359.
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(8) Barton, H. A.; Marletta, M. A. *J. Biol. Chem.* **1988**, *263*, 5825–5832.

Table II. Interaction Parameters in ln K_i Units for the Site Model Corresponding to Table I

atom	site regions	
	r_1	r_2
H	0.84	−0.21
C	0.78	0.28
NH_2	−0.75	−0.24
OH	0.08	0.99

that since compound **2** binds better than **5**, this pocket may be narrow. The simplest Voronoi site of this kind is a five-region site obtained by having four generating points at the vertices of a tetrahedron and the fifth one lying inside it. The resulting site has a tetrahedron-shaped finite central region r_1 and four infinite regions (r_2–r_5) which respectively extend outward from each face of r_1 (see Figure 1). In order to get a more physical picture of the actual site, we blocked r_3–r_5 so that a ligand can only bind to r_1 and r_2. In this way, r_1 is supposed to be the hydrophobic pocket; the infinite region opening up on the bottom, r_2, may represent access to the solvent; and the other three regions are a priori chosen to be infinitely repulsive, so as to represent the sterically forbidden walls of the binding pocket. After some experimentation on compounds **1**–**10**, we adjusted the geometry so that the bottomward-facing side of the inner tetrahedron (which opens out onto the solvent region) is an equilateral triangle having side length 8.9 Å, and the remaining three edges have length 12.7 Å. Then, the program for determining interaction parameters was able to find several solutions, one of which is shown in Table II. Compounds **2, 4, 7, 8, 12, 14,** and **15** were enough to guide the random search to these parameters, i.e. these seven ligands could constitute the training set while the other nine could be used for testing predictions. Note that hydrogen and carbon atoms have a good (positive) interaction with the definitely hydrophobic pocket r_1 and a small interaction with r_2, presumed to be the solvent. An amino group is slightly repelled by the solvent region, but more so by the interior pocket, while a hydroxyl group experiences no interaction with the pocket but a good one with the solvent. In each case, the energetic preference of the various atom types is consistent with the physical interpretation of the two regions, and the trends are in the right direction, but the values we have calculated for the interaction parameters are largely artifacts of the fitting procedure and should not be overinterpreted. Table I gives the calculated binding energies $\Delta G_{m,calc}$ and the optimal modes of binding for this set of parameters. Note that compound **8** and **11** have two optimal modes depending on the location of their amino group. Figure 2 shows the predicted optimal binding mode of benzo[*a*]pyrene (**1**).

The most time-consuming part of the whole method was the calculation of the geometrically allowed binding modes (between 36 and 70 modes, depending on the ligand molecule) which took between 5 min (compound **8**) and 7 h (compound **14**) of CPU time on a SUN 4/280S computer.

As mentioned above, sets of interaction parameters other than the one given in Table II could also give correct calculated binding energies for the 16 compounds, although very small changes in the carbon and hydrogen parameter values were obtained. More specifically, the following ranges of values were found: $\epsilon_{r1,H} = [0.81, 0.92]$, $\epsilon_{r2,H} = [-0.24, -0.20]$, $\epsilon_{r1,C} = [0.75, 0.80]$, $\epsilon_{r2,C} = [0.25, 0.30]$. Mild or small variations were obtained for the remaining parameters values except for the hydroxyl group–inner pocket interaction since only compound **12** was found to bind its hydroxyl there: $\epsilon_{r1,NH_2} = [-1.1, -0.72]$, $\epsilon_{r2,NH_2} = [-0.66, -0.22]$, $\epsilon_{r1,OH} = [0.02, 1.3]$; $\epsilon_{r2,OH} = [0.97, 1.04]$.

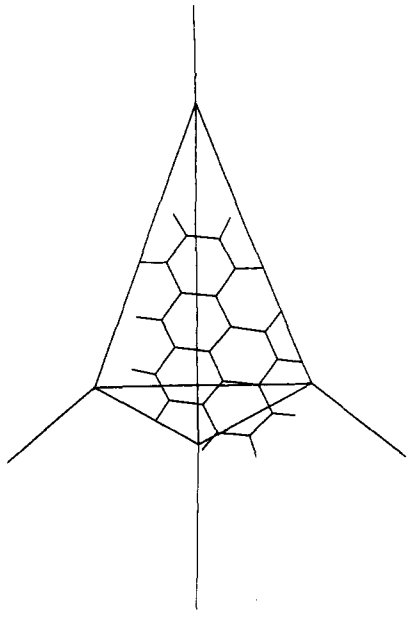

Figure 2. Benzo[*a*]pyrene in its predicted optimal binding mode. This is the same view of the r_1 pyramid as in Figure 1, and the atoms barely touch the boundary surfaces and edges.

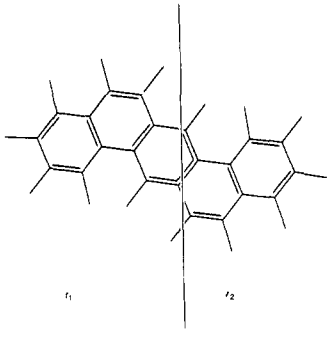

Figure 3. Dibenzo[*a*,*h*]anthracene. In its predicted optimal binding mode, 12 C and 8 H are in r_1, the rest being in r_2.

Considering the stability of the above carbon and hydrogen parameter values found for the Voronoi site model of Figure 1, predictions of the binding energy of other PAHs made of only these two types of atoms should be relatively accurate, no matter what the molecular shape is, since our method allows global exploration of all accessible conformations and orientations upon binding. Furthermore, the relevant calculation is straightforward since a Voronoi model of the binding site has already been determined. All one needs to do is to determine the geometrically allowed modes of binding of the chosen PAH to the site and then to use the previously determined interaction parameters to calculate the binding energy. For example, the set of parameters of Table II predict a binding energy of 17.6 units for dibenzo[*a*,*h*]anthracene (see Figure 3). A small molecule like benzene is able to fit entirely in the hydrophobic pocket r_1, so that its calculated binding energy is 6(0.84 + 0.78) = 9.7 units from Table II. In terms of IC_{50}, this corresponds to about 120 μM, which means benzene and other monoaromatic ring compounds should be very weak competitors for the B[*a*]P site. Safrole (4-allyl-1,2-(methylenedioxy)benzene) is indeed a very weak competitor for this site.[9] In the same

(9) Kwon, H.; Marletta, M. A., unpublished results.

way, small benzene derivatives like aniline or phenol find their optimal mode by fitting their phenyl rings in the pocket while having their substituent lying in the solvent region r_2. In any case, the above parameters give poor binding energies leading to weak competition.

Just how precisely determined the site model is and how great its predictive powers are are questions we continue to explore. As explained above, compounds 1–10 were used to determine the geometry of the site, and only compounds 2, 4, 7, 8, 12, 14, and 15 influenced the final values of the interaction parameters. Therefore, it would be fair to say that the binding affinities of compounds 11, 13, and 16 were legitimately predicted. Finding any solution is rather laborious, given the present state of development of our computer programs, so we have not yet tried any sort of cross-validation test of the method. The determination of the geometry of the site model is the one subjective feature of the approach, although once a general shape has been chosen, the two critical dimensions of the one central region in this example (length of an edge of the equilateral triangle base of the trigonal pyramid and its altitude) had to be adjusted to the order of 0.1 Å in order to produce a solution. It is possible, however, that there is another, equally simple, very different geometry that can also account for the observed binding. Similarly, as discussed above, the interaction parameters were locally determined to an accuracy of 0.1 unit, but there may be another very different family of parameters that would do as well. Altogether we had to adjust eight interaction parameters and two geometric dimensions at least in a local sense in order to fit 13 compounds and predict three more. At first glance that may sound like overfitting the data, but remember that a site model involving four coplanar generating points failed to fit the observed binding, and that has five geometric degrees of freedom and at least eight interaction parameters. Since finding a correct binding site model is more of a global combinatorial problem than a linear least squares fitting procedure, the usual statistical methods for assessing the quality of the model cannot be readily applied. This is a challenging topic for further work.

Conclusions

PBP has been purified and partially characterized. Studies with the protein, including a rigorous physical characterization of this hydrophobic binding site using methods such as X-ray crystallography, have been hampered by the small amounts of the protein available after purification. In addition, as we have reported, the protein exists in a number of isoforms,[8] and this further complicates more detailed studies of the binding site. The results reported here show how the Voronoi modeling method has provided us for the first time with a way to view this binding site and also with a model to further test against other ligands. Additional binding data would presumably add more geometric detail to the picture we now have, although the method tends toward relatively simple explanations for the data. Of course, this method can be broadly applied to other receptor binding systems.

Experimental Methods

Materials. Male C57BL/6J mice aged 6–8 weeks were obtained from Jackson Laboratories (Bar Harbor, ME). At the time of cytosol preparation, the mice were typically 8–12 weeks of age. [^{3}H]B[a]P (specific activity ~69 Ci/mmol) was obtained from New England Nuclear and purified before use as reported previously.[6] All other chemicals were of the highest purity available.

Competition Binding Assays. These assays were carried out as described previously.[6-8] Briefly, mouse liver cytosol (100000g supernatant) from C57BL/6J was prepared and stored at −70 °C. The binding assays were carried out in HEDG buffer consisting of 25 mM Hepes, 5 mM EDTA, 1 mM dithiothreitol, and 10% glycerol (v/v), pH 7.5. Competition was measured by the ability of potential ligands to compete with [^{3}H]B[a]P in an equilibrium binding assay. After incubation of the cytosol, [^{3}H]B[a]P, and the unlabeled competing ligand for 40–60 min at 20 °C, the separation of bound and free ligand was accomplished by the addition of dextran-coated charcoal followed by centrifugation. The supernatant from this spin was counted in a liquid-scintillation counter.

The series of compounds of Chart I have been tested for their ability to compete for the [^{3}H]benzo[a]pyrene-binding site of the protein, and their IC_{50} were experimentally determined. The corresponding binding energies were determined from the IC_{50} as $-\ln K_i$ where K_i is the affinity constant of the inhibitor with the receptor assuming Michaelis–Menten competitive kinetics. More precisely, we have

$$K_i = \frac{IC_{50}}{1 + [L]/K_D} \quad (1)$$

where K_D and [L] are respectively the dissociation constant and the concentration of [^{3}H]benzo[a]pyrene. In these experiments, $K_D = 4.5 \pm 1.5$ nM and [L] = 4 ± 1 nM. In the same way, error ranges on $-\ln K_i$ were determined from the ones on IC_{50}, K_D, and [L].

Computational Methods

Atomic coordinates of the ligand molecules of Chart I were obtained by either locating the relevant structure in the Cambridge Structural Database or using the commercially available molecular modeling package QUANTA of Polygen, in which case molecular structures were entered graphically and coordinates were obtained after minimization of a molecular mechanics potential function, such as CHARMM.

Then each ligand molecule was converted to our linearized format.[2] This involves specifying the overall translation of the molecule with respect to an external reference frame by a translation vector pointing to a centrally located atom and then setting up local coordinate systems in terms of unit vectors for mutually rigid group of atoms. This linearized representation of the molecule is also convenient in summarizing the global range of conformations which are energetically accessible. In this work, we excluded only those conformations suffering from van der Waals contacts. For the sake of simplicity, amino and hydroxyl groups were considered as single composite atoms. For each molecule, a topological database made of convexity rules involving groups of atoms was determined.[4] Use of this database allows rapid processing of those binding modes which can be eliminated on combinatorial knowledge of the molecule alone, thus avoiding any time-consuming numerical calculation. This database is now automatically generated from the atomic coordinates.

At this stage, a site geometry was proposed and the set of all geometrically allowed binding modes for each ligand molecule was determined by either use of topological and "distance" databases or use of numerical calculation as described previously.[4] Then, the interactions parameters were determined so that the calculated binding energy $\Delta G_{m,calc}$ for each ligand molecule m of the set falls within its respective experimental range. In other words, we require an absolute fit to the given ranges

$$\Delta G_{m-} \le \Delta G_{m,calc} \le \Delta G_{m+} \qquad \text{for all } m \quad (2)$$

where ΔG_{m-} and ΔG_{m+} are the bounds of the experimental range for molecule m. Note that, for all the feasible modes, the molecule m is said to have a calculated binding energy, $\Delta G_{m,calc}$, corresponding to that of the energetically most favorable mode, i.e.

$$\Delta G_{m,calc} = \max_{b \in B_m} \Delta G(b) \quad (3)$$

where B_m is the set of geometrically feasible binding modes for molecule m, and $\Delta G(\mathbf{b})$ is the total interaction energy for the mode **b**. (In this paper we take the convention that algebraically greater values denote better interaction.) Since the interaction energy of a molecule is assumed to be the sum of its atomic contributions, we have

$$\Delta G(\mathbf{b}) = \sum_{\text{region r}} \sum_{\substack{\text{atoms a} \\ \text{in r}}} \epsilon_{r,type(a)} \quad (4)$$

where $\epsilon_{r,type(a)}$ is the interaction energy parameter between the site region r and the atom-type of atom a. Once these interaction parameters are determined, they can be used to calculate the binding energy of a molecule outside the original set of compounds. However, if no solution can be found, the proposed site geometry is rejected, a more complex one is considered, and the above procedure is repeated until the ligand molecules of the set can be fitted to the experimental data.

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Registry No. 1, 50-32-8; 2, 215-58-7; 3, 218-01-9; 4, 129-00-0; 5, 27208-37-3; 6, 206-44-0; 7, 56-49-5; 8, 134-32-7; 9, 153-78-6; 10, 610-49-1; 11, 947-73-9; 12, 17573-21-6; 13, 57404-88-3; 14, 58886-98-9; 15, 37571-88-3; 16, 82911-12-4.

1,4-Dihydronaphthoquinones, Hydroindoloquinones, Benzofurans, and Benzothiophenes as Inhibitors of 5-Lipoxygenase. Synthesis and Structure–Activity Studies

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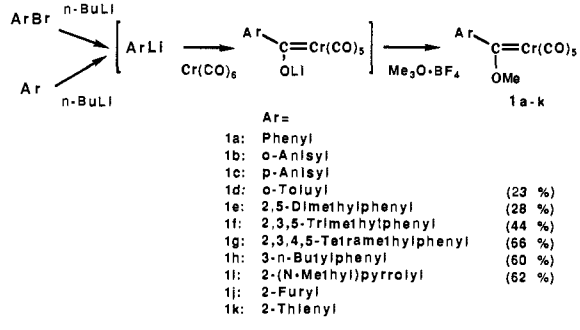
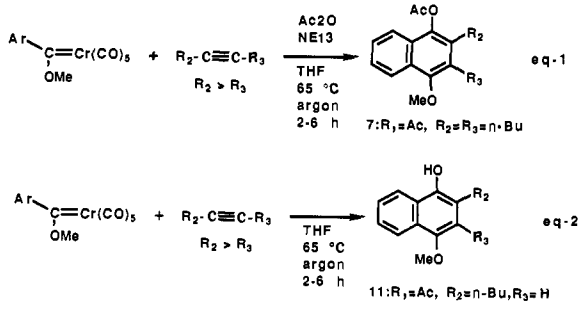
A series of substituted 1,4-dihydronaphthoquinones, hydroindoloquinones, benzofuran-4,7-dihydroquinones, and benzothiophene-4,7-dihydroquinones were synthesized and evaluated for inhibitory activity against 5-lipoxygenase. These compounds were found to be active in vitro for LTC_4/D_4 inhibition with the potencies (IC_{50}'s) ranging from 0.2 to 85 μM. Active 1,4-dihydronaphthoquinone acetates ($IC_{50} < 20$ μM) were evaluated in an ex vivo LTB_4 inhibition assay. The acetates of 1,4-dihydronaphthoquinones containing the alkyl substituent(s) (2-*n*-butyl, 11, and 2,3-diethyl, 15) exhibited the best activity in LTC_4/D_4 inhibition (IC_{50} = 0.2–0.4 μM, in vitro) as well as in LTB_4 inhibition (60–75% inhibition).

The metabolism of arachidonic acid (AA), catalyzed by the enzyme 5-lipoxygenase, produces 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE), which undergoes further bioconversions to 5-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) and to the leukotrienes (LTA_4, LTB_4, LTC_4, LTD_4, and LTE_4).[1] These potent biological substances have been implicated as important mediators of inflammation and allergic reactions. For example, LTC_4 and LTD_4 are potent bronchioconstrictors of human bronchi,[2] LTB_4 is a powerful chemotactic factor for leukocytes,[3] and inhibition of 5-lipoxygenase may be of therapeutic value in the treatment of inflammatory and allergic diseases. On the basis of current knowledge of the enzymatic mechanisms of related lipoxygenases,[4] it is reasonable to assume that the reaction of oxygen with AA to form 5-HPETE requires a metal species, putatively iron, in the active site of the enzyme. Considering this premise, there are several examples of rationally designed inhibitors of 5-lipoxygenase. Common approaches involve the preparation of acetylenic,[5] allenic,[6] aryl,[7] or dimethyl[8] analogues of AA. Other approaches include the synthesis of analogues of 5-HPETE[9] or LTA_4.[10] We have found that

Scheme I



Scheme II



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