Equation 11 was used to predict the activities of this series. The results are shown in Table VIII and Figure 4. A satisfactory prediction of binding affinities is obtained, certainly of sufficient accuracy to guide a synthetic program. The scatter observed is probably due to the use of data from a different laboratory.

A linear regression analysis incorporating both Kontula's and Raynaud's work results in eq 12.

Equation 12 (rabbit): log relative binding affinity = 1.92 + 0.21 (±0.11) π_a + 1.5 (±0.20) π_b + 0.009 (±0.002) (surface area in hydrophobic pockets) − 0.013 (±0.003) (surface area out of hydrophobic pockets) − 1.27 (±0.17) MK − 0.21 (±0.05) (conformational changes). $n = 65$, $r = 0.88$, $s = 0.53$, $F = 35$.

Our results thus represent a QSAR approach having predictive value and indicate that surface area is a logical and useful parameter to model hydrophobic binding. Like the work of Hansch, they show also that receptor mapping can be effectively carried out through QSAR techniques.

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A Model for the Prostaglandin Synthetase Cyclooxygenation Site and Its Inhibition by Antiinflammatory Arylacetic Acids

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Conformational analysis of indomethacin and other nonsteroidal antiinflammatory drugs leads to formulation of a hypothetical complementary receptor site model. The same model can serve to describe the prostaglandin cyclooxygenase active site, and, indeed, arachidonic and other polyunsaturated fatty acids could be folded on the model in a manner which rationalizes their stereospecific transformation to cyclic *endo*-peroxides (PGG). The model rationalizes the structure–activity relationships of enzyme substrates and inhibitors and appears to be in agreement with biochemical studies of the enzyme.

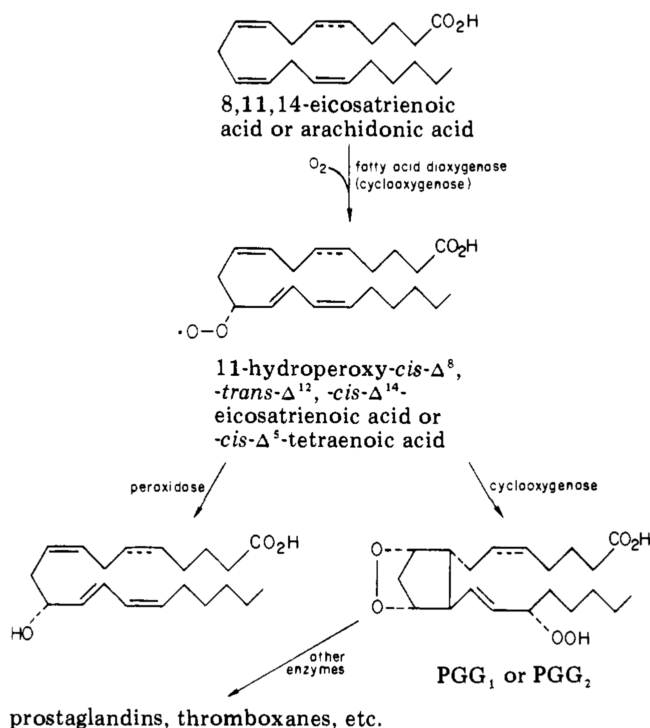
Over 10 years ago, on the basis of observed in vivo structure–activity relationships for indomethacin (1) analogues, an antiinflammatory receptor site was hypothesized[1,2] to consist of two noncoplanar hydrophobic regions and a cationic center. After the 1971 discovery[3-5] that indomethacin and other antiinflammatory drugs inhibit prostaglandin (PG) synthesis, this receptor was equated to the PG synthetase active site.[6] A related hypothetical receptor site was proposed from the shape of some antiinflammatory benzoic acid derivatives.[7]

We have modeled the three-dimensional structures of some antiinflammatory arylacetic acids and found common spatial features. We have hypothesized a complementary receptor site model, which can also accommodate some polyunsaturated fatty acids in a conformation which rationalizes their stereospecific conversion into cyclic *endo*-peroxides.

It is now well established that prostaglandins and their metabolites are involved in the inflammatory process and that many antiinflammatory drugs inhibit the PG synthetase enzyme complex at physiological concentrations.[7-10] While prostaglandin synthesis is a complex, multistep process[11-15] (Scheme I), we only concern ourselves here with the initiation step—substrate binding by fatty acid dioxygenase—since this is the step inhibited by aspirin,[16] indomethacin, and other antiinflammatory agents.[12]

Modeling Methods. Molecular structures were generated from standard bond lengths and angles, or from crystallographic coordinates where available, and viewed interactively on a Tektronix 4010 display terminal.[17] Conformational energies were calculated by quantum mechanical (CNDO/2[18]) and classical mechanical (MODBUILDER[19]) methods. Favored conformations were

Scheme I. Summary of Prostaglandin Biosynthesis



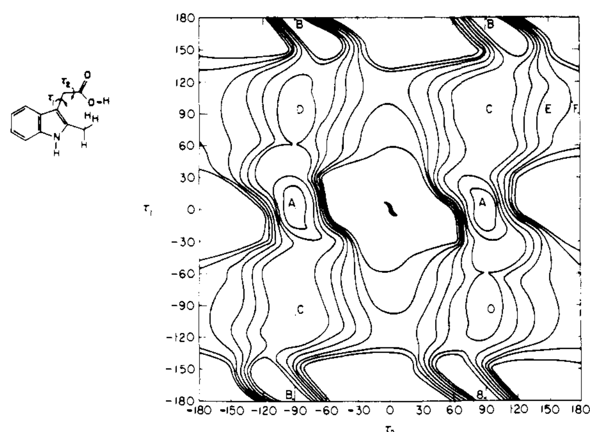


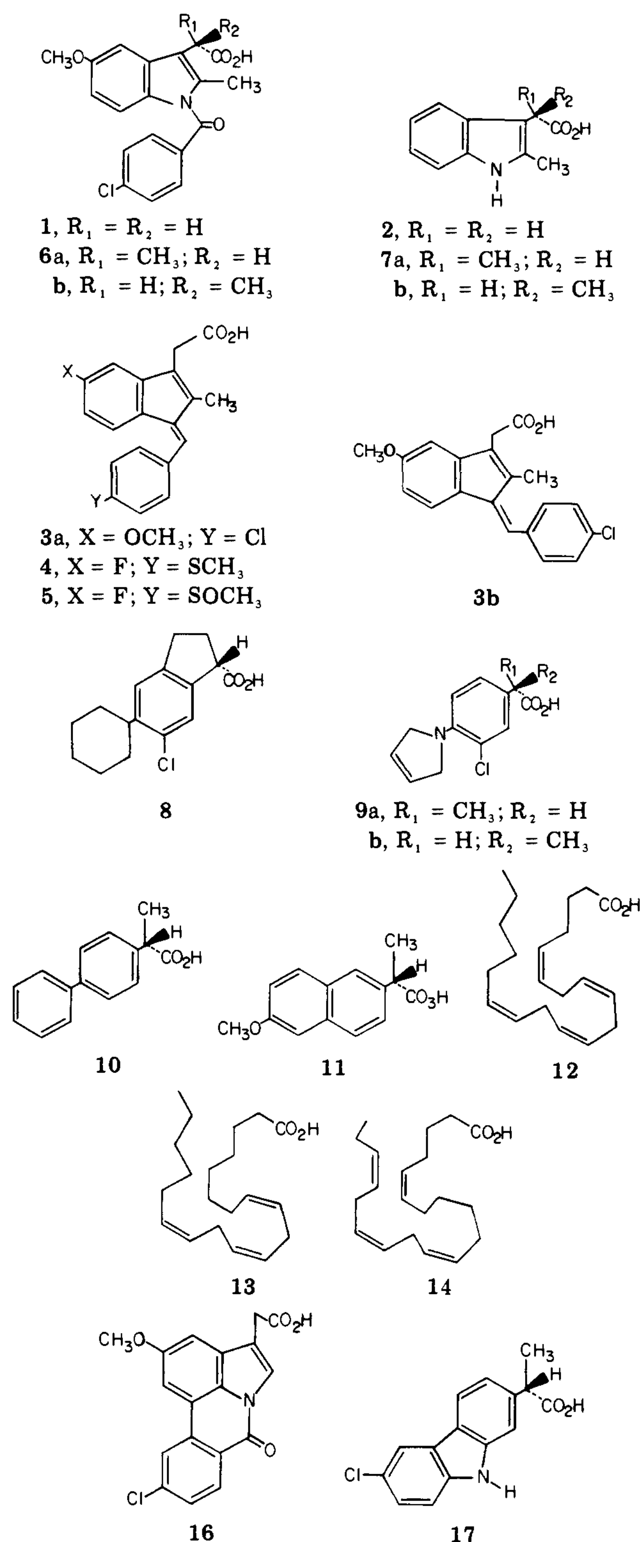
Figure 1. CNDO/2 calculated rotational energy surface for the side chain of 3-(2-methylindolyl)acetic acid. (Results were similar for the corresponding carboxylate anion.) Isobars are drawn at 0.5-kcal intervals. At the global minimum A, the carboxy carbon is in the plane of the ring atoms; solvation effects should destabilize this conformation (note the steepness of the energy "well" for A). Local minima appear at B (0.5 kcal higher in energy), C (1.1 kcal higher), and D (1.3 kcal). The indomethacin side-chain crystal conformation (ref 19) is E; in the 3-indolylacetic acid crystal [I. L. Karle, K. Britts, and P. Gum, *Acta Crystallogr.*, 17, 496 (1964)] it is F.

compared in order to find common spatial features, and a complementary receptor topography was hypothesized. Manipulation of a CPK model of arachidonic acid on the hypothetical receptor surface led to the proposed mechanism of cyclic *endo*-peroxide formation.

Molecular Conformational Analysis. Molecules studied are collected in Chart I. Indomethacin (1) has conformational flexibility; therefore, the crystal[20] and bioactive conformations are not necessarily identical. The acetic acid side chain of 1 appears to be quite flexible; CNDO calculations on a model compound, 3-(2-methylindolyl)acetic acid (2), give a rotation barrier of ca. 3 kcal/mol (Figure 1).

While the benzoyl group of 1 may also rotate, the corresponding group in the benzylidenindene isostere 3 is

Chart I. Structures of Antiinflammatory Compounds and PG Synthetase Substrates Studied



fixed. We modeled 3 using the dihedral angles found in the crystal structure of indomethacin[20] and obtained an excellent fit with the two-dimensional crystal projection[21] of the *Z* isomer **3a**. The *Z* form **3a** is thermodynamically more stable and possesses five times more antiinflammatory activity than the *E* isomer (**3b**).[21] Our calculations suggest that the new antiinflammatory drug sulindac [USAN name for (*Z*)-5-fluoro-2-methyl-1-[4-(methylsulfinyl)phenyl]methylene-1*H*-indene-3-acetic acid (**5**)] and its active metabolite[22] **4** prefer analogous conformations.

In an attempt to determine the bioactive conformation

of the acetic acid group in 1, the less flexible α-methylindomethacin (6) was modeled. For the model compounds **7a** and **7b**, full geometric minimization by the classical mechanical method[19] was performed, starting from various single-bond rotamers to assure that the global minimum was found. The calculations suggest that the bioactive *S* isomer **6a** should exhibit a small preference (0.8 kcal/mol) for the "carboxy down" conformation (CO_2H below the plane of the paper in the view of **6** shown), while the substantially less active *R* isomer **6b** should prefer a "carboxy up" conformation by an equal amount. CNDO/2 binding energies of the strain-minimized structures tended to parallel the classical energies, but again the differences were small. Solvation of the carboxy group should favor the minimum energy conformation by a greater amount.

The bioactive conformation of the acetic acid group may be assigned by reference to the crystal structure[23] of 6-chloro-5-cyclohexylindan-1-(*S*)-carboxylic acid (d-TAI-284) (8), where the carboxy group is constrained by attachment to a five-membered ring. This drug superposes best with the "carboxy-down" conformation of (*S*)-α-methylindomethacin (**6a**), with the α-methyl group of **6a** coinciding with a ring carbon of 8.

Pirprofen (9), an antiinflammatory agent that reversibly inhibits PG synthetase,[24] was modeled by a combination of CNDO/2 and classical techniques. A strong preference for a coplanar arrangement of the rings was found by both methods. There is, of course, no appreciable preference for a "carboxy-up" vs. "carboxy-down" conformation for this ortho-unsubstituted molecule. We propose a bioactive conformation of the *S* isomer **9a** which is complementary to that of (*S*)-α-methylindomethacin (**6a**). Presumably other antiinflammatory arylacetic acids,[1,6] e.g., **10** and **11**, may adopt comparable conformations.

Bioactive Conformations of Antiinflammatory Arylacetic Acids. Some of our hypothesized bioactive conformations are shown in Figure 2. The indomethacin (1) conformation is essentially that observed in the crystal state.[20] The conformation shown has the benzoyl ring and carboxy group on opposite sides of the plane containing the indole ring (anti). A conformer with these groups on the same side (syn) should also be present in solution, according to our calculations; we tentatively assign bioactivity to the anti conformer on the basis of fatty acid substrate modeling described below. (*S*)-α-Methylindomethacin (3a) and sulindac metabolite[22] 4 active conformations are proposed to be analogous to that shown for 1. The conformation shown for 6-chloro-5-cyclohexylindan-1-(*S*)-carboxylic acid (8) is that in the crystal;[23] the conformation of the cyclohexane ring may be different when bound to the receptor. Similarly, our hypothesized active conformer of (*S*)-pirprofen (9) is shown; the other antiinflammatory arylacetic acids could bind in a comparable orientation.

It should be pointed out that other drugs, e.g., benzoic and anthranilic acid derivatives, are not accommodated well by the model. We will return to this point.

Model of Fatty Acid Substrates Bound to the Antiinflammatory Receptor. Since prostaglandin synthesis is inhibited by these drugs,[12] it was possible that the natural substrates of PG synthetase might bind at the same receptor site. We attempted to assess this possibility by a molecular modeling study. Since there are a very large number of conformations possible[25] for arachidonic acid (12) and other enzyme substrates, and since there is no reason to suppose that the global minimum energy conformation corresponds to the bound conformation for such a flexible molecule, no exhaustive calculation of conformational energies was undertaken. Rather, a CPK space-filling model of arachidonic acid was manipulated in an effort to find a conformation which could not only fit the hypothesized receptor site of indomethacin but could also make sense of the several mechanistic steps required to form cyclic *endo*-peroxide (PGG). The conformation shown in Figure 2d appears to accommodate all the data.

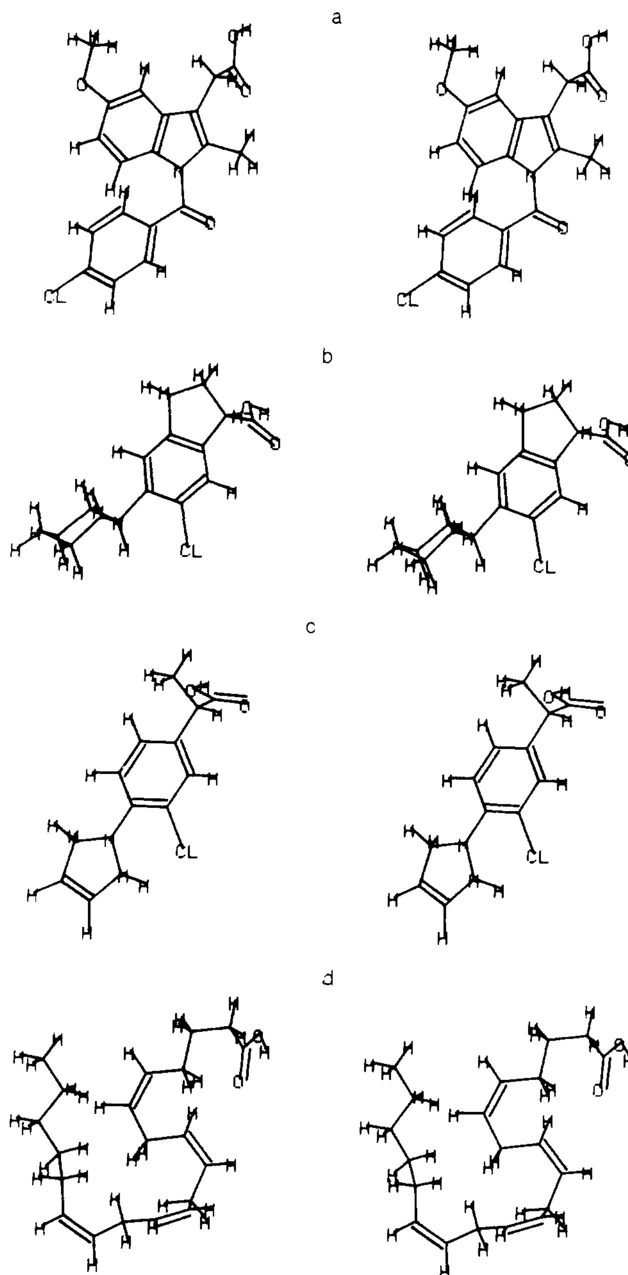


Figure 2. Proposed bioactive conformations (stereo pairs) of (a) indomethacin (1), (b) 6-chloro-5-cyclohexylindan-1-(*S*)-carboxylic acid (8), (c) pirprofen (**9a**), and (d) arachidonic acid (12). A stereoviewer is required to see these figures in three dimensions.

Proposed PG Synthetase Fatty Acid Binding Site. Our model for the PG synthetase binding site, with features complementary to arachidonic acid (12) in its hypothetical bound conformation, is shown in Figure 3. A carboxy binding center is adjacent to a broad hydrophobic binding region, while the lower right-hand part of Figure 3 represents a hydrophobic groove into which a portion of the substrate must fit. π-Electron acceptor regions bind the Δ^8, Δ^{11}, and/or Δ^{14} double bonds from the underside of the figure (the Δ^5 double bond may only be bound

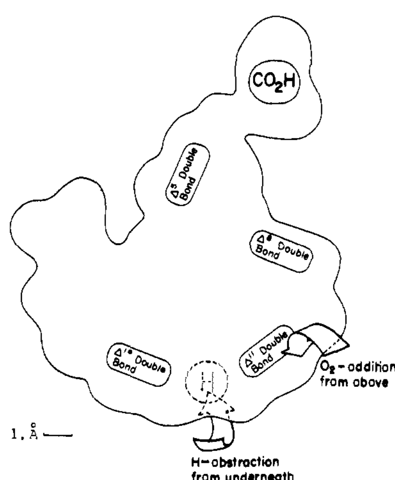


Figure 3. Model of the fatty acid substrate binding site of prostaglandin synthetase.

hydrophobically, since **13** is oxidized more rapidly than **12** by the enzyme[12]). Hydrogen atom abstraction (by metal-containing prosthetic group?) occurs stereospecifically from the underside of the figure, while addition of 2 mol of oxygen occurs from the topside face of the groove.

Proposed Mechanism for Fatty Acid Substrate Cycloperoxidation. Operationally, reaction may occur as illustrated (Figure 4) for arachidonic acid (**12**). Initial binding may center on the carboxylate group to anchor the substrate, which is then folded onto the enzyme hydrophobic surface, possibly with change of enzyme conformation to form the hydrophobic "groove" or "pocket". The pro-*S* hydrogen at C-13 is abstracted homolytically from the bottom side of the folded substrate (step 1 of Figure 4a). This is immediately followed by topside allylic addition of molecular oxygen (step 2 of Figure 4a) to form the (*R*)-11-peroxy radical (Figure 4b). Metal cations may be involved in one or both of these steps.

The peroxy radical may abstract a hydrogen atom to form the hydroperoxy acid, which may be released from the enzyme and then reduced to the isolable hydroxy acid by peroxidase (see Scheme I). Normally, however, formation of the peroxy radical likely causes a conformational change of the enzyme–substrate complex, orienting the substrate for ring closure at C-9 (step 3 of Figure 4b). There must then be a (nonconcerted) conrotatory ring closure at C-8 and C-12 (step 4). Finally, the resulting allylic radical adds another oxygen molecule at C-15 (step 5). The resulting cyclic peroxy radical (Figure 4c) abstracts a hydrogen atom to form PGG and then is released from the enzyme surface to exert its biological actions and to be further transformed by other enzymes (Scheme I).

Support for the proposed receptor and cyclooxygenation mechanism comes from analogy, from enzyme studies, and from structure–activity relationships among enzyme substrates and inhibitors.

Evidence for the Cyclooxygenation Mechanism. The proposed mechanism is simply an elaboration of the basic mechanism proposed by Samuelsson[26] as modified by Nugteren et al.,[27] with a more explicit role for the enzyme.

The first step of the mechanism is a lipoxidase type oxidation reaction,[28-30] and, indeed, PG synthetase causes a lipoxidase reaction to occur with linoleic and 11,14-eicosadienoic acids.[29] Consequently, we may look for analogy of mechanism in these enzymes.

While the allylic oxidation observed in the first step could occur by a cyclic mechanism involving singlet oxygen,[30] such a mechanism requires that the hydrogen be

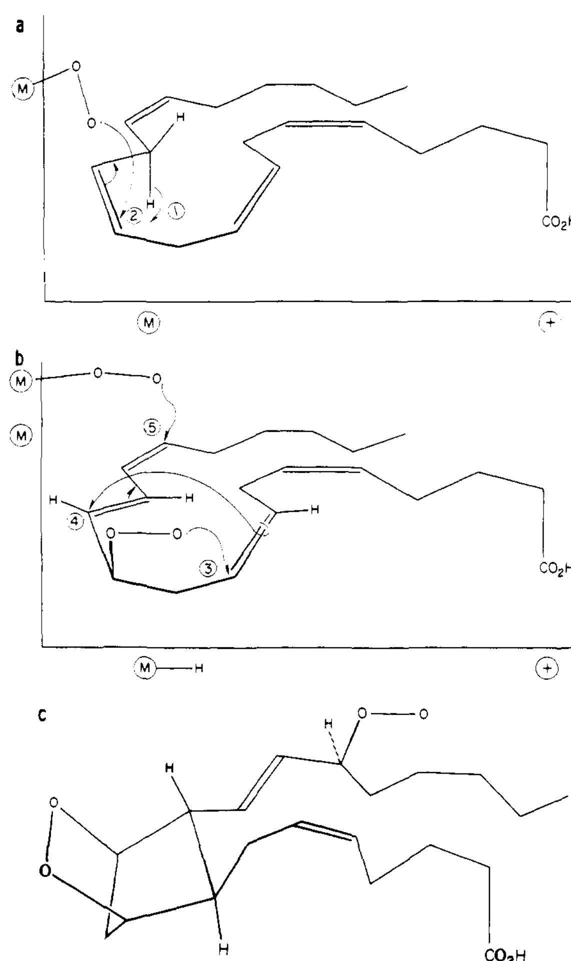
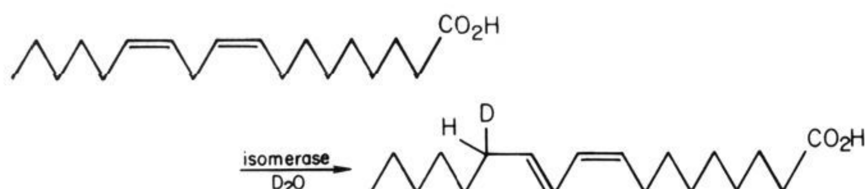


Figure 4. Mechanism of PGG formation from arachadonic acid.

abstracted on the same side that oxygen is added, that is, the pro-*R* hydrogen at C-13 for the conformation shown, while Hamberg and Samuelsson have shown that the pro-*S* hydrogen is removed.[31] Alternatively, a more extended conformation of **12** would allow abstraction of the pro-*S* hydrogen from the same side as oxygen addition—but then a cis-Δ^{12} (rather than the observed trans) product would be formed. In any case, singlet oxygen mechanisms require ca. 22 kcal/mol of energy[30] and are therefore rare in physiological processes. Furthermore, a free-radical mechanism seems well established, both for lipoxygenase,[28-30] where an ESR signal appears when linoleic acid is added,[32] and for PG synthetase,[29] where an ESR signal in the enzyme is enhanced upon binding of substrate.[27] For some time these enzymes were thought not to contain metal ions,[28-30] rendering the mechanism of allylic hydrogen abstraction obscure. However, lipoxygenase has recently been shown to contain iron,[33] and PG synthetase also apparently contains both heme and nonheme iron.[34] Very recently, a hemoprotein peroxidase activity has been found associated with prostaglandin synthetase in sheep vesicular gland microsomes.[35]

Hydrogen abstraction occurs prior to (or, less likely, concurrent with) oxygen addition, since Hamberg and Samuelsson[31] showed that 13*L*-tritiated 8,11,14-eicosatrienoic acid reacted more slowly with PG synthetase than unlabeled substrate. Similar results were found for lipoxygenase,[36] again indicating stereospecific hydrogen abstraction in the rate-determining step. Evidence against the participation of oxygen in the initiation step is that a similar hydrogen abstraction from unsaturated fatty acids occurs in anaerobic bacteria.[37]



This enzyme also appears to have carboxyl, hydrophobic, and olefinic binding sites.[37]

Once the peroxy intermediate is formed, there is experimental evidence[38] for the hypothesis that it can close to the cyclic peroxide, even without enzyme control.

Lipoxygenase undergoes fast reaction in the presence of fatty acid substrate, molecular oxygen, and peroxide product.[12,39] Similarly, PG synthetase undergoes fast reaction in the presence of fatty acid substrate, molecular oxygen (2 mol), and bound product peroxide; in the absence of product peroxide, a slower reaction occurs.[12,40] This suggests to us that product binding may enhance reaction allosterically (at least for PG synthetase) rather than participating directly in the transfer of oxygen. Both lipoxygenase and PG synthetase undergo slow autocatalytic inactivation,[12] perhaps by occasional binding of the intermediate substrate radical to an irreversible location on the enzyme.

Our mechanism shows oxygen being "guided" by metal ion at the active site (Figure 4). The regiospecificity of oxygen attack on the first intermediate pentadienyl radical (at the carboxyl end in PG synthetase, at the terminal end in lipoxygenase) and regiospecific addition of the second mole of oxygen to an allyl radical require such "guidance". A less satisfactory hypothesis would find one end of the free pentadienyl radical "buried" in the hydrophobic groove, making attack at the other end more likely. We see no advantage to supposing an epoxy–hydroperoxide intermediate.[41] Recent experiments with more highly purified enzyme[34] are in agreement with our model, including addition of both molecules of oxygen while the substrate is bound to the same site.

Substrate Specificity. A large number of fatty acids have been tested as enzyme substrates.[29] Fastest conversion is for 8,11,14-eicosatrienoic acid (**13**) into the PG_1 series.[12] 5,8,11,14-Eicosatetraenoic acid (arachidonic acid, **12**) is converted to the PG_2 series, while 5,8,11,14,17-eicosapentaenoic acid (**14**) leads to the PG_3 series.[29] These substrates can all form coiled conformations like that shown for **12** in Figure 2d. PG analogues are also formed from 10,13,16-docosatrienoic acid and 7,10,13-nonadecatrienoic acid;[29] these would have to undergo a somewhat different folding onto the receptor site. Methyl substitution at the 2 or 5 position of eicosa-8,11,14-trienoic acid (**13**) does not hinder prostaglandin formation;[42] our model can accommodate these results, although we predict that the chirality of the methyl group is important (apparently only the racemic materials have been studied[42]).

Enzyme Inhibitors. PG synthetase inhibitors[10,29] include simple fatty acids such as α-linolenic, linoleic, oleic, and decanoic acids, which may be folded onto the receptor model. Two conjugated fatty acids, 5,8,12,14-eicosatetraenoic and 8,12,14-eicosatrienoic acids are strong inhibitors;[43] since they are analogues of the first hydroperoxy intermediate (Scheme I), they should also fit the postulated receptor.

Indomethacin (**1**), which has been shown to inhibit PG synthetase competitively with arachidonic acid,[12] can fit on the receptor model as shown in Figure 5. This model suggests the following binding points: (a) coulombic or hydrogen bonding to the carboxy group; (b) hydrophobic binding to the indole ring; (c) the electron-accepting group, which binds to the Δ^8 double bond in arachidonic acid,

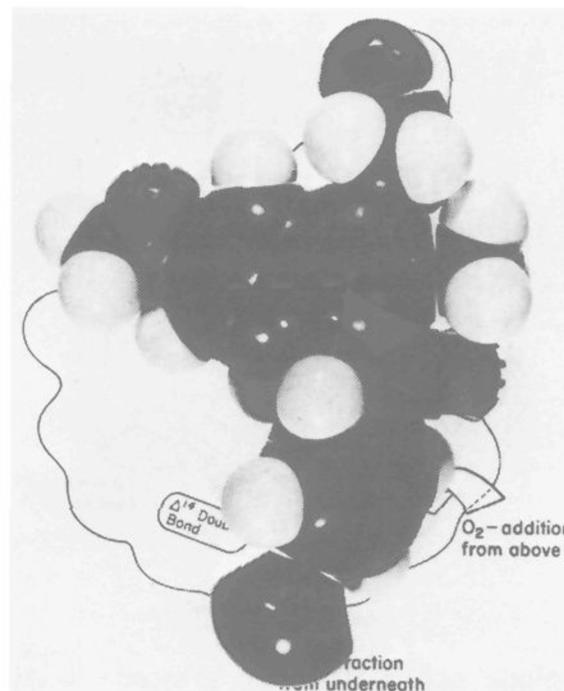


Figure 5. Binding of indomethacin to the fatty acid binding site model.

binding to the indole nitrogen in **1**; (d) the aryl group fitting in the hydrophobic groove, with the *p*-chloro group coordinated to the metal cation which abstracts the C-13 pro-*S* hydrogen of arachidonic acid. Not all these points of interaction need prevail immediately—the time-dependent irreversible inhibition of PG synthetase[24] is compatible with a conformational change in the enzyme for optimal binding.

The extensive structure–activity studies on indomethacin analogues[1,2,6] are in general agreement with our model. Thus, the *N*-carbonyl group may be replaced by CH_2, diminishing but not eliminating antiinflammatory activity. The amide function may be replaced by a *Z* double bond (**3a**), with essentially no change in conformation and good retention of activity. (The *E* isomer **3b**, which would fit the receptor poorly, is five times less active.) In **3a** the enzyme olefin binding region presumably binds to the benzylidene double bond. A coplanar analogue **16**, which does not fit the receptor, is inactive.[44] Finally, replacing *p*-methylthio (**4**) by *p*-methylsulfoxide (**5**) effectively abolishes in vitro binding to PG synthetase,[22] suggesting direct participation of substituents at that position.

We attempted statistical correlation of enzyme inhibition data of indomethacin analogues[45] with substituent constants, with limited success (not surprising for substrate binding to receptor, where steric interactions may swamp other effects). Electron-donating groups on the benzoyl ring generally favored activity (positive σ favorable), especially in the para position, and lipophilic groups favored while ortho, meta, or bulky para substituents disfavored activity—in agreement with our proposed receptor binding model.

Other arylacetic acid antiinflammatory compounds, for example, pirprofen (**9a**), may bind to the same receptor as shown in Figure 6. The carboxy group is bound as usual, and the rings sit on the hydrophobic surface. The *m*-chloro group coordinates to the enzyme Δ^8-olefin binding site. Pirprofen binding to PG synthetase is reversible, while indomethacin binding shows time-dependent irreversible behavior.[24] Possibly pirprofen, because it has a smaller surface area, does not occupy the hydrophobic groove as efficiently as indomethacin. Antiinflammatory compounds **8**, **10**, **11**, and *d*-6-chloro-α-methylcarbazole-2-acetic acid[46] (**17**) appear to be accommodated by the proposed receptor site. A free carboxy group and a π donor at the appropriate location have been

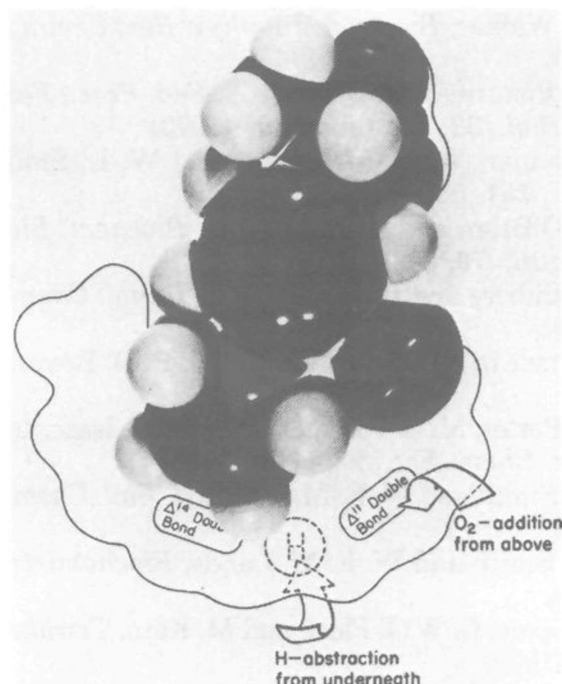


Figure 6. Binding of pirprofen to the fatty acid binding site model.

suggested to be essential for irreversible binding,[47] in agreement with our model.

It has been observed[23,48] that, for many antiinflammatory arylacetic acids, an (*S*)-methyl group α to the carboxyl is well tolerated, while an (*R*)-methyl or two methyls result in manyfold reduction of activity. In principle, this could be a conformational effect and/or a steric effect at the enzyme surface. However, it is unlikely to be a conformational effect, at least for the relatively unhindered *ortho*-unsubstituted derivatives. If it is a steric effect, then either carboxy is in the plane of the ring and the (*R*)-methyl group points into the receptor site to prevent binding,[7] or the carboxy group points down and the (*R*)-methyl group causes an unfavorable interaction at the edge of the receptor (upper right of Figure 3). Evidence against the former hypothesis is the high activity[23] of the constrained compound **8** and the greater availability of carboxy for receptor binding when out of the plane (according to our calculations).

Limitations of the Receptor Model. There are classes of potent PG synthetase inhibitors which do not appear to fit our hypothetical receptor well: for instance, salicylic acids such as aspirin and diflunisal; anthranilic acids such as meclofenamic acid and flufenamic acid; and enolic acids such as phenylbutazone and sudoxicam. Furthermore, a referee has suggested that these classes (as well as the arylacetic acids and the PG precursors) may all be accommodated on a receptor site hypothesized by Scherrer.[7] Scherrer's receptor has a carboxy binding region in the same plane as the ring binding region, rather than below the plane as in ours; it has a rough equivalent to our groove; and it has flat areas (for hydrophobic binding) on either side of the ring binding region.

Our objections to carboxy binding in the same plane as the ring are based on our energy calculations for indomethacin (**1**) and α-methylindomethacin (**6**) and the activity of the constrained compound **8**. There seem to be no other major inconsistencies between the two receptor models.

As to the ability of other antiinflammatory agents to fit the same receptor, aspirin acts by the unique mechanism of acetylating the enzyme.[16] Furthermore, acetylation of cyclooxygenase by aspirin is only partially blocked by indomethacin (P. W. Majerus, private communication). Other synthetase inhibitors which are not accommodated by our model may be bound in a different orientation or—if the enzyme undergoes conformational changes during PG formation, as seems likely—may be bound to the receptor in a different conformation of the enzyme.

Inflammation is a complex process, and prostaglandin synthesis is only one manifestation of this process. Furthermore, steroidal and nonsteroidal antiinflammatory drugs may act at different steps in the pathways for PG synthesis. Some drugs, like fenamates, are also PG antagonists. Given this complexity, and the large number of effects besides receptor binding which affect drug potency, we are not surprised that all classes of drugs cannot be accommodated by our model of the receptor site.

Summary

We have used conformational analysis of antiinflammatory arylacetic acids to hypothesize a detailed model for the active site of the fatty acid dioxygenase (cyclooxygenase) unit of the PG synthetase enzyme, and we have interpreted the mechanism of PGG formation in terms of this model. The model rationalizes observed structure–activity relationships among enzyme substrates and inhibitors, including several nonsteroidal antiinflammatory drugs.

While crystal structure analysis of the purified enzyme will no doubt in due time give the most definitive picture of the active site, we expect that the present model will prove useful in unifying and organizing results to date, in guiding further studies of the enzymes, and in designing novel, specifically acting antiinflammatory drugs.

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Supplementary Material Available: A listing of coordinates of modeled structures (3 pages). Ordering information is given on any current masthead page.

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Synthesis and Gastric Antisecretory Properties of 15-Deoxy-16-hydroxyprostaglandin E Analogues

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The preparation and gastric antisecretory activity of a series of 15-deoxy-16-hydroxyprostaglandin analogues are described. The compounds were tested intravenously in histamine-stimulated Heidenhain pouch dogs in relation to the reference standards PGE_1 and PGE_1 methyl ester (PGE_1ME). The parent compound of this series, (±)-15-deoxy-16α,β-hydroxyprostaglandin E_1 methyl ester (**3**), was found to be equipotent to the reference standard PGE_1ME. Methylation at C-16 of **3** produced **8** which was found to be some 40 times more potent than PGE_1. In sharp contrast, addition of two methyl groups to **3** at C_{15} or C_{17} markedly reduced the antisecretory action. The 16-ethyl analogue of **3** also showed reduced potency. Removal or epimerization of the C-11 hydroxy group of **8** reduced the activity. Likewise, hydrogenation or changing the stereochemistry of the 13,14 double bond from trans to cis decreased the activity. On the other hand, ω-homologation of **8** or the introduction of a cis-5,6 double bond did not affect the potency. From these studies, it appears that **8**, **16**, and **17** possess optimum gastric antisecretory effects in this series.

In preliminary communications[1-3] we described the influence on biological activity of transposing the 15-hydroxy group of PGE_1 and PGE_2 to carbon 16. For example, the transposition of the C-15 hydroxy group to the adjacent C-16 position significantly improved the gastric antisecretory and antiulcer actions of PGE_1. In fact, this modification confers oral activity, decreases the typical PGE_1 side effects, and prolongs biological action.[3]

We now wish to report the full experimental details of our work and define some structure–activity relationships (SAR) with respect to gastric antisecretory effects in the dog.

Chemistry. The synthesis of the parent compound of this series, (±)-15-deoxy-16α,β-hydroxyprostaglandin E_1 methyl ester (**3**), was accomplished by the stereospecific conjugate addition of the cuprate species **2** to the cyclopentenone **1b**,[4] followed by mild acid hydrolysis and purification by chromatography (Scheme I).

The cuprate reagent **2** was prepared (Scheme II) by reaction of the *tert*-butyldimethylsilyl ether of 1-octyn-4-ol (**4**) with catechol borane,[5] followed by hydrolysis to obtain the *trans*-boronic acid **5**. Treatment of **5** with sodium hydroxide in methanol followed by iodine gave the required *trans*-vinyl iodide **6**. The reaction of **6** with 1 equiv of *n*-butyllithium at −60 °C, followed by addition of an ethereal solution of 1-pentynylcopper solubilized with hexamethylphosphorous triamide,[6] yielded **2**. Although 2 equiv of *tert*-butyllithium is customarily employed to