Structure–Activity Relationship of 3,3′-Dihydroxy-α,β-diethyldiphenylethane and Its Related Compounds

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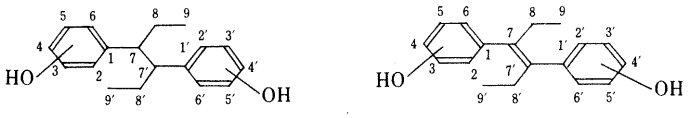
3,3′-Dihydroxy-α,β-diethyldiphenylethane (I), 3,3′-dihydroxy-α,β-diethylstilbene (II), hexestrol (III) and diethylstilbestrol (IV) have already been reported to show hypotensive effects on rats and exhibit phytogrowth-inhibitory activities. We have proposed that two phenolic hydroxyl groups in these compounds are necessary for the biological activities, and a structure–activity relationship for I-related compounds was accomplished using molecular-mechanics (MM) calculations. As a result, the following three findings were obtained; 1) the minimized conformational energy obtained from MM calculations, which is a parameter expressing the molecular stability, showed a relatively high correlation with the biological activities, 2) as results of quantitative structure–activity relationship (QSAR) analyses, the combination of the distance between two phenolic hydroxyl oxygens led to the regression equations with high correlation values, and 3) the idealized molecular model of the most active compound (I) showed the highest stability and had a particular conformation which differed from the other compounds (II—IV).

Keywords 3,3′-dihydroxy-α,β-diethyldiphenylethane; phenolic hydroxyl group; conformation; molecular mechanics calculation; quantitative structure–activity relationship analysis

In the previous papers from our laboratory, diethylstilbestrol-related compounds such as 3,3′-dihydroxy-α,β-diethyldiphenylethane (I, Fig. 1), [1-4] 3,3′-dihydroxy-α,β-diethylstilbene (II, Fig. 1),[5,6] hexestrol (III, Fig. 1)[1,2,7,8] and diethylstilbestrol (IV, Fig. 1)[1,5,7,9] were found to show the following four kinds of biological activities; hypotensive effects in rats, phytogrowth-inhibitory activities, coronary vasodilator actions on the isolated guinea-pig heart and antifungal activities. Among these compounds, I exhibited the strongest inhibitory activity in all experiments except for coronary vasodilator action on the isolated guinea-pig heart. It was also found that acylation of the phenolic hydroxyl groups of these compounds abolished the inhibitory activities.[5] The findings suggest that these compounds require at least free phenolic hydroxyl groups to show the above-mentioned activities. Considering that I showed the most potent inhibitory activity, its stable conformation seems to play an important role in this inhibition. However, the conformational studies and a quantitative structure–activity relationship (QSAR) analysis have not been performed on the effect of phenolic hydroxyl groups on the inhibitory activities of these compounds. There have also been no reports about the conformation of I.

In this work, as a preliminary step to clarify the mechanism of the inhibitory action of I, the relationship between the conformation and hypotensive and phytogrowth-inhibitory activities was investigated using I and its related compounds (II—IV). The effects of the phenolic hydroxyl groups on the inhibitory activity were also calculated by the QSAR analysis.



I : C(3)=C(3′)=−OH
II : C(3)=C(3′)=−OH
III : C(4)=C(4′)=−OH
IV : C(4)=C(4′)=−OH

Fig. 1. Chemical Structures and Atomic Numbering System for 3,3′-Dihydroxy-α,β-diethyldiphenylethane-Related Compounds

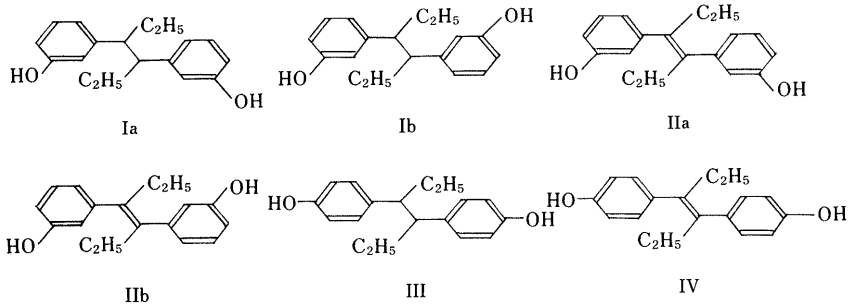
Materials and Methods

Materials The chemical syntheses and purifications of compounds 3,3′-dihydroxy-α,β-diethyldiphenylethane (I), *E*-3,3′-dihydroxy-α,β-diethylstilbene (II), hexestrol (III) and *E*-diethylstilbestrol (IV) have been previously described.[1-9]

Measurement of Hypotensive Activity The measurement of hypotensive activities of 3,3′-dihydroxy-α,β-diethyldiphenylethane (I)-related compounds in normotensive rats have been reported previously.[3,6,8]

Phytogrowth-Inhibitory Activity The phytogrowth-inhibitory effects of 3,3′-dihydroxy-α,β-diethyldiphenylethane (I)-related compounds against *Brassica rapa* L. and *Raphanus sativus* L. var. *rahanistroides* MAKINO have been reported previously.[2,6,8]

Model Building and Conformational Energy Minimization of 3,3′-Dihydroxy-α,β-diethyldiphenylethane (I)-Related Compounds To obtain optimal and energetically-stable conformations of the 3,3′-dihydroxy-α,β-diethyldiphenylethane (I)-related compounds, an energy minimization was



Ia Ib IIa IIb III IV

Fig. 2. The Structures of 3,3′-Dihydroxy-α,β-diethyldiphenylethane-Related Compounds Used for the MMFF Program Calculation

employed. The structures of the I-related compounds, shown in Fig. 2, were drawn directly onto the terminal screen using the molecular design program; DRAWMOL[10] and PRXBLD.[11] The final goal of intramolecular conformational analysis is to identify all the energetically-stable structural states of the molecule. The molecular mechanics-based conformational analysis is at least as accurate as the semi-empirical quantum-mechanics approaches or, in some cases, more accurate. Therefore, the molecular geometries of the I-related compounds were optimized using a program, molecular mechanics-based force field (MMFF)[12] for adjusting bond lengths, bond angles and torsional angles in order to find local minimum energy conformations.

Calculation of Quantitative Structure–Activity Relationships of 3,3′-Dihydroxy-α,β-diethyldiphenylethane (I)-Related Compounds The quantitative structure–activity relationships (QSAR) were calculated by the program, QSAR[13] using the results of the MMFF program in the CHEMLAB-II system.[14] The parameters of the optimal and energetically-stable conformations of the 3,3′-dihydroxy-α,β-diethyldiphenylethane (I)-related compounds obtained from the results of the MMFF program were chosen for the QSAR analyses. We chose the following parameters; 1) the minimized conformational energy of each molecule (MCE), 2) the distance between the two oxygen atoms in the two phenolic hydroxyl groups (δO), and 3) the molecular surface area of each molecule (MSA). The MSA was calculated using the van der Waals radii accepted for respective atoms. The values of δO (Å), MSA (Å^2), and MCE (kcal/mol) were obtained from the results of the MMFF program, respectively.

Preparations of Stereoscopic ORTEP Diagrams To evaluate the direction of the hydroxyl groups in the idealized molecular models, the stereoscopic ORTEP diagrams of each 3,3′-dihydroxy-α,β-diethyldiphenylethane (I)-related compounds were prepared by using the data derived from the MMFF program. All calculations were carried out using the Micro VAX II computer in the Osaka University of Pharmaceutical Sciences.

Results

Evaluation of Conformational Energy Minimization of 3,3′-Dihydroxy-α,β-diethyldiphenylethane (I) The minimized conformational energy obtained from the molecular-mechanics (MM) calculations is shown in Table I. The optimal and energetically-stable conformations of the 3,3′-dihydroxy-α,β-diethyldiphenylethane (I)-related compounds were Ia, IIa, III, and IV and their minimized conformational energies (MCE) were 8.50, 37.18, 11.74, and 37.10 (kcal/mol), respectively. The idealized molecular model of the most active compound (Ia) is more stable than those of other compounds. The distance between the two oxygen atoms in the two phenolic hydroxyl groups (δO) of Ia is the shortest of all the compounds (Table I).

Evaluation of Quantitative Structure–Activity Relationships (QSAR) of 3,3′-Dihydroxy-α,β-diethyldiphenylethane (I)-Related Compounds It is a main aim of this work to examine whether energetically-stable conformations of the 3,3′-dihydroxy-α,β-diethyldiphenylethane (I)-related compounds reflect their hypotensive and phytogrowth-inhibitory activities against *Brassica rapa* L. and *Raphanus sativus* L. var. *rahanistroides* MAKINO. The linear-correlation coefficients between the MCE and biological activities are given in Table II. It is worthy of note that the MCE, which is a parameter describing the molecular stability, showed negative correlations with the hypotensive and phytogrowth-inhibitory activities. It was found for the first time that the MCE of I-related compounds is important for their biological activities. Furthermore, in order to clarify the relationship between the conformational parameters and their biological activities, the QSAR analyses were carried out. The parameters of the idealized molecular models obtained from MM calculations listed in Table I were chosen for QSAR analyses. The results are summarized in Table III. The values of the standard deviations of the MCE and the δO (Eq. 2 in Table III) are a little high, because the measurement of the phytogrowth-inhibitory activity against *Brassica rapa* L. is much more difficult to perform compared with those of the other biological activities. Although no significant correlations with the activities were observed for δO ($r=-0.61$—-0.37) and MSA ($r=0.40$—0.57), the linear combinations of δO and MCE or the molecular surface area (MSA) give good regression equations (Eqs.

TABLE I. Conformational Parameters Used for the QSAR Analyses

Compd.	Bioact.[a] HY	PIB	PIR	MCE (kcal/mol)[b]	δO (Å)[c]	MSA (Å^2)[d]
Ia[e]	1.000	0.03	0.16	8.502	9.22 (O(3)–O(3′))	338.30
Ib				19.322	—	—
IIa[f]	0.233	0.46	0.83	37.183	9.45 (O(3)–O(3′))	325.50
IIb				37.339	—	—
III[g]	0.400	0.49	0.41	11.735	11.74 (O(4)–O(4′))	344.23
IV[h]	0.410	0.43	0.65	37.095	12.43 (O(4)–O(4′))	335.57

a) Bioact. HY: the effect of 3,3′-dihydroxy-α,β-diethyldiphenylethane (I) on blood pressure in rat at a dosage of 10 mg/kg (i.v.) was normalized as 1.000. PIB: phytogrowth-inhibitory effects of I-related compounds on *Brassica rapa* L.. PIR: phytogrowth-inhibitory effects of I-related compounds on *Raphanus sativus* L. var *raphanistroides* MAKINO. Growth in control experiments after 7 d was taken as 1.00. Concentration: 50 ppm. Quantity of light: I and II (9000 lx), III and IV (600 lx). Experimental size: 20 seeds/group, 2 groups. *b*) MCE: the minimized conformational energy obtained from the MMFF program.[12] *c*) δO: the distance between two oxygen atoms in the two phenolic hydroxyl groups. *d*) MSA: the molecular surface area of each molecule. *e*) The idealized molecular model of 3,3′-dihydroxy-α,β-diethyldiphenylethane (I). *f*) The idealized molecular model of 3,3′-dihydroxy-α,β-diethylstilbene (II). *g*) The idealized molecular model of hexestrol (III). *h*) The idealized molecular model of diethylstilbestrol (IV).

TABLE II. Linear-Correlation Coefficients of the Minimized Conformational Energy

	r (HY)[a]	r (PIB)[b]	r (PIR)[c]
MCE[d]	−0.7047 (±0.2065)	−0.6122 (±0.4060)	−0.8760 (±0.1318)

a) Linear-correlation coefficient between the MCE and the hypotensive activity on rats. *b*) Linear-correlation coefficient between the MCE and the phytogrowth-inhibitory activity against *Brassica rapa* L. *c*) Linear-correlation coefficient between the MCE and phytogrowth-inhibitory activity against *Raphanus sativus* L. var *raphanistroides* MAKINO. *d*) MCE: the minimized conformational energy obtained from the program MMFF.[12]

TABLE III. Correlation Equations of QSAR for Hypotensive and Phytogrowth-Inhibitory Activities

	N[a]	r[b]	S.D.[c]
(1) Correlation equation of hypotensive activity			
Eq. 1 $ID^{d}=-8.6519+0.0323$ (MSA) $-0.1574(\delta O)$ (± 4.7580) (± 0.0151) (± 0.0731)	4	0.7824	0.1813
(2) Correlation equation of phytogrowth-inhibitory activity against *Brassica rapa* L.			
Eq. 2 $\log 1/IC^{e}=3.0489-0.0191$ (MCE) -0.1835 (δO) (± 1.2342) (± 0.0120) (± 0.1169)	4	0.7830	0.3194
(3) Correlation equations of phytogrowth-inhibitory activity against *Raphanus sativus* L. var *raphanistroides* MAKINO			
Eq. 3 $\log 1/IC^{e}=-10.7474+0.0381$ (MSA) -0.1579 (δO) (± 2.8585) (± 0.0091) (± 0.0439)	4	0.9171	0.1089

a) Number of compounds used for correlations. *b*) Correlation coefficients obtained by the QSAR program.[13] *c*) Standard deviations. *d*) Inhibitory dose. *e*) Inhibitory concentration.

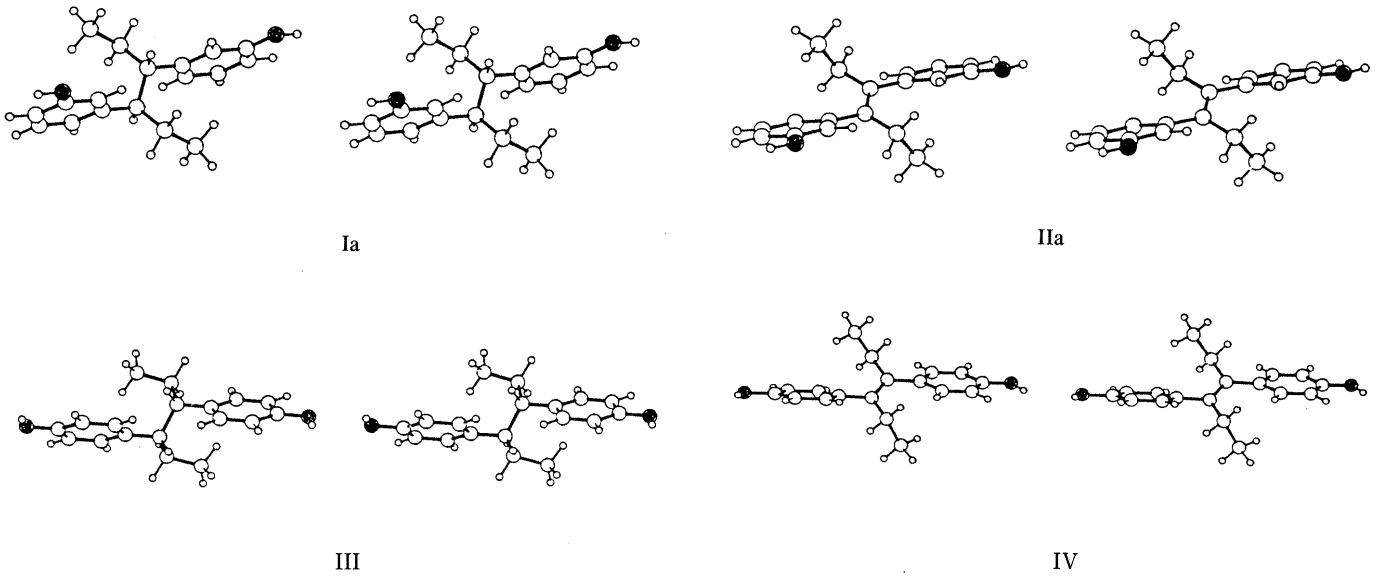


Fig. 3. Stereoscopic Diagrams of 3,3′-Dihydroxy-α,β-diethyldiphenylethane(Ia), 3,3′-Dihydroxy-α,β-diethylstilbene(IIa), Hexestrol(III) and Diethylstilbestrol(IV)

●, oxygen; ○, carbon; o, hydrogen.

1—3; Table III).

Discussion

In addition to our experimental findings that the two phenolic hydroxyl groups of the 3,3′-dihydroxy-α,β-diethyldiphenylethane (I)-related compounds are necessary for the observed biological activities,[5] the results of QSAR analyses indicate that the δO makes a major contributed to the correlations. Especially, the correlation coefficient of Eq. 3 is high compared with those of Eqs. 1 and 2. However the correlations of Eqs. 1 and 2 are not poor, and compound I showed the strongest biological activities. The following discussions are based on the ORTEP diagrams of the idealized conformations of I-related compounds. Attention was focused on the two phenolic hydroxyl groups, as shown in Fig. 3. Those of the most active compound (Ia) face in the same direction, so this conformation makes it easy to bind another substituent. As the rotamer of C(7)—C(7′) is free, because C(7) and C(7′) atoms have a sp^3 hybrid orbital, so the distance between the two phenolic hydroxyl groups can vary. In particular, the ethyl groups of Ia do not interfere with the two phenolic hydroxyl groups, because the benzene rings are turned in the anti-direction with respect to the ethyl groups. On the other hand, the two phenolic hydroxyl groups of III and IV lie nearly in one plane and take their positions in the anti-direction. For this reason, there could be considerable steric interference between phenolic hydroxyl groups and ethyl groups. In IIa, the two phenolic hydroxyl groups face in the same direction as the ethyl groups, so the ethyl groups interfere with them. As mentioned above, Ia exhibits a conformational significance which is important for its biological activities. To exhibit potent biological activities, the δO of I-related compounds must be immovable. The MCE and MSA are important factors to determining the δO. Our experimental findings were also supported by these results.

From the standpoint of the structure–activity relationship, the strong biological activities of I,[1-4] already reported, are of considerable interest. It has also been found that I[15] and II[16] have no hormonal side-effect, while III and IV do. In this respect, further studies on the correlation mechanisms involving their biological activities and the conformations are in progress, together with the mechanisms of action of I.

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