CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 16 No. 1 January 1968

[Chem. Pharm. Bull. 16(1) 1 — 5 (1968)]

UDC 615.41-014.4-011 : 577.16K

# Effects of Electron Donors on the Photodecomposition of Menadione in Aqueous Solution.[1] III.[2] The Relation between the Structure of the Complex in Electronic Aspect and the Rate of Stabilization

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(Received July 2, 1966)

In a previous paper, it was reported that the photodecomposition of menadione in aqueous solution was inhibited by the formation of the complex with various electron donors, and it was suggested that the complex formation among them might be attributed to charge-transfer force.

The relationship between the structure of the complex in electronic aspect and the rate of stabilization were investigated by a molecular orbital method described in this paper. As a result, it was concluded that suppression of the photodecomposition of menadione with various electron donors is due to the charge transfer complex formation among them.

It has previously been reported that the photodecomposition rate of menadione in aqueous solution was substantially decreased by the formation of complexes with various electron donors. It has been suggested in the preceding paper of this series that the complex formation might be attributed to the charge-transfer force.

On this assumption, the authors have investigated, in this paper, the relation between the structure of the complex in electronic aspect and the rate of stabilization, in order to contribute to get the solution in explaining the mechanism of stabilization with menadione. In the first place the net charge of menadione and of various electron donors were calculated, and next, the stabilization energy between various electron donors and menadione, and in addition the quantity of charge transfer which has been defined recently by Nagata, *et al.*[4] were calculated. As a result, the mechanism of stabilization was explained well by charge transfer complex formation between various electron donors and menadione.

## Method of Calculation and the Structure of the Charge Transfer Complex

Calculation was made by means of the simple LCAO MO method. The parameters of coulomb and resonance integrals for substituent groups are the same as the values cited in a previous paper.[5]

Being pointed out by Karreman,[6] the structure of the charge transfer complex may be determined by the electrostatic interactions predominantly when both of the components

1) This work was reported at the Meeting of Kanto Branch, Pharmaceutical Society of Japan, December 25, 1965.
2) Part II: *Chem. Pharm. Bull.* (Tokyo), **15**, 1791 (1967).
3) Location: *Ukima-machi, Kita-ku, Tokyo.*
4) C. Nagata, A. Imamura, K. Fukui, and H. Saito, *Gann*, **54**, 401 (1963).
5) Part I: *Chem. Pharm. Bull.* (Tokyo), **15**, 1796 (1967).
6) C. Karreman, *Ann. N.Y. Acad. Sci.*, **96**, 1029 (1962).

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have a net charge. The sterical orientations of menadione and various electron donors were determined in such a way that the electrostatic attraction among them became the greatest. Thus, the most conceivable orientation, as shown in Fig. 1, between various electron donors and menadione was considered. The places marked with circles indicate the location where the overlap of the molecular orbital is assumed to take place. Numerals in Fig. 1 are net charge of the molecules.

These results are summarized in Table I. If various electron donors and menadione are assumed to be orientated as shown in Fig. 1, the stabilization energy and the quantity of charge transfer are easily obtained.

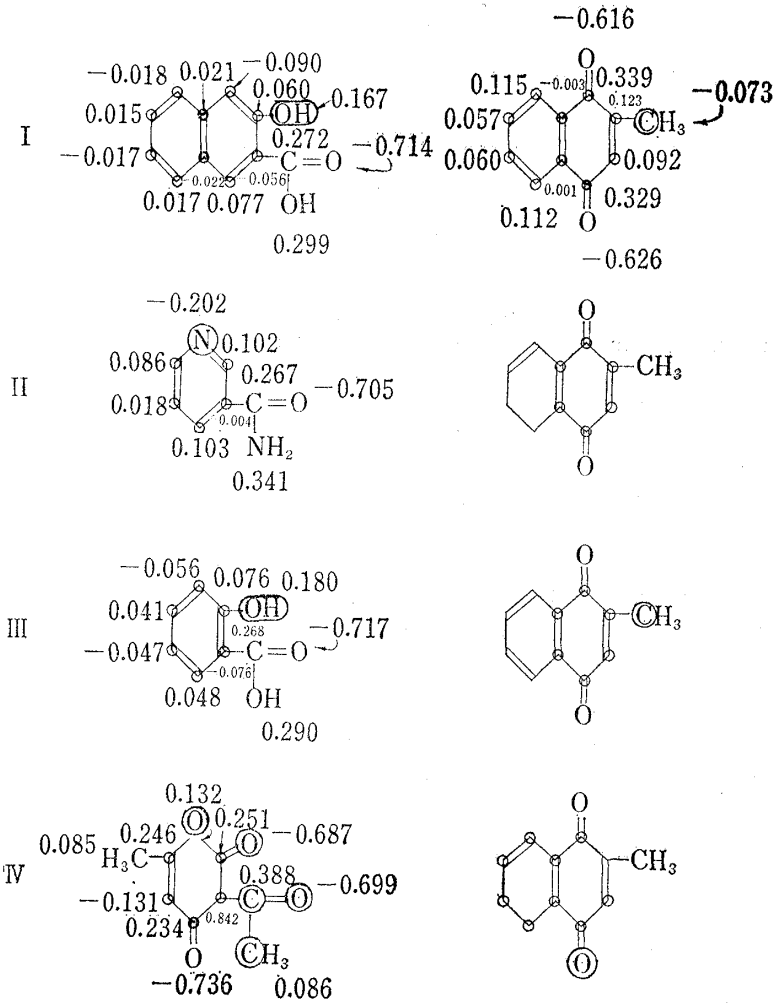


Fig. 1. The Most Probable Orientation between Menadione and Various Electron Donors determined from Consideration of an Electrostatic Interaction

If the charge transfer complex formation is represented schematically as shown in Fig. 2, the stabilization energy and the quantity of charge transfer will be given by the following formula (1) and (2), shown below respectively.

$$\delta E=-2\left[\sum_{j}^{\text{occ}}\sum_{k}^{\text{vac}}-\sum_{j}^{\text{vac}}\sum_{k}^{\text{occ}}\right]\frac{(c_r^j c_s^k l_1+c_i^j c_u^k l_2+\cdots\cdots)^2}{\varepsilon_{1j}-\varepsilon_{2k}}(\beta')^2 \qquad (1)$$

$$\delta Q=2\left[\sum_{j}^{\text{occ}}\sum_{k}^{\text{vac}}-\sum_{j}^{\text{vac}}\sum_{k}^{\text{occ}}\right]\frac{(c_r^j c_s^k l_1+c_i^j c_u^k l_2+\cdots\cdots)^2}{(\varepsilon_{1j}-\varepsilon_{2k})^2}(\beta')^2 \qquad (2)$$

where $c_r^j$ is a coefficient of the $r$th atomic orbital in the $j$th molecular orbital, $\varepsilon_{1j}$[7] is the

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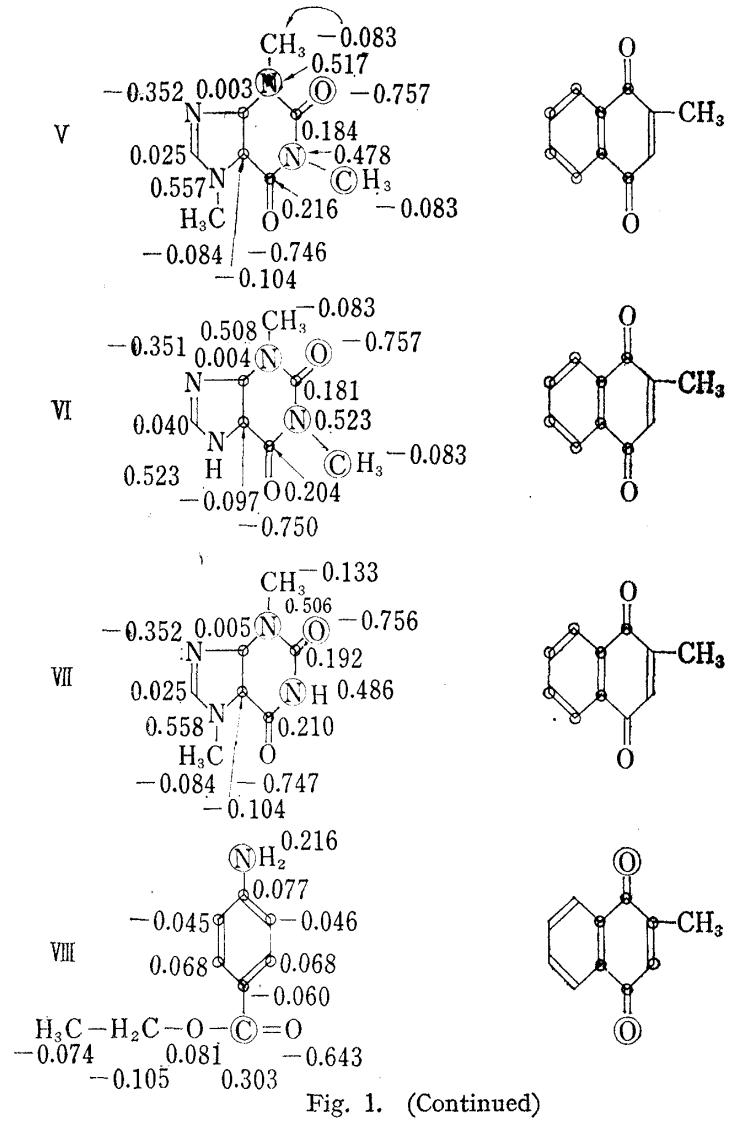


Fig. 1. (Continued)

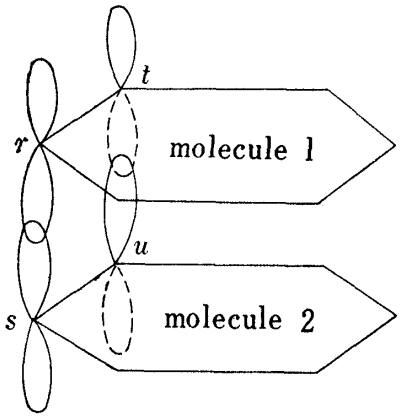


Fig. 2. Schematic Representation of $\delta$-$\delta$ Type Overlap of the Atomic Orbitals (2 p$\pi$)

energy level of the $j$th molecular orbital of molecule 1, and both $\sum^{occ}$ and $\sum^{vac}$ are the summation of the occupied and vacant orbitals respectively. $l_1\beta'$ is the resonance integral between the orbital at the $r$th atom of molecule 1 and the $s$th atom of molecule 2 as schematically shown in Fig. 2, where $\beta'$ is the magnitude of resonance integral between the atomic orbitals of carbon atoms of the charge transfer complex, the relative magnitude of resonance integrals can approximately be shown by the relative ratio of $l_1$ *etc.*[4]

## Results and Discussion

In Table II, the stabilization energy between various electron donors and menadione, and the quantity of charge transfer among them were calculated. The stabilization energy is a measure of the charge-transfer force, then the relationships between the stabilization energy and the free energy change or the enthalpy change of the complex formation which were obtained in the preceding paper,[5] were discussed. The results thus obtained are shown in Fig. 3 and 4.

Being expected, the elevation of the stabilization energy enhanced either the free energy change or the enthalpy change in the complex formation.

Next, the relationship between the rate of stabilization which described in a previous paper[2] and the stabilization energy was investigated. Being clearly shown in Fig. 5, the stabilization energy of the substances I—IV which show greater stabilizing ability are greater than that of the substances V—VIII showing smaller stabilizing ability. In addition, Fig. 6

7) $\varepsilon=\alpha+\lambda\beta$, where $\alpha$ is a coulomb integral of carbon atom in benzene, and $\beta$ is a resonance integral between the carbon atom in benzene. $\lambda$ is the parameter for the energy level of the molecular orbital.

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Table I. Atomic Location of Menadione where Overlap of the Molecular Orbital is Assumed to Occur

| | Compound | Atomic Location of Menadione[a] | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| I | β–Hydroxynaphthoic acid | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | | | ○ |
| II | Nicotinamide | ○ | ○ | ○ | ○ | | | | | ○ | ○ | | | |
| III | Salicylic acid | ○ | ○ | ○ | ○ | | | | | ○ | ○ | | | ○ |
| IV | Dehydroacetic acid | ○ | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | | ○ | |
| V | Caffeine | ○ | | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | | | |
| VI | Theophylline | ○ | | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | | | |
| VII | Theobromine | ○ | | | | ○ | ○ | ○ | ○ | ○ | ○ | | | |
| VIII | Ethyl aminobenzoate | ○ | ○ | ○ | ○ | | | | | | | ○ | ○ | |

a)

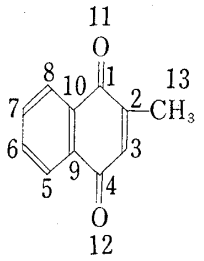


Table II. Reactivity Indices

| Compound | $\delta E$ in units of $-(\beta')^2/\beta$ | $\delta Q$ in units of $(\beta'/\beta)^2$ |
|---|---|---|
| β–Hydroxynaphthoic acid | 2.3372 | 2.4149 |
| Salicylic acid | 1.6109 | 0.6092 |
| Ethyl aminobenzoate | 1.1946 | 0.4670 |
| Theophylline | 1.0198 | 0.2196 |
| Caffeine | 0.9966 | 0.1866 |
| Dehydroacetic acid | 0.9575 | 0.1223 |
| Nicotinamide | 0.7712 | 0.1740 |
| Theobromine | 0.6236 | 0.0943 |

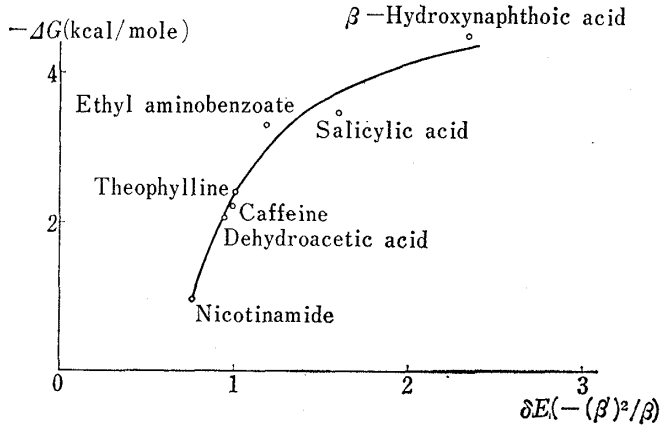


Fig. 3. Relation between Free Energy Change ($\Delta G_{27°}$) and Stabilization Energy ($\delta E$)

shows that stability of menadione tends to be increased by the elevation of the quantity of charge transfer.

Hence, it is concluded by these facts that suppression of photodecomposition of menadione with various electron donors is due to the charge transfer complex formation among them.

There are obviously other factors taking part in the complex formation of general organic substances: steric hindrance of molecules, contribution of non-bonding electron pairs or the influence of Van der Waal's force *etc.* It is not proper, therefore, to discuss an intermolecular complex formation only in terms of the above findings. Nevertheless, it is assumed that these findings men-

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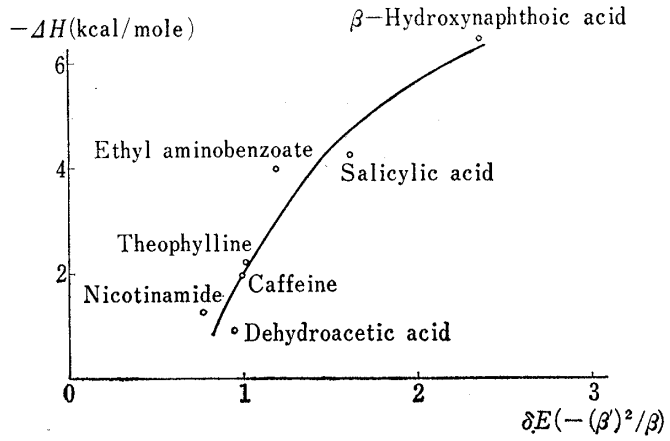


Fig. 4. Relation between Enthalpy Change ($\Delta H$) and Stabilization Energy ($\delta E$)

tioned above are frequently useful in dealing with such a molecular complex which is formed due to the mutual reactions of $\pi$-electrons in the related molecules.

Although complexation in solution does not always result in the stabilization of pharmaceutical preparations concerned, it may accelerate decomposition, such a case being rarely encountered insofar as our experience is concerned. Rather, complexation in solution has proved to have a favorable effect on their stability. Therefore, the stabilization energy which might be a measure of the charge transfer complex formation will become in future one of the indicators to find out stabilizers of pharmaceutical preparations.

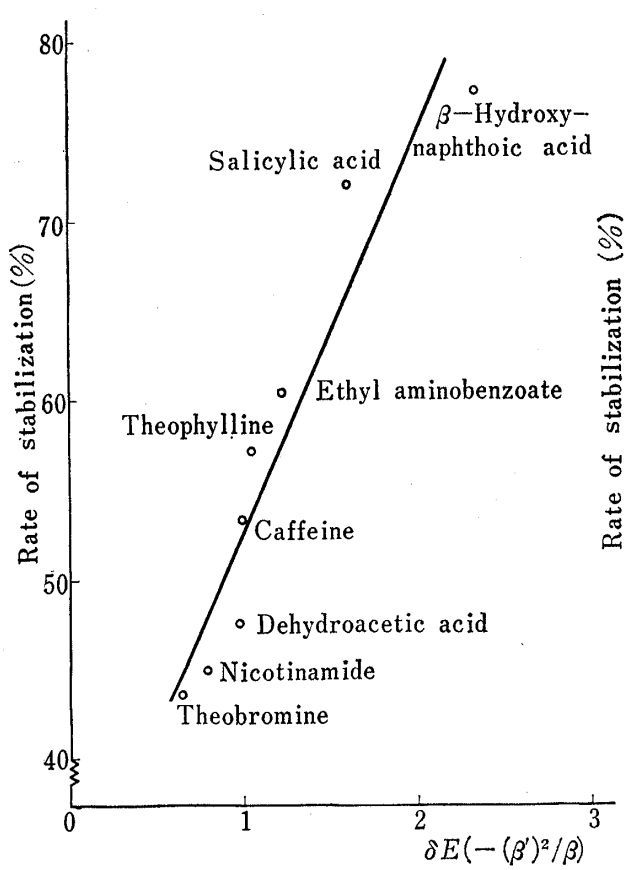


Fig. 5. Relation between Rate of Stabilization and Stabilization Energy ($\delta E$)

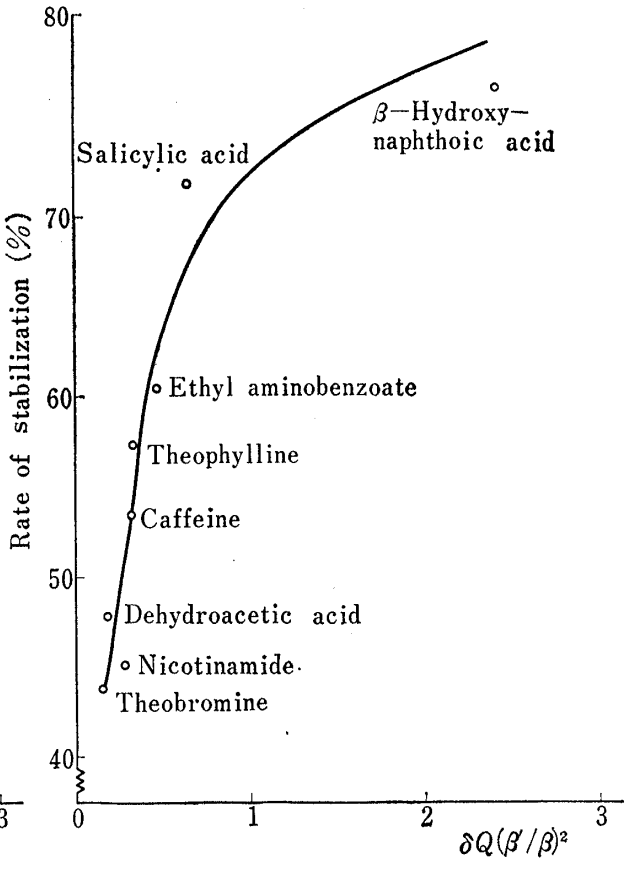


Fig. 6. Relation between Rate of Stabilization and the Quantity of Charge Transfer ($\delta Q$)

**Acknowledgement** The authors would like to express their deep gratitude to Dr. C. Nagata, Chief of Department of Biological Physics, the National Cancer Center Research Institute, for his kind guidance.

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