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Quantitative structure–activity relationship studies for antioxidant hydroxybenzalacetones by quantum chemical- and 3-D-QSAR(CoMFA) analyses

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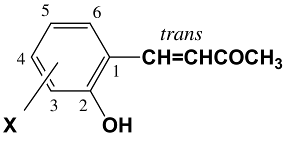
Abstract—Antioxidant activities for a series of hydroxybenzalacetones, **OH-BZ**, evaluated by their inhibitory potencies against lipid peroxidation induced by γ-ray irradiation or *t*-BuOOH, were analyzed quantitatively using quantum-chemical parameters calculated by semi-empirical molecular orbital (MO) calculations. The energy of the highest occupied molecular orbital (E_{HOMO}) and frontier electron densities (HOMO) on the phenolic oxygen atom ($F_{\text{H},O}$), together with the steric parameter (E_s) for the substituent *ortho* to the phenolic oxygen, showed excellent correlations. We also performed 3D-QSAR studies by using the comparative molecular field analysis (CoMFA) model. The results were compared with the corresponding classical QSAR correlations.

1. Introduction

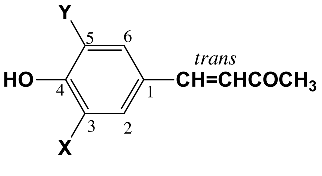
Phenols, ArOH, are known to exert antioxidant activities by breaking the radical chain reaction of the peroxidized lipid radical, LOO$^\bullet$, according to[1]

$$\text{LOO}^\bullet + \text{ArOH} \rightarrow \text{LOOH} + \text{ArO}^\bullet$$

Substituent effects governing the activity are well investigated,[2–6] and show that introduction of electron-donating substituent(s) into the phenol ring and/or steric crowding around the phenolic OH group tend to enhance the activity. However, there are only a few examples of quantitative structure–activity relationship (QSAR) studies.[4–6] In a previous study,[6] we measured inhibitory potencies of variously substituted hydroxybenzalacetones (**2OH-BZ** and **4OH-BZ**) against lipid peroxidation induced by γ-ray irradiation or BuOOH (*tert*-butyl hydroperoxide). The relationship between their structure and activity was analyzed quantitatively by using free-energy related substituent parameters. The activity, expressed as log(1/IC$_{50}$), was shown to correlate nicely with the electronic(σ^+)[7] and steric parameters (E_s),[8] yielding Eqs. 1 and 2 for γ-ray irradiation and BuOOH, respectively, where $\Sigma\sigma^+ = \sigma^+(\text{X})$ for **2OH-BZ** and $\Sigma\sigma^+ = \sigma^+(\text{X}) + \sigma^+(\text{Y})$ for **4OH-BZ**, and where the steric term is applied only to the *ortho* substituent, namely $\Sigma E_s = E_s(3\text{-}X)$ for **2OH-BZ** and $\Sigma E_s = E_s(3\text{-}X) + E_s(5\text{-}Y)$ for **4OH-BZ**. The I_p parameter is an indicator variable, where $I_p = 1$ for **4OH-BZ** and 0 for others.



2OH-BZ



4OH-BZ

γ-ray

$$\log(1/\text{IC}_{50}) = -1.091\Sigma\sigma^+ - 0.229\Sigma E_s - 0.523 I_p + 4.57$$
$$n = 18,\ \ r = 0.909,\ \ s = 0.261,\ \ F = 22.1,\ \ q^2 = 0.678 \qquad (1)$$

Keywords: Antioxidant activity QSAR hydroxybenzalacetone.

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BuOOH

$$\log(1/\mathrm{IC}_{50}) = -0.763\Sigma\sigma^{+} - 0.277\Sigma E_{\mathrm{s}} - 0.338 I_{p} + 3.76$$
$$n = 18,\ \ r = 0.948,\ \ s = 0.153,\ \ F = 41.2,\ \ q^{2} = 0.829 \qquad (2)$$

In these equations and throughout this paper, n is the number of compounds used for calculations, r is the correlation coefficient and s is the standard deviation. F is the value of the F-ratio between the variances of the observed and calculated values, and q^2 represents the correlation coefficient obtained from the leave-one-out cross-validation.

Although these classical QSAR equations are physicochemically explicable, analyses attempted with physicochemical parameters derived from experimental results often suffer from unavailability of the required parameters. To clarify the usefulness of the above QSAR results as a general formula, application to a wider range of substituents would be necessary. This prompted us to find alternative electronic parameters readily accessible from calculation. In this work, we attempted a computational approach to analyze the same activity data by using quantum chemical descriptors derived from the AM1[9] and PM5[10] semi-empirical MO calculations. We chose the semi-empirical methods by two criteria: (1) since the present assays are used as a first screening test, rapid calculations are desirable; and (2) it has been shown in the literature that the AM1 method gives satisfactory results compared with the ab initio (3-21G) calculations in the study of theoretical parameters to characterize antioxidant like vitamin E analogs.[11] We also performed 3D-QSAR studies by using the comparative molecular field analysis (CoMFA) model.[12] The results were compared with the classical QSAR equations.

2. QSAR analyses by using quantum chemical parameters

The activity data used for analyses were taken from our previous work (Table 1).[6] Antioxidant activities (IC_{50}) were assessed by measuring the inhibitory effect of **OH-BZ** against peroxidation of rabbits' red blood cell (RBC) membrane ghost induced by γ-ray irradiation or BuOOH.

MO calculations were carried out by the AM1 and PM5 methods by CAChe Work System Pro (v. 5.04) (Fujitsu).[10] With the optimized conformations, we calculated various descriptors such as the heat of formation, the energy of the highest occupied molecular orbital (E_{HOMO}), the net charge on each atom, and the frontier electron densities (HOMO) on the phenolic oxygen atom ($F_{\mathrm{H},O}$). Regression analyses for **OH-BZ** were carried out by using these parameters. Most of the studies so far reported have revealed[3,11,13] that the antioxidant activity or radical-scavenging effect of phenolic antioxidants is well correlated with such parameters as the HOMO energy and the difference in heat of formation between antioxidant (ArOH) and its radical ($\mathrm{ArO}^{\bullet}$), which characterizes the O–H bond dissociation energy. Our preliminary investigation showed that the difference in heat of formation was not satisfactory for this system. We describe here in detail the development of correlation equations only for γ-irradiation of **OH-BZ** using

Table 1. Activities, physicochemical and quantum chemical parameters for hydroxybenzalacetones

No.	Substituent(s)	$\log(1/\mathrm{IC}_{50})$[a]		E_{H}[b] (AM1)	$F_{\mathrm{H},O}$ (AM1)	E_{HOMO}[b] (PM5)	$F_{\mathrm{H},O}$ (PM5)	E_{s}	I_p
		BuOOH	γ-ray						
2OH-BZ									
1	H	3.824	4.423	−9.029	0.08963	−9.013	0.12489	0.00	0
2	3-Me	4.274	5.440	−8.984	0.09766	−8.951	0.14018	−1.24	0
3	3-*t*-Bu	4.793	5.662	−8.911	0.09890	−8.905	0.12299	−2.78	0
4	3-F	3.690	4.291	−9.271	0.11046	−9.351	0.15319	−0.46	0
5	3-OMe	4.604	5.488	−8.925	0.13732	−8.878	0.16728	−0.55	0
6	3-OEt	4.434	5.479	−8.891	0.13778	−8.830	0.16565	−0.55	0
7	3-OH	4.573	5.708	−9.016	0.18126[c]	−8.977	0.24765[c]	−0.55	0
8	4-OMe	3.542	4.449	−8.798	0.04296	−8.833	0.05504	0.00	0
9	5-Me	4.102	5.097	−8.895	0.09597	−8.839	0.12838	0.00	0
10	5-*t*-Bu	4.205	5.070	−8.887	0.09400	−8.840	0.12610	0.00	0
11	5-Cl	3.790	4.220	−9.113	0.09457	−9.086	0.12461	0.00	0
12	5-OMe	4.212	5.400	−8.728	0.10146	−8.698	0.12215	0.00	0
13	5-OH	4.487	5.845	−8.832	0.19084[c]	−8.803	0.23927[c]	0.00	0
4OH-BZ									
14	H	3.256	4.180	−8.962	0.09214	−8.944	0.12187	0.00	1
15	3-OMe	4.301	4.939	−8.789	0.10580	−8.755	0.13177	−0.55	1
16	3-OH	4.439	5.631	−8.863	0.16283[c]	−8.842	0.21221[c]	−0.55	1
17	3,5-di-Me	4.582	5.199	−8.811	0.09638	−8.757	0.12852	−2.48[d]	1
18	3,5-di-OMe	4.764	5.599	−8.642	0.13151	−8.621	0.16176	−1.10[d]	1

[a] IC_{50}: in M.

[b] In eV.

[c] $\Sigma F_{\mathrm{H},O}$.

[d] $\Sigma E_{\mathrm{s}} = E_{\mathrm{s}}(X) + E_{\mathrm{s}}(Y)$.

Table 2. Regression coefficients and constant terms in correlation analyses of antioxidant activities for **OH-BZ** by $\log(1/\mathrm{IC}_{50}) = hE_{\mathrm{HOMO}} + f\Sigma F_{\mathrm{H},O} + e\Sigma E_{\mathrm{s}} + iI_p + \mathrm{const.}$

Oxidant	E_{HOMO}	$\Sigma F_{\mathrm{H},O}$	ΣE_{s}	I_p	Const.	n	r	s	F	q^2	Eq. no
AM1											
γ-ray	2.286	10.680	−0.288	−0.493	21.22	18	0.962	0.177	40.4	0.861	4
	(0.704)[a]	(2.554)	(0.115)	(0.227)	(6.31)						
BuOOH	1.395	7.001	−0.319	−0.289[b]	12.73	18	0.937	0.175	23.2	0.726	5
	(0.695)	(2.523)	(0.114)	(0.224)	(6.23)						
PM5											
γ-ray	2.312	8.036	−0.283	−0.495	24.43	18	0.969	0.160	49.8	0.869	6
	(0.566)	(1.816)	(0.104)	(0.204)	(5.05)						
BuOOH	1.466	5.170	−0.315	−0.297[c]	16.36	18	0.942	0.168	25.4	0.756	7
	(0.591)	(1.899)	(0.109)	(0.213)	(5.28)						

The terms of Eqs. 4–7 are justified above the 99.9% level unless otherwise noted.

[a] The figures in parentheses are the 95% confidence intervals.

[b] Justified at the 98.4% level.

[c] Justified at the 98.9% level.

the AM1 Hamiltonian; all the other results, being of similar qualities, are summarized in Table 2. First, for the sake of simplicity, analyses were undertaken with 13 compounds of the **2OH-BZ** series. As Eqs. 1 and 2 indicate electron-donating substituents enhance the activity, the HOMO energy is expected to be a useful predictor. In fact, among the parameters tested, E_{HOMO} in combination with E_{s}, gave the best correlation but even in this case, the quality of the correlation was statistically poor ($r = 0.677$ and $s = 0.460$). Nakao et al.[5] have analyzed the inhibitory activity of variously substituted hydroxyphenylureas against lipid peroxidation and derived satisfactory results by using the $R(\mathrm{O}_{\mathrm{phenol}})$ parameter, defined by $R(\mathrm{O}_{\mathrm{phenol}}) = -100 \times F_{\mathrm{H},O}/E_{\mathrm{HOMO}}$, which approximates to the superdelocalizability, as an electron-releasing index. In our case, attempts to use this parameter in combination with E_{s}, however, failed to improve the correlation: the colinearity between E_{HOMO} and $R(\mathrm{O}_{\mathrm{phenol}})$ was very high, leading to a result statistically similar to that with E_{HOMO} and E_{s}. Consequently, we examined various combinations of plausible parameters and found that addition of an $F_{\mathrm{H},O}$ term to E_{HOMO} and E_{s}, provided excellent correlation as shown by Eq. 3. The parameters used for the analyses are listed in Table 1.

$$\log(1/\mathrm{IC}_{50}) = 2.393E_{\mathrm{HOMO}} + 9.934\Sigma F_{\mathrm{H},O} - 0.327\Sigma E_{\mathrm{s}} + 22.24$$
$$n = 13,\quad r = 0.962,\quad s = 0.178,\quad F = 39.7,\quad q^2 = 0.703 \qquad (3)$$

The definition of ΣE_{s} is the same as that for Eqs. 1 and 2, and $\Sigma F_{\mathrm{H},O}$ represents the sum of frontier electron densities (HOMO) on the two phenolic oxygens for **7** and **13**, otherwise $\Sigma F_{\mathrm{H},O} = F_{\mathrm{H},O}$. Analyses for the combined data set, **2OH-BZ** and **4OH-BZ**, were performed by introducing the indicator variable I_p, as used above, led to Eq. 4 which is statistically of a quality equivalent to that of Eq. 3.

$$\log(1/\mathrm{IC}_{50}) = 2.286E_{\mathrm{HOMO}} + 10.680\Sigma F_{\mathrm{H},O} - 0.288\Sigma E_{\mathrm{s}} - 0.493I_p + 21.22$$
$$n = 18,\quad r = 0.962,\quad s = 0.177,\quad F = 40.4,\quad q^2 = 0.861 \qquad (4)$$

As explained in a previous paper,[6] the variable I_p is thought to represent a constant steric contribution derived from the fixed substituent: that is, the steric term for **2OH-BZ** is given by the sum of E_{s} for the 3-X-substituent and that for the fixed substituent, $\Sigma E_{\mathrm{s}} = E_{\mathrm{s}}$ (3-X or H) + E_{s}(CH=CHCOMe), where the contribution from the latter term is expected to remain constant, and hence be adequately accommodated in an I_p term. Although the number of compounds is insufficient to avoid chance correlations, stability of the correlation between Eq. 3 for **2OH-BZ** and Eq. 4 for the combined set (**2OH-BZ** + **4OH-BZ**) is excellent, suggesting that the results are reliable. Similarly, correlations for other combinations of oxidants and Hamiltonians were derived as is shown in Table 2, with similar statistical precision. Comparison of the classical QSAR (Eqs. 1 and 2) with those in Table 2 indicates that the coefficients of the ΣE_{s} and I_p terms remained more or less unchanged for a given assay (Eqs. 1, 4 and 6 for γ-ray and Eqs. 2, 5 and 7 for BuOOH); this fact also seems to indicate the reliability of the correlations obtained. Plots of log(1/IC$_{50}$) observed and calculated by AM1 and PM5 methods are shown in Figures 1 and 2, respectively.

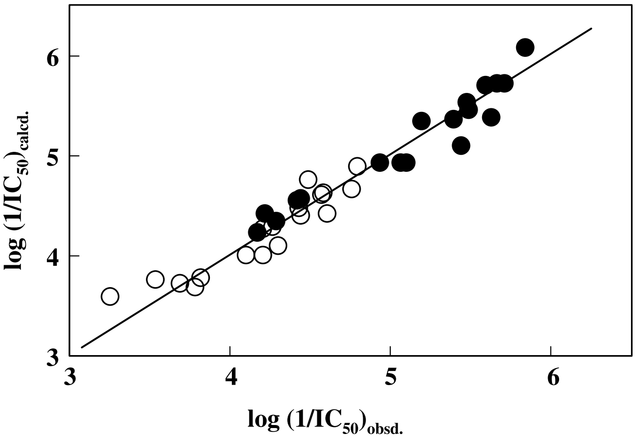


Figure 1. Plot of log(1/IC$_{50}$) observed and calculated by the AM1 method. Closed circles: Oxidation by γ-ray irradiation (Eq. 4), open circles: Oxidation by BuOOH (Eq. 5). The line is drawn with unit gradient.

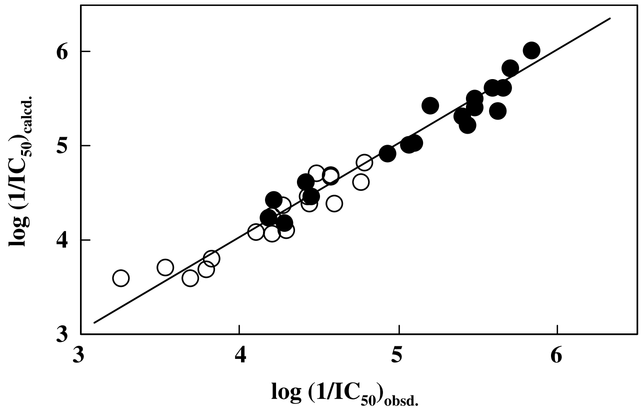
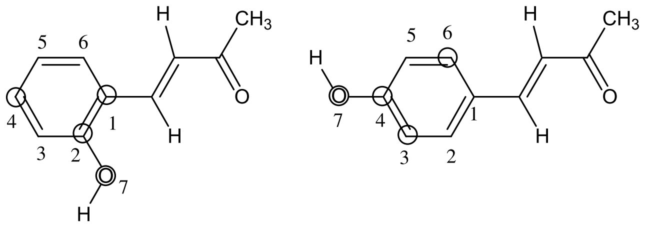


Figure 2. Plot of log(1/IC$_{50}$) observed and calculated by the PM5 method. Closed circles: Oxidation by γ-ray irradiation (Eq. 6), open circles: Oxidation by BuOOH (Eq. 7). The line is drawn with unit gradient.



2OH-BZ **4OH-BZ**

Figure 3. Optimized geometry of **2OH-BZ** and **4OH-BZ**, and atoms for superposition (open circles).

The above results demonstrate that the higher the HOMO energy and frontier electron density (HOMO) on phenolic *O*-atom(s), and the bulkier *ortho* substituent(s), the greater the antioxidant activity. Since the former two factors are related to the facility of electron-donating ability of substituents, the QSARs obtained here are considered to have a physical meaning comparable to that of the previous classical QSARs (Eq. 1 or 2). The difference in oxidant seems to be reflected in the contributions of electronic factors: the coefficients of E_{HOMO} and $\Sigma F_{\mathrm{H},O}$ terms are larger in the assay with γ-ray irradiation than with BuOOH, whereas the coefficients of ΣE_{s} remain almost unchanged regardless of the oxidants. The steric factor is thought to increase the activity by stabilizing the resultant phenoxy radical. Hence, once the radical is formed, the steric constraints would exert similar effects in both assays. On the other hand, use of γ-irradiation, which is able to supply higher energy than BuOOH, is expected to facilitate hydrogen abstraction from phenols. In total, the results obtained strongly suggest that the critical process for antioxidant activity could be the process of formation and stabilization of phenoxy radicals.

3. CoMFA studies

Although the above QSARs using quantum-chemical parameters are quite useful, the steric parameters used are those derived experimentally. To examine the possibility of analysis by calculations alone, we performed 3D-QSAR studies with the same data set for the BuOOH assay using the Advanced CoMFA module of Sybyl 6.8.[12] A full geometric optimization was carried out using the AM1 Hamiltonian, and with the optimized geometry thus obtained (Fig. 3), single point calculations were performed using the ab initio 3-21G calculations by Spartan[14] to obtain esp charges. Neither AM1 nor PM5 charges provided statistically significant correlations in the CoMFA analysis. The four atoms 1, 2, 4, and 7 for **2OH-BZ** and 3, 4, 6, and 7 for **4OH-BZ**, respectively, were superposed (Fig. 3). The aligned set of active conformers was placed in an automatically created lattice of 18.5 Å × 12.4Å × 20.5Å ($X = -7.8$ to 10.7, $Y = -6.2$ to 6.2, $Z = -9.1$ to 11.4) with 2 Å spaces. The steric and electrostatic field energies were calculated using an sp^3 carbon probe atom with a + 1 charge at all lattice intersections. The data matrix was analyzed by the partial least squares (PLS) method.[15] We initially selected the number of compounds in the set as the number of the cross-validations and then performed the analysis using the optimum number of latent variables, deduced from the cross-validation tests without actual cross-validation. Thus, Eq. 8 was obtained as the most reasonable correlation for all the compounds.

$$\log(1/\mathrm{IC}_{50}) = -0.067 + [\text{CoMFA field terms}]$$
$$n = 18,\quad CN = 4,\quad s = 0.107,\quad r^2 = 0.954,\quad s_{\mathrm{CV}} = 0.342,$$
$$q^2 = 0.528,\quad RC_{\mathrm{el.}} = 0.516,\quad RC_{\mathrm{st}} = 0.484 \tag{8}$$

Here, CN is the number of components, and s_{CV} represents the standard error obtained from the leave-one-out cross-validation. The relative contributions (%) of electrostatic and steric fields are RC$_{\mathrm{el}}$ and RC$_{\mathrm{st}}$, respectively. Graphical representations of Eq. 8 showed that positive electrostatic and sterically favorable regions appeared near the phenolic OH group, indicating that electron-donating and/or bulky groups in the *ortho* position to the phenolic OH are preferred for enhancement of the activity. This prediction is qualitatively consistent with the result of classical and quantum-chemical QSARs (Eqs. 2,5 and 7).

However, the CoMFA analysis for the assay with γ-ray irradiation failed to give statistically acceptable correlations. The reason why satisfactory results are obtained for BuOOH but not for γ-radiation is difficult to rationalize. One possibility would be that, in the CoMFA method, atomic charges are used to characterize the electronic properties of compounds, which may be less appropriate than the electronic descriptors used in Eqs. 4–7. In going from the assay with BuOOH to γ-irradiation, the electronic contribution becomes more important, and hence the CoMFA results would be degraded to a larger extent in the assay with γ-irradiation. Therefore, we reanalyzed the same data by replacing the CoMFA electrostatic field term with the quantum chemical electronic parameters, E_{HOMO} and $\Sigma F_{\mathrm{H},O}$, in terms of Eq. 9 as a general formula, which yielded reasonable correlations for the BuOOH and γ-irradiation assays.

Table 3. Correlations obtained by the CoMFA analysis of antioxidant activities for **OH-BZ** in terms of $\log(1/IC_{50}) = hE_{HOMO} + f\Sigma F_{H,O}$ + [CoMFA steric field term] + const. *CN*(Number of components) = 4

Oxidant	E_{HOMO}	$\Sigma F_{H,O}$	const.	n	r^2	s	q^2	s_{CV}	RC			Eq. no
									E_{HOMO}	$\Sigma F_{H,O}$	*Steric*	
AM1												
γ-ray	2.231	9.439	20.61	18	0.906	0.199	0.764	0.315	0.275	0.292	0.433	10
BuOOH	1.151	5.532	10.52	18	0.836	0.202	0.588	0.320	0.206	0.248	0.547	11
PM5												
γ-ray	2.163	7.311	19.98	18	0.902	0.203	0.768	0.312	0.306	0.295	0.399	12
BuOOH	1.200	4.330	10.94	18	0.842	0.198	0.756	0.168	0.238	0.246	0.516	13

$$\log(1/IC_{50}) = hE_{HOMO} + f\Sigma F_{H,O} + [\text{CoMFA steric field term}] + \text{const.} \quad (9)$$

The resultant correlations are summarized in Table 3, where the coefficients of the electronic terms are similar to the corresponding values for Eqs. 4–7 in Table 2. The I_p term for Eqs. 4–7 is thought to be incorporated in the CoMFA steric filed term for Eqs. 10–13. Typical graphical representations are given in Figure 4, which shows stereo views of the major steric contour maps according to Eq. 10 with the most potent compound **3** and the parent compound **14** of **4OH-BZ**. As shown in Figure 4, sterically favorable (green) regions appear near the phenolic OH group, indicating that bulky groups in the *ortho* position to the phenolic OH are preferred for enhancement of the activity. The sterically unfavorable regions (yellow) lying around the *para* position (at C-5 in **2OH-BZ**) seem to reflect the fact that the activities for *para* substituted phenols are relatively low compared to those for the *ortho* substituted phenols. Although the CoMFA analysis has the advantage that the analysis can be executed on various compounds of different substitution patterns and also of different skeletal structures only by calculations, in the present case, the classical and quantum-chemical QSARs correlations are thought to be more informative than the correlations derived from the CoMFA.

The present work has shown that the QSAR analysis for antioxidant activities of **OH-BZ** by using quantum-chemical parameters, E_{HOMO} and $\Sigma F_{H,O}$, provided correlations equivalent in quality to those from classical QSARs. Both approaches led us to conclude that the activity is increased by electron-donating substituents and/or by bulky *ortho* substituents: the former is likely to facilitate the hydrogen abstraction from phenols and the latter is considered to function to stabilize the resultant phenoxy radical. Although classical QSAR using various experimentally derived physicochemical parameters affords more straightforward information about the reaction mechanism, the successful prediction of activity by quantum chemical QSARs in terms of parameters obtained by rapid semiempirical MO calculations will permit their wider application in the search for antioxidant compounds.

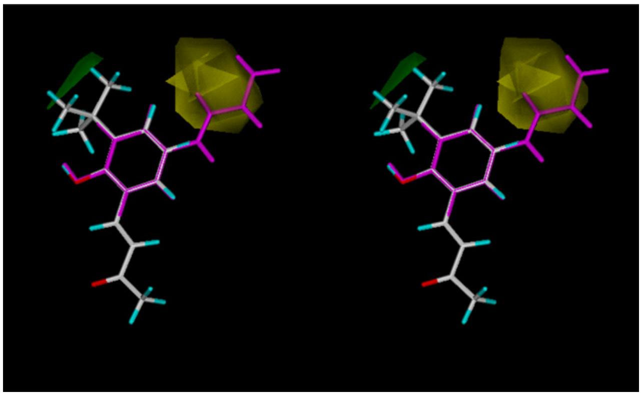


Figure 4. Stereo views of contour diagrams of the steric fields with compounds **3** (colored by atom type; carbon: white; hydrogen; cyan; oxygen: red) and **14** (magenta) according to Eq. 10. Green: Sterically favored for the activity. Yellow: Sterically unfavored.

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