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230. Shun-ichi Hata, Koji Mizuno, and Suiichi Tomioka*[1]: Effects of Electron Donors on the Photodecomposition of Menadione in Aqueous Solution.*[2],[3] I. The Interaction between Electron Donors and Menadione in Aqueous Solution.

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Among nine pharmaceutical preparations, the values of parameters $\lambda_{h.o.}$ and $\lambda_{l.e.}$ representing the energy levels of the highest occupied molecular orbital and the lowest empty molecular orbital were obtained by a molecular orbital method, simple LCAO MO method of π-electrons.

On the basis of these calculations, it was found that eight electron donors used formed the molecular complex with menadione in aqueous media. The free energy changes in the complex formation tend to be increased by the addition of better electron donors. As a result, it was suggested that the driving force of the complex formation would be due to charge transfer force.

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The stabilizing method of pharmaceutical preparations by complex formations has long been known[1] and it has been proved to be one of the effective means for stabilization. However, it is very difficult to predict the formations of molecular complexes, and so trial-and-error-experiments have to be repeated so far. A formation of molecular complexes is due to the mutual reaction of electrons in the relative molecules which are accompanied with electron donation and acceptance.

The complex is readily formed especially when an electron donor and acceptor are present, and the compounds thus formed are thought to be stabilized.

Assuming, therefore, that the ionization potential and electronic affinity of molecules are known as a measure of capacity in electron donation and acceptance system, it may well be thought possible to estimate tendencies of complex formations to a certain extent and hence to find out some systems which might contribute to the stabilization of pharmaceutical preparations. However, ionization potentials and electronic affinities of molecules have never been determined experimentally, because of pharmaceutical preparations are organic substances of complicated structure, so that it will be required to obtain alternative values by a quantum mechanical calculation of their molecules.

The authors obtained, in this report, the values of the energy level of molecular orbitals which is a measure of capacity of donating and accepting electrons among some of organic substances having π-electrons, according to the simple LCAO MO method of π-electrons being one of the quantum chemical methods. Based upon these results, it was found that menadione formed molecular complexes with various electron donors in aqueous solution.

Method of Calculation

Calculations were made by means of the simple linear-combination-of-atomic-orbitals molecular orbital (LCAO-MO) method neglecting overlap integral. α and β are coulomb and resonance integrals respectively, and those of heterogeneous atoms and various

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*[2] This work was reported at the Kanto Branch Meeting of Pharmaceutical Society of Japan, December 25, 1965.

*[3] A preliminary account of this study has appeared in This Bulletin, **13**, 96 (1965).

1) T. Higuchi, L. Lachman: J. Pharm. Sci., **44**, 521 (1955).

substituents were obtained by correcting the parameters,[2] shown in Table I. The results obtained are shown in Table Ⅱ.

Experimental

Materials——Menadione, ethyl aminobenzoate, theophylline, theobromine and sodium dehydroacetate were G.R. grade-chemicals, purchased from Tokyo Kasei Co., Ltd. Sodium salicylate was G.R. grade-chemical, purchased from Wako Junyaku Co., Ltd. Caffeine and nicotinamide were commercially available preparations, according to the Japanese Pharmacopoeia Ⅶ. β-Hydroxynaphthoic acid was E.P. grade-chemical, purchased from Tokyo Kasei Co., Ltd., and was used after recrystallization.

Measurements of Absorption Spectra——Visible absorption spectra were measured with a Hitachi photoelectric spectrophotometer EPU-2A equipped with thermospacers which maintained the cell compartments at 27±0.1° and 14±0.1°, and the cell length was 10 mm.

The sample solutions were prepared by dissolving in phosphate buffered solution (N/15) of pH 7.0.

TABLE I. Parameter used for Calculations

Substitution group	a_X[a]	a_r[b]	l[c]
=O	2	0.2	1.4
-O-	2	0.2	0.6
-OH	0.6	0	0.7
=N-	0.6	0.1	1
-N<	1	0.1	1
$-NH_2$	0.4	0	0.6
$-CH_3$	3	−0.1	1

[a] Coulomb integral of the substituent X: $\alpha_X=\alpha+a_X\beta$
[b] Coulomb integral of the carbon atom adjacent to X: $\alpha_{adj}=\alpha+a_r\beta$
[c] Resonance integral of the carbon atom and X: $\beta_{C-X}=l\beta$

TABLE Ⅱ. Energy Levels of Molecular Orbitals ($\varepsilon=\alpha+\lambda\beta$)[a]

Compound	$\lambda_{h.o.}$[b]	$-\lambda_{l.e.}$[c]
Menadione	0.972	0.228
Salicylic acid	0.438	0.555
Caffeine	0.633	0.687
Theophylline	0.656	0.690
Theobromine	0.633	0.688
Nicotinamide	0.563	0.465
Ethyl aminobenzoate	0.363	0.386
Dehydroacetic acid	0.822	0.546
β-Hydroxynaphthoic acid	0.384	0.450

[a] ε: Energy level of molecular orbital obtained by simple LCAO MO method
α: Coulomb integral of carbon atom in benzene.
β: Resonance integral of carbon atom in benzene.
[b] Parameter for energy level of the highest occupied molecular orbital.
[c] Parameter for energy level of the lowest empty molecular orbital.

Results and Discussion

The visible spectra of menadione to various compounds added are shown in Fig. 1. For the measurements, to buffer solutions of pH 7.0, various compounds were added at various concentrations as indicated in Fig. 1.

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[2] T. Yonezawa, *et al.*: "Ryoshi-Kagaku Nyumon" vol. 1, p. 55, Kagaku-dojin, Kyoto (1963).

Because of a large absorbancy of the compound added, measurements were attempted to carry out in the region of either 320 mμ or 330 mμ and higher wave length where the absorption spectra of menadione were always transitional.

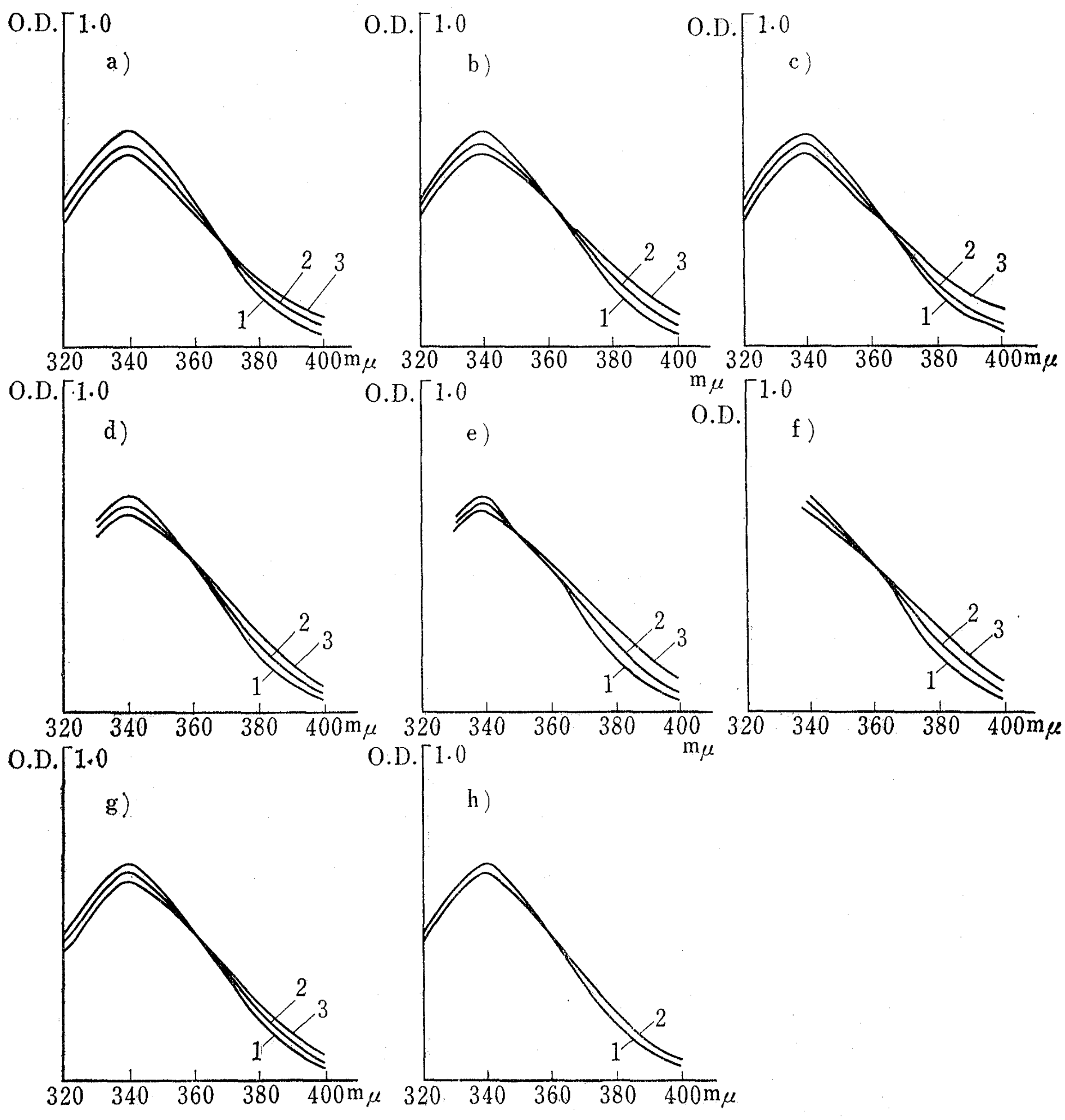

Fig. 1. The Absorption Spectra of Menadione ($6.97 \times 10^{-4} M$/L.) when Various Concentrations of Electron Donors are added in pH 7.0 Phosphate Buffer at 27°

a) Caffeine, 1 : 0M/L., 2 : $1.03 \times 10^{-2} M$/L., 3 : $2.06 \times 10^{-2} M$/L.

b) Theophylline, 1 : 0M/L., 2 : $1.11 \times 10^{-2} M$/L., 3 : $2.22 \times 10^{-2} M$/L.

c) β-Hydroxynaphthoic acid, 1 : 0M/L., 2 : $5.31 \times 10^{-4} M$/L., 3 : $1.06 \times 10^{-3} M$/L.

d) Salycylic acid (Na salt), 1 : 0M/L., 2 : $1.25 \times 10^{-2} M$/L., 3 : $2.50 \times 10^{-2} M$/L.

e) Ethyl aminobenzoate, 1 : 0M/L., 2 : $1.02 \times 10^{-3} M$/L., 3 : $2.04 \times 10^{-3} M$/L.

f) Dehydroacetic acid (Na salt), 1 : 0M/L., 2 : $9.61 \times 10^{-3} M$/L., 3 : $1.92 \times 10^{-2} M$/L.

g) Nicotinamide, 1 : 0M/L., 2 : $1.63 \times 10^{-1} M$/L., 3 : $3.26 \times 10^{-1} M$/L.

h) Theobromine, 1 : 0M/L., 2 : $1.86 \times 10^{-3} M$/L.

Incidentally, absorption of the compound added existed still in the region of wave length at 320 mμ and higher wave length, but respective absorption was measured independently, and the absorption spectra of the complexes were obtained by subtracting from the combined absorbancy. Because of low solubility, the absorption spectrum was measured only at a concentration of a certain level in the case of theobromine. Spectral changes observed in each case can be considered to be due to the characteristic molecular interactions between menadione and various compounds added, and the possibility of complex formation between them will be recognizable.

From the fact that isosbestic points appeared in most cases, as is shown in Fig. 1, it may be considered that a formation of only one species of molecular complex in the ratio of one to one may be general in each system, in which menadione and the compounds added are present. On this assumption, apparent formation constants of the complex $K_{app.}$ were tried to determined. Thus the concentration-dependent spectral changes shown in Fig. 1 were analyzed according to the Nagakura's equation,[3,4] as given by equation (1), where d_0, d_1, and d_2 were observed absorbance of menadione when molar concentration of the compound added were 0, c_1, and c_2, respectively. They are shown in Table Ⅲ to Ⅳ.

Using $K_{app.}$ values thus obtained, free energy, enthalpy and entropy changes, ΔG, ΔH and ΔS, in the complex formations were also obtained by equations (2) and (3), being listed in Table V.

$$K_{app}=\frac{c_1(d_0-d_2)+c_2(d_1-d_0)}{c_1\cdot c_2(d_2-d_1)} \qquad (1)$$

$$-R \ln K_{app}=\Delta H/T-\Delta S \qquad (2)$$

$$\Delta G=-RT \ln K_{app} \qquad (3)$$

TABLE Ⅲ. Apparent Formation Constant at 27°C

Compound added	380 mμ	390 mμ	400 mμ	mean
β-Hydroxynaphthoic acid	2352	1881	1411	1881
Salicylic acid (Na salt)	280.2	440.3	320.2	346.9
Ethyl aminobenzoate	245.8	245.8	245.8	245.8
Theophylline	78.84	45.04	45.04	56.30
Caffeine	29.12	59.33	35.30	41.25
Dehydroacetic acid (Na salt)	25.99	51.99	25.99	32.49
Nicotinamide	6.10	6.10	3.05	5.08
Theobromine	—	—	—	—

TABLE Ⅳ. Apparent Formation Constant at 14°C

Compound added	380 mμ	390 mμ	400 mμ	mean
β-Hydroxynaphthoic acid	3293	2822	2822	2979
Salicylic acid (Na salt)	320.2	640.5	440.3	467.0
Ethyl aminobenzoate	327.8	327.8	327.8	327.8
Theophylline	57.34	81.08	58.56	65.66
Caffeine	35.30	67.96	40.45	47.90
Dehydroacetic acid (Na salt)	34.66	34.66	34.66	34.66
Nicotinamide	9.16	4.58	3.05	5.59
Theobromine	—	—	—	—

It has now become clear that entropy changes in most of all systems studied decreased in complex-formation processes, and that enthalpy changes were shown to be of a few kcal./mole. The values obtained for parameter which represents the energy

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[3] S. Nagakura, H. Baba: J. Am. Chem. Soc., **74**, 5693 (1952).
[4] S. Nagakura: J. Am. Chem. Soc., **76**, 3070 (1954).

Table V. ΔG, ΔH and ΔS related to the Complex Formation

Compound added	$-\Delta G_{27^\circ}$ (kcal./mole)	$-\Delta H$ (kcal./mole)	ΔS (e.u.)
β-Hydroxynaphthoic acid	4.49	6.52	−7.23
Salicylic acid (Na salt)	3.48	4.23	−2.76
Ethyl aminobenzoate	3.28	4.00	−2.66
Theophylline	2.40	2.19	0.66
Caffeine	2.22	2.00	0.57
Dehydroacetic acid (Na salt)	2.07	0.92	3.71
Nicotinamide	0.97	1.36	−1.38
Theobromine	—	—	—

levels of the highest occupied molecular orbital and the lowest empty molecular orbital ($\lambda_{h.o.}$ and $\lambda_{l.e.}$ respectively) of such substances are shown in Table II. Those which are smaller in $\lambda_{h.o.}$ correspond to lower ionization potential and are better electron donors, while those having larger $\lambda_{l.e.}$ are stronger in electronic affinity and can be better electron acceptors. Although the values of coulomb and resonance integrals are not always as same as various substances, they may be considered approximately equal each other to correlate with those compounds which might be regarded as the similar groups in this series, such as those having a conjugate system. Therefore, it may be possible to make a comparison of λ-values. A substance whose absolute value of λ is smaller than 0.7, will fairly be better electron donor or acceptor, and when the value becomes smaller than 0.3, the property is extremely intensified. This is explained by the fact that for benzene having a relatively low inter-electronic interaction with other molecules, the value of $\lambda_{h.o.}$ and $\lambda_{l.e.}$ are +1 and −1, respectively.⁵⁾

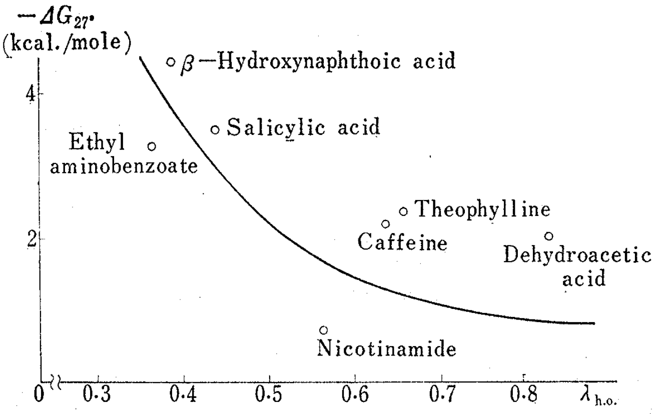

Fig. 2. Relation between Apparent Free Energy Change (ΔG_{27°) and $\lambda_{h.o.}$

Assuming from λ values as shown in Table II, it may be possible to consider that menadione is a better electron acceptor, and that most of the compound added behaves as fairly a better electron donor. Therefore, the stronger ability of complex formation between them may well be explained. The relationship between the free energy change at 27°, ΔG_{27°, and the parameter for energy levels of the highest occupied molecular orbital, $\lambda_{h.o.}$, is shown in Fig. 2. It is to be noted that the free energy changes, ΔG_{27°, tend to be increased by the addition of such a substance as β-hydroxynaphthoic acid, ethyl aminobenzoate or salicylic acid which are grouped as better electron donors. As a result, it will be concluded that the complex formation, appeared to be at least partially, may due to specific charge transfer interactions. The resulted complex may suppress the photodecomposition of menadione, and the details of which will be described in next paper.

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5) B. Pullman, A. Pullman: "Les Théories Électroniques de la Chimie Organique", p. 190, Masson et Cie, Paris (1952).