Steric and Electronic Requirements for Chloroflavone Congeners as Hepatic Microsomal Monoxygenase Inducers

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We previously classified chloroflavone congeners into 3-methylcholanthrene (MC)-type, phenobarbital (PB)-type and mixed (MC plus PB)-type inducers of hepatic microsomal monoxygenases in rats. In the present study, we examined the structure-activity relationship involved in the capability of congeners to induce the described regioselective O-demethylation activity of scoparone. The steric and electronic parameters of congeners were calculated by the MM2 molecular mechanics and Extended Hückel MO methods, respectively. The molecular rectangle-area/depth ratios related well to the ratios of scoparone 6-7-O-demethylation activities induced by the congeners. The molecular dimensions characterized the MC-type congeners as nearly planar molecules and the PB-type congeners as bulky and nonplanar. Moreover, the ratio of scoparone 6-7-O-demethylation activities had significant correlation with both the LUMO energy ($E_{LUMO}$) and the difference ($\Delta E$) between $E_{LUMO}$ and HOMO energy for the congeners. The $E_{LUMO}$ and $\Delta E$ were less in the MC-type congeners than in the PB-type. These correlations suggest that the steric and electronic features of chloroflavone congeners are responsible for the induction of cytochrome P450 isozymes and associated monoxygenase activities.

Keywords: chloroflavone congener; monoxygenase induction; structure-activity relationship; scoparone O-demethylation; molecular mechanics; molecular orbital calculation

Several synthetic and naturally occurring flavonoids are active inducers of the cytochrome P450-dependent monoxygenase system. 1) We recently reported that synthetic chloroflavone congeners (1–10) are good inducers of this system (Fig. 1). 2) These congeners are classified as 3-methylcholanthrene (MC)-type, phenobarbital (PB)-type and mixed (MC plus PB)-type inducers based mainly on their effects on the ratio of the two regioselective O-demethylation activities of scoparone (12) in rat liver microsomes. 2a) Several research groups have used scoparone as a probe substrate for distinguishing between MC-type and PB-type inducers. 3,4) We demonstrated that the ratio of scoparone 6-7-O-demethylation activities was about 3.7 in MC-induced, 0.82 in PB-induced and 2.2 in MC plus PB-induced microsomes. 3a, 4) Moreover, Müller-Enoch et al. reported that the major MC-inducible rat P450 isozymes, CYP1A1 and CYP1A2 caused the ratios of 4.4 and 3.8, respectively; in contrast, the two PB-inducible isozymes, CYP2B1 and CYP2B2 caused the ratio of 0.8. 4) These results suggest that the variation in the ratios of scoparone 6-7-O-demethylation activities quantitatively reflects the expression pattern of P450 isozymes induced. 4, 5

Polycyclic aromatic hydrocarbons and polychlorinated aromatic hydrocarbons which belong to a class of MC-type inducers cause induction of P450 isozymes by binding to the cytosolic Ah (aromatic hydrocarbon) receptor. 5, 6) The affinity with which most molecules bound to the Ah receptor in vitro correlates well with the potencies in vivo as inducers of P450 isozymes or associated monoxygenase activities. 6) Similarly, receptor-dependent mechanisms involved in PB-induction are considered although no receptor has been identified in mammals. 8) Information as to the nature of drug-receptor interactions can often be gained indirectly by examining the steric and electronic features of drug molecules. 5–7, 9

In this study, we calculated the steric and electronic parameters of chloroflavone congeners by the MM2 molecular mechanics 10) and Extended Hückel MO methods, 9) respectively. An MM2 molecular mechanics program brings about the most stable structure of a molecule. 10) Although drug molecules do not always exist in vivo in the most stable structure, they may often exert a biological response in a more stable structure. 9) The Extended Hückel MO program, on the other hand, is an earlier qualitative method but is nevertheless appropriate to be applied to calculate the HOMO and LUMO energies ($E_{HOMO}$ and $E_{LUMO}$) for π-electronic compounds. 9) The quantitative structure-activity relationship (SAR) was examined between the molecular dimensions and the ratio of scoparone 6-7-O-demethylation activities in rat liver microsomes induced by the chloroflavone congeners (1–10) described 2a) and 2',6'-dichloroflavone (DCF) (11). The SARs involving the $E_{LUMO}$ and the difference ($\Delta E$) between $E_{LUMO}$ and $E_{HOMO}$ of congeners were also examined for the ratio of scoparone 6-7-O-demethylation activities.

MATERIALS AND METHODS

Chloroflavone Congeners

$2',6'-DCF$ (11) was synthe-

![Chemical Structures of Chloroflavone Congeners (1–11) and Scoparone (12)](attachment)

Fig. 1. Chemical Structures of Chloroflavone Congeners (1–11) and Scoparone (12)

1: 6,8-dichloroflavan (DCF), 2: 4-chloroflavone (CF), 3: 3',6-DCF, 4: 3',5,6-trichloroflavone (TFC), 5: 3'-CF, 6: 2',4,6-DCF, 7: 6-CF, 8: 2',6-DCF, 9: 2'-CF, 10: 2',4-DCF, 11: 2',6'-DCF.

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sized by cyclization of 1-(2-hydroxyphenyl)-3-(2,6-dichlorophenyl)-1,3-propanedione according to the method of Wheeler,11 and purified by recrystallization from acetone, mp 126—127°C. EI-MS m/z: 290 (M+), 120 (base peak). UV \( \lambda_{\text{max}} \text{nm (e):} \) 240 (sh, 16100), 265 (sh, 7600). As shown in Table I, UV spectral wave numbers (cm\(^{-1}\)) of the cinnamoyl and benzoyl absorption bands12 were calculated for 11. Those of the other congeners (1—10) were also calculated with the data cited from previous work.2a

**Scopolamine O-Demethylation Activities** The ratio of scopolamine 6-/7-O-demethylation activities was determined in hepatic microsomes from male Wistar rats pretreated with 2’,6’-DCF (11) (80 mg/kg/d, once a day for 3 d), as described previously.2a The regioselective ratios after treatment with the other congeners (1—10) are cited from previous work.2a

**Octanol/Water Partition Coefficients** According to the method of Yamagami et al.,13a the logarithm of octanol/water partition coefficient (log P) was determined by reversed phase HPLC. That is, the retention time of each chloroflavone congener on a Capcellpack C18 AG 120 column (5 μm, 4.6 × 15 cm, Shiseido Co., Japan) was measured in a MeOH–0.01 m phosphate buffer (7:3 v/v, pH 7.4) mobile phase at 1.0 ml/min flow rate. From the retention time, log P was calculated by comparing logs of flavone, flavonol13b and flavanone.13c

**Computational Chemistry Methods** The MM2 molecular mechanics calculation was carried out on a Chem 3D Plus program (Cambridge Scientific Computing, Inc., U.S.A.). This program has been improved for π-electronic systems by a semi-empirical Pariser–Parr–Pople self-consistent field MO method.14 After energy minimization, the steric energy, z-matrix element and molecular dimension including the atomic van der Waals radii were calculated for chloroflavone congeners. The rectangle-area/depth ratios (Å) for the congeners were as follows: 1, 40.8; 2, 35.3; 3, 32.5; 4, 32.0; 5, 26.1; 6, 21.6; 7, 35.4; 8, 20.2; 9, 18.3; 10, 19.9; 11, 13.6. The z-matrix elements obtained were used in an Extended Hückel MO calculation program.15 The MO calculation gave data of the \( E_{\text{HOMO}} \), \( E_{\text{LUMO}} \) and MO coefficients.

**RESULTS**

The ratios of scopolamine 6-/7-O-demethylation activities in rat liver microsomes induced by chloroflavone congeners (1—10) were practically invariant at doses of 40—160 mg/kg, and are cited at a dose level of 80 mg/kg from our previous studies.3a 2’,6’-DCF (11) caused the ratio of about 0.76 and therefore is grouped among PB-type inducers, as described previously.2a These regioselective ratios did not significantly correlate with the log P values of congeners shown in Table I.

**Correlation with the UV Wave Number** UV spectral data of chloroflavone congeners provided preliminary information on the electronic states of molecules. Table I shows the UV wave numbers in flavone cinnamoyl and benzoyl absorption bands12 of 2’,6’-DCF (11). Those of the other congeners (1—10) were calculated from previous data on wavelength.5a Quantitative SARs could be confirmed between the wave numbers of π→π* transition in the individual bands and the ratios of scopolamine 6-/7-O-demethylation activities (Fig. 2A and B). A series of wave numbers in each of the two bands was smaller in the MC-type congeners, 6,8-DCF (1), 4’-chloroflavone (CF) (2), 3’,6-DCF (3), 3’,5’,6-trichloroflavone (TFCF) (4) and 3’-CF (5) than in the PB-type, 2’-CF (9), 2’,4’-DCF (10) and 2’,6’-DCF (11). The mixed-type, 2’,4’,6-TCF (6), 6-DCF (7) and 2’,6-DCF (8) showed roughly intermediate values. From these results, it is clear that the MC-type congeners (1—5) can be promoted electronically from ground to excited states with lower energy than can the PB-type congeners (9—11).

**Correlation with the Molecular Dimension** When the van der Waals radii were included, all the structures of chloroflavone congeners (1—11) calculated by the MM2 program could be roughly fitted into a rectangle of 8.2 × 14.5 Å. This two-dimensional size is similar to the rectangle of about 8 × 14 Å that has been proposed by

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**Table I. Lipophilicity and UV Spectral Data of Chloroflavone Congeners**

<table>
<thead>
<tr>
<th>Compound(^a)</th>
<th>The wave number (10(^4) cm(^{-1})) of π→π* transition in the systems(^b)</th>
<th>log P(^b)</th>
<th>Cinnamoyl</th>
<th>Benzoyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.76</td>
<td>3.33</td>
<td>3.92</td>
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<tr>
<td>2</td>
<td>3.89</td>
<td>3.37</td>
<td>3.89</td>
<td></td>
</tr>
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<td>4.38</td>
<td>3.39</td>
<td>3.92</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4.83</td>
<td>3.44</td>
<td>3.79</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3.91</td>
<td>3.45</td>
<td>3.91</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4.57</td>
<td>3.51</td>
<td>4.00</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3.92</td>
<td>3.36</td>
<td>3.94</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4.09</td>
<td>3.53</td>
<td>4.07</td>
<td></td>
</tr>
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<td>10</td>
<td>4.13</td>
<td>3.52</td>
<td>4.03</td>
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<tr>
<td>11</td>
<td>3.79</td>
<td>3.77</td>
<td>4.17</td>
<td></td>
</tr>
</tbody>
</table>

\( a \) Compounds (1—11) are described in the legend for Fig. 1. \( b \) log of octanol/water partition coefficient. \( c \) Determined in EtOH solution.

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**Fig. 2. Correlation between the Wave Number of π→π* Transition in the Cinnamoyl (A) or Benzoyl (B) System and the Ratio of Scopolame 6-/7-O-Demethylation Activities in Rat Liver Microsomes**

Compounds (1—11) are described in the legend for Fig. 1: A: γ = 0.797, p < 0.01. B: γ = 0.842, p < 0.01.
Lewis et al.\textsuperscript{16} as a fitting of ligands for the Ah receptor.

Molecular mechanics calculations subsequently provided the optimal three-dimensional features for the MC-type (1–5) and PB-type (9–11) congeners. In general, MC-type inducers are planar molecules and PB-type inducers are bulky and nonplanar.\textsuperscript{5,6} To demonstrate this we analyzed the conformations of chloroflavone congeners and calculated the parameters of rectangle-area/depth ratio. The torsion angle between the phenyl ring and the rest of the molecule was about 16° for the MC-type congeners (1–5) and 3'-CF (7). In contrast, the angle for 2',6'-DCF (11) with the 2',6'-dichlorophenyl ring was 68°. For 2',4',6-TCF (6), 2',6-DCF (8) and the PB-type congeners (9 and 10) with the 2'-chlorophenyl ring the angle was about 42°. These differences resulted in the MC-type congeners (1–5) having area/depth ratios clearly larger than those of the PB-type congeners (9–11). Thus, a good significant SAR could be established between the spatial parameter of area/depth ratio and the ratio of scoparone 6-/7-O-demethylation activities (Fig. 3).

Of the mixed-type congeners, 6-CF (7) had area/depth ratio similar to those of MC-type congeners (1–4). In contrast, 2',4',6-TCF (6) and 2',6-DCF (8) showed spatial parameters similar to those of the PB-type congeners (9 and 10). Explanation of their complicating features is not yet possible, but they are probably attributable to the 6-chloro substituent in the flavone system.

**Correlation with the LUMO Energy** Table II shows the electronic structural parameters for chloroflavone congeners (1–11) calculated by the Extended Hückel MO program. The $E_{\text{HOMO}}$ values had no SAR with the ratio of scoparone 6-/7-O-demethylation activities. However, the $E_{\text{LUMO}}$ of MC-type congeners (1–5) were minus values lower than those of PB-type (9–11) and mixed-type congeners (6 and 8) except 6-CF (7). There was a significant SAR between the $E_{\text{LUMO}}$ values and the ratio of scoparone 6-/7-O-demethylation activities (Fig. 4).

**Correlation with the Difference between LUMO and HOMO** Table II shows the electronic structural parameters for chloroflavone congeners (1–11) calculated by the Extended Hückel MO program. The $E_{\text{HOMO}}$ values had no SAR with the ratio of scoparone 6-/7-O-demethylation activities. However, the $E_{\text{LUMO}}$ of MC-type congeners (1–5) were minus values lower than those of PB-type (9–11) and mixed-type congeners (6 and 8) except 6-CF (7). There was a significant SAR between the $E_{\text{LUMO}}$ values and the ratio of scoparone 6-/7-O-demethylation activities (Fig. 4).

**Fig. 3.** Correlation between Molecular Dimensions and the Ratio of Scoparone 6-/7-O-Demethylation Activities in Rat Liver Microsomes

Compounds (1–11) are described in the legend for Fig. 1. Rectangle-area/depth ratios are shown in Materials and Methods. $\gamma = 0.853$, $p < 0.001$.

**Table II.** Extended Hückel MO Energy Levels for Chloroflavone Congeners

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>$E_{\text{HOMO}}$ (eV)</th>
<th>$E_{\text{LUMO}}$ (eV)</th>
<th>$\Delta E$ (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-12.08</td>
<td>-9.86</td>
<td>2.22</td>
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<td>2</td>
<td>-12.19</td>
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<td>2.35</td>
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<tr>
<td>3</td>
<td>-12.22</td>
<td>-9.89</td>
<td>2.33</td>
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<tr>
<td>4</td>
<td>-12.22</td>
<td>-9.89</td>
<td>2.33</td>
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<tr>
<td>5</td>
<td>-12.23</td>
<td>-9.88</td>
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<td>-12.23</td>
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</tr>
<tr>
<td>8</td>
<td>-12.21</td>
<td>-9.78</td>
<td>2.43</td>
</tr>
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<td>-9.78</td>
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<tr>
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<td>-12.11</td>
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<tr>
<td>11</td>
<td>-12.20</td>
<td>-9.68</td>
<td>2.52</td>
</tr>
</tbody>
</table>

*Compounds (1–11) are described in the legend for Fig. 1.*

**Fig. 4.** Correlation between $E_{\text{LUMO}}$ and the Ratio of Scoparone 6-/7-O-Demethylation Activities in Rat Liver Microsomes

Compounds (1–11) are described in the legend for Fig. 1. $\gamma = -0.797$, $p < 0.01$.

**Fig. 5.** Correlation between $\Delta E$ and the Ratio of Scoparone 6-/7-O-Demethylation Activities in Rat Liver Microsomes

Compounds (1–11) are described in the legend for Fig. 1. $\gamma = -0.798$, $p < 0.01$. 

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HOMO Energies As shown in Table II, $\Delta E$ values are less in the MC-type congeners (1—5) than in the PB-type congeners (9—11). A significant SAR could be confirmed between the $\Delta E$ and the ratio of scopolamine O-demethylation activities (Fig. 5). Of the mixed-type congeners, 2,4,6-TCF (6) and 6-CF (7) showed $\Delta E$ values similar to those of MC-type congeners. In contrast, 2,6-DCF (8) showed $\Delta E$ value similar to those of the PB-type congeners (9 and 11). The $\pi \rightarrow \pi^*$ transition shown in the UV spectral data (Table I), being a promotion of an electron from HOMO to LUMO, is probably related to the $\Delta E$ calculated by an MO method. Wave number of $\pi \rightarrow \pi^*$ transition in each of the cinnamoyl ($\gamma = 0.862$, $p < 0.001$) and benzoyl ($\gamma = 0.760$, $p < 0.01$) systems significantly correlated with the $\Delta E$ of chloroflavone congeners shown in Table II. Thus, the UV spectral data of congeners support the validity of MO energy values calculated by the Extended Hückel MO program.

DISCUSSION

In this study, we quantitatively correlated the capability of chloroflavone congeners (1—11) inducing the regioselective O-demethylation activity of scopolamine to their steric and electronic parameters. Scopolamine has been a probe substrate for deciding whether the congeners cause an MC-type or a PB-type induction in rat liver microsomes. Previous studies proposed that the variation in the ratios of scopolamine 6-/7-O-demethylation activities quantitatively reflects the expression pattern of P450 isozymes induced. We calculated the structural parameters of chloroflavone congeners by the MM2 molecular mechanics and Extended Hückel MO methods. All of the molecular rectangle-area/depth ratios, $E_{\text{LUMO}}$ and $\Delta E$ values significantly correlated with the ratios of scopolamine 6-/7-O-demethylation activities induced by the congeners (1—11); however, there was no SAR involving the log $P$ of congeners. It seems, therefore, that an in vivo passive transport process for the congeners does not affect the ratio of scopolamine 6-/7-O-demethylation activities.

All the chloroflavone congeners (1—11) studied had molecular structures that roughly fit into a rectangle of $8.2 \times 14.5 \AA$ including the van der Waals radii. This size is similar to the rectangle of $8 \times 14 \AA$ proposed as fitting ligands for the Ah receptor. As the earliest model for ligands of the Ah receptor when the van der Waals radii are not included, a rectangle of $3 \times 10 \AA$ was noted by Poland and Knutton. However, the $3 \times 10 \AA$ rectangle could not account for the binding of unchlorinated aromatic ligands such as MC, benzo[a]pyrene and 5,6-benzoflavone. In contrast, the $8 \times 14 \AA$ rectangle brings about a good fit to the unchlorinated ligands as well as polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs) and planar polychlorinated biphenyls (PCBs). Three-dimensional parameters calculated by the MM2 program elucidated that the MC-type congeners (1—5) are nearly planar molecules confirmed by a small depth and a large area/depth ratio. In contrast, the PB-type congeners (9—11) are bulky and nonplanar molecules confirmed by a small area/depth ratio and greater torsion in molecular conformation. Therefore, the MC-type and PB-type congeners are probably different from each other in steric requirements for the binding sites as ligand. The MC-type and PB-type PCBs have similarly been distinguished by their area/depth ratios and also by their binding affinities for the Ah receptor.

Although at present a receptor for chloroflavone congeners is unidentified, the apparent correlation between the steric dimensions of congeners (1—11) and their inductive activities may be rationalized in terms of steric interaction for the formation of drug—receptor complex, which can be provided by certain similarities in molecular structure among chloroflavone congeners and PCBs.

There were also important similarities in electronic features among chloroflavone congeners and polychlorinated aromatic ligands such as PCDDs, PCDFs and PCBs. Both $E_{\text{LUMO}}$ and $\Delta E$ values were less in the MC-type chloroflavone congeners (1—5) than in the PB-type (9—11), and these two classes of congeners can be characterized and differentiated by the two MO values. In $E_{\text{LUMO}}$ value represents the electron-accepting capacity of a molecule. Therefore, the MC-type congeners (1—5) are good electron acceptors, whereas the PB-type congeners (9—11) are relatively poor electron acceptors. Cheney and Tolly showed that the electron-accepting capacities of PCDD and PCDF ligands correlate with the in vitro binding affinities to the Ah receptor and the potencies as in vivo inducers of aryl hydrocarbon hydroxylase. These polychlorinated ligands have also been proposed to act as electron acceptors in a charge—transfer complex with the Ah receptor. In general, the stabilization of a charge—transfer complex between two molecular species is inversely proportional to the $\Delta E$ between the $E_{\text{LUMO}}$ of the acceptor molecule and the $E_{\text{HOMO}}$ of the donor molecule. Moreover, this stabilization energy may be referred to by analogy with the $\Delta E$ in one of the two species. Based on the $\Delta E$ values in the individual PCB congeners, Kobayashi et al. classified PCBs as MC-type and PB-type according to the enzyme inducing abilities. They proposed that the MC-type PCBs having small $\Delta E$ form stable complexes with the Ah receptor, whereas the PB-type PCBs having large $\Delta E$ are unstable in a complex formation. Therefore, it seems that several of the chloroflavone congeners (1—11) also form charge—transfer complexes with receptor(s) including the Ah receptor.

Fukui et al. demonstrated, using MO calculations, that the electronic features of HOMO and LUMO are important for reactivity of organic compounds, and referred to these as frontier orbitals. They were able to show that the most easily electron-accessible position of the LUMO within an aromatic molecule could be correlated with the position of nucleophilic reaction. The accepting capacity for nucleophilic attack was referred to as the frontier electron density in LUMO, otherwise known as $f^{(n)}$. We calculated $f^{(n)}$ values of the chloroflavone congeners (1—11) with the MO coefficients in LUMO (data not shown). High $f^{(n)}$ values were distributed in the 4-pyrene moiety of the flavone system, especially at the carbonyl group, for all the congeners. The Ah receptor,
on the other hand, has been shown to contain only one
binding site and to bind avidly but noncovalently with the
ligand.5) This binding appears to involve one or more
sulphydryl groups whose integrity is essential for the
Ah receptor to bind ligands specifically and with high
affinity.2) The information suggests that at least MC-type
chloroflavone congeners (I—5) may be bound to the Ah
receptor by the charge-transfer and/or hydrogen bonding
interaction via the carbonyl and sulphydryl groups.

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