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REGRESSION ANALYSIS IN THE CHARACTERIZATION OF HYDROGEN-BONDED COMPLEX SYSTEM INVOLVING 2-PYRIDONE IN TERMS OF MELTING POINTS BEFORE AND AFTER COMPLEXATION†

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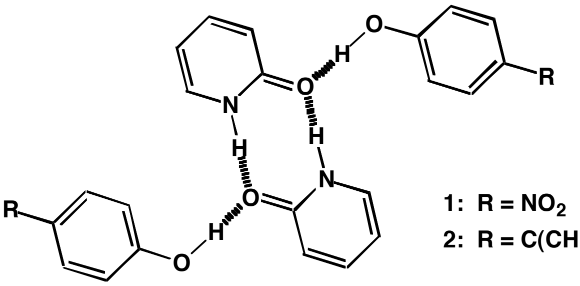
<u>Abstract</u> ---- A series of crystalline molecular complexes between 2-pyridone and hydroxy compounds were prepared. Regression analysis utilizing melting points before and after complexation is also discussed.

Molecular recognitions based on weakly interactive forces have been recognized as crucial phenomena in view of homeostases of lifeforms in recent years. Among such recognitions, a hydrogen bonding is most frequently evaluated, since it is indispensable for nucleic acid to hybridize and function. The key component in hydrogen-bond formation of biomolecules can be defined as an amide (or lactam) structure.[1]



1: R = NO_2
2: R = $C(CH_3)_2C_6H_4OH$ (*p*)

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†Dedicated to the memory of late Professor Kenji Koga.

Previously we reported the formation of a molecular crystal between 2-pyridone (2-pyridinol) and *p*-nitrophenol (**1**) in 1:1 ratio, where two pyridone units formed a cyclic dimer and phenolic hydroxyl groups tangled each of amide carbonyls through hydrogen bondings.[2,3] This "2:2 construction module" can be found in the related molecular complex system involving 2-quinolone reported by Toda and co-workers.[4] In connection, we found that a series of endocrine disruptive phenol derivatives also formed molecular crystals with 2-pyridone, among which the complex between 2-pyridone and bisphenol A (**2**) possessed structural tendencies similar to those described above.[5] On the other hand, we reported on the hydrogen-bonded complex-forming ability of triphenylphosphine with 6-chloro-2-pyridinol (enol form), too.[6]

From the standpoint of environmental detoxification, our desirable near-future goal is to establish some strategy/tactics to design and synthesize novel molecular captors, which can selectively/specifically immobilize the compound whenever its structure is given. However, the ambition has often been obstacled by a number of difficulties existed in at once the obtention of some useful information out of solid-state spectral measurements and the lack of methods to execute them into some working hypotheses to go forth. Altough we tentatively proposed that the "not-applied-for-*X*-Ray molecular crystals" in our previous work would possess structures based on hydrogen-bonded dimeric pyridones too,[5] direct evidences through establishments of crystallography have been difficult to reach. It is evidently necessary to grasp some new concept with which we can quickly characterize a series of molecular complexes into the circumstantial evidence of their class consistency. If some useful indices are available out of it, we would be able to choose a "most probable" molecular captor to a given guest among a number of (commercially) available candidates (2-pyridone derivatives, *etc*.). In this study, we propose a novel method to define the structural consistency of a series of molecular complexes based on the regression analysis utilizing melting point data of guests before and after complexation.

Starting materials appeared in the present study were purchased and used without further purifications. Molecular crystals involving 2-pyridone (mp 107°C) were prepared according to the procedures we reported previously.[5] Purity and molar ratio between 2-pyridone and hydroxylic guests were determined by ^{1}H NMR spectra. When components were not in 1:1 ratio, crude samples were subjected to recrystallization. Melting points (mp's) were uncorrected values. In the present study, molecular crystals with <5 °C of mp range were adopted as complexes (in total 31 samples thus far). In order to make things clear, mid-point values of mp's were adopted for plotting. For example, when mp of a hydroxylic guest (x axis) was 64-66 °C and that of complex (y axis) was 108-110 °C, then $(x, y) = (65, 109)$ was plotted on an x-y plane. Results are shown as Figure 1.

The following tendencies were apparent.

(a) Distribution pattern of data points on the x-y plane was thoroughly in the shape of a convex lens. Therefore, a regression line was adapted to the set of given data, according to the standard procedure,[7] to afford a positively proportional equation ($y = 44.602 + 0.588\,x$) together with a large regression coefficient ($r_{xy} = 0.87$). If all of these mp trends were merely derived from the mp depression upon mixing of different compounds, the regression line *must* be parallel to x axis, since molar ratio of components are always 1:1. The result obtained in the present study indicated that mp's of complex are directly proportional to that of hydroxylic guests as a whole. These trends would be the circumstantial evidence that complexes possess some common "construction module" throughout.

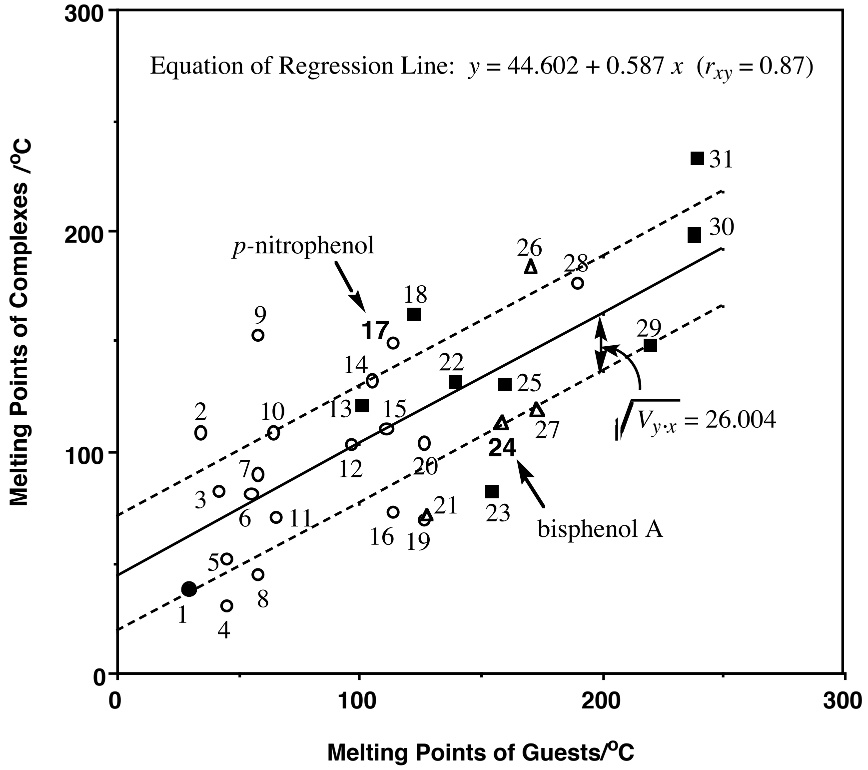

Figure 1. Plot of melting points of guests before and after complexation with 2-pyridone.

Symbols are as follows: ●: alcohol; ○: phenol; ■: benzoic acid; △: diphenol.
Names of guests were as follows:
1: *m*-nitrobenzyl alcohol (MNBA); 2: pentafluorophenol;
3: 2,4-dichlorophenol (#); 4: 2-nitrophenol (#); 5: 4-trifluoromethylphenol;
6: 2,3-dichlorophenol; 7: 2,5-dichlorophenol; 8: *p*-*n*-nonylphenol (#);
9: 2,3,5-trichlorophenol; 10: 2,4,6-trichlorophenol (#);
11: 3,4-dichlorophenol (#); 12: 3-nitrophenol; 13: pentafluorobenzoic acid;
14: 2-chloro-4-nitrophenol; 15: 4-cyanophenol; 16: 4-hydroxybenzaldehyde;
17: *p*-nitrophenol ($); 18: 3-fluorophenol; 19: 3-pyridinol;
20: 3-methyl-4-nitrophenol; 21: 2-*tert*-butylhydroquinone (#);
22: 3-nitrobenzoic acid; 23: 3-chlorobenzoic acid; 24: bisphenol A (#);
25: salicylic acid; 26: diethylstilbestrol (#), 27: hydroquinone (#);
28: pentachlorophenol (#); 29: 4-cyanobenzoic acid; 30: 4-nitrobenzoic acid;
31: 4-chlorobenzoic acid.
(#) Ref. 5. ($) Refs. 2 and 3.

(b) Although four different types of guest compounds were utilized (alcohol, phenol, benzoic acid, and diphenol) to cover up a wide range of mp area, the distribution pattern of data points did not appear as a jumble of wheat and tares but rather as a systematic settlement. Especially, benzoic acids, widely known by their strongly hydrogen-bonded dimeric structures and lay in relatively higher mp area in the present study, did not appear to drop out from the trends as a whole. These results could be explicable if only relatively weaker intermolecular hydrogen-bondings (*i.e.*, C=O…H-N of 2-pyridone and O-H…O-H of hydroxylic guests) were broken and replaced by those to build up a 2:2 construction module.

(c) Standard deviation value in the mp of complex was calculated as 26.004 (°C).[7] Considering that the *y* axis intercept was 44.602 (°C), it is assumed that the immobilization of liquid sample by solidification with use of 2-pyridone itself may be difficult.

(d) As to the cause of deviation described in (c), our first two crystallographically analyzed complexes may be clues for interpretation. Thus, mp data point from *p*-nitrophenol (#17) was located above the regression line, whereas that from bisphenol A (#24) was inversely located. Focusing on the crystal packings of these complexes, stackings between dimeric 2-pyridone rings are large in the complex between 2-pyridone and *p*-nitrophenol (**1**; Figure 2), which are relatively smaller in the complex between 2-pyridone and bisphenol A (**2**; Figure 3). Although some more crystals should successfully be solved before the obtention of a clean-cut proof, we anticipate that these features are the largest possible cause of deviation in the present stage.

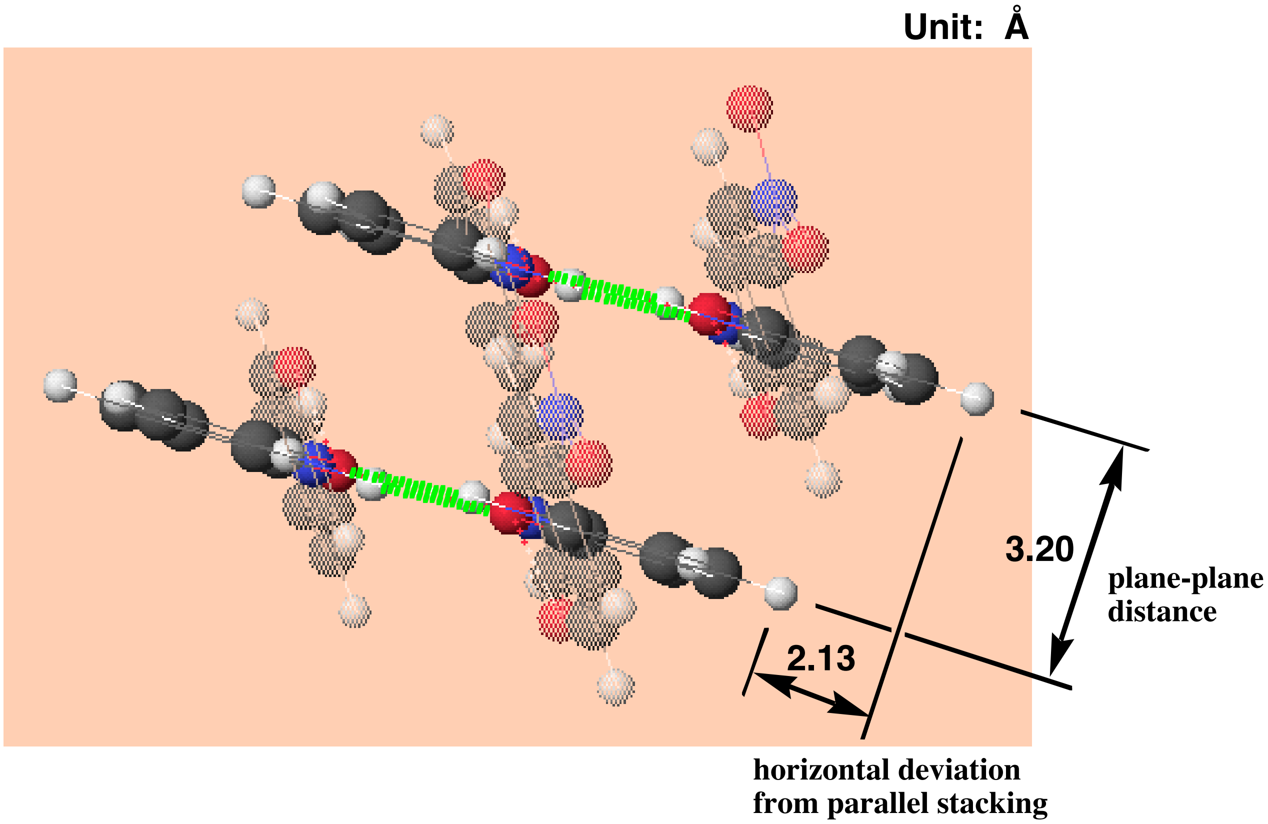

Figure 2. Side view of the complex between 2-pyridone and *p*-nitrophenol

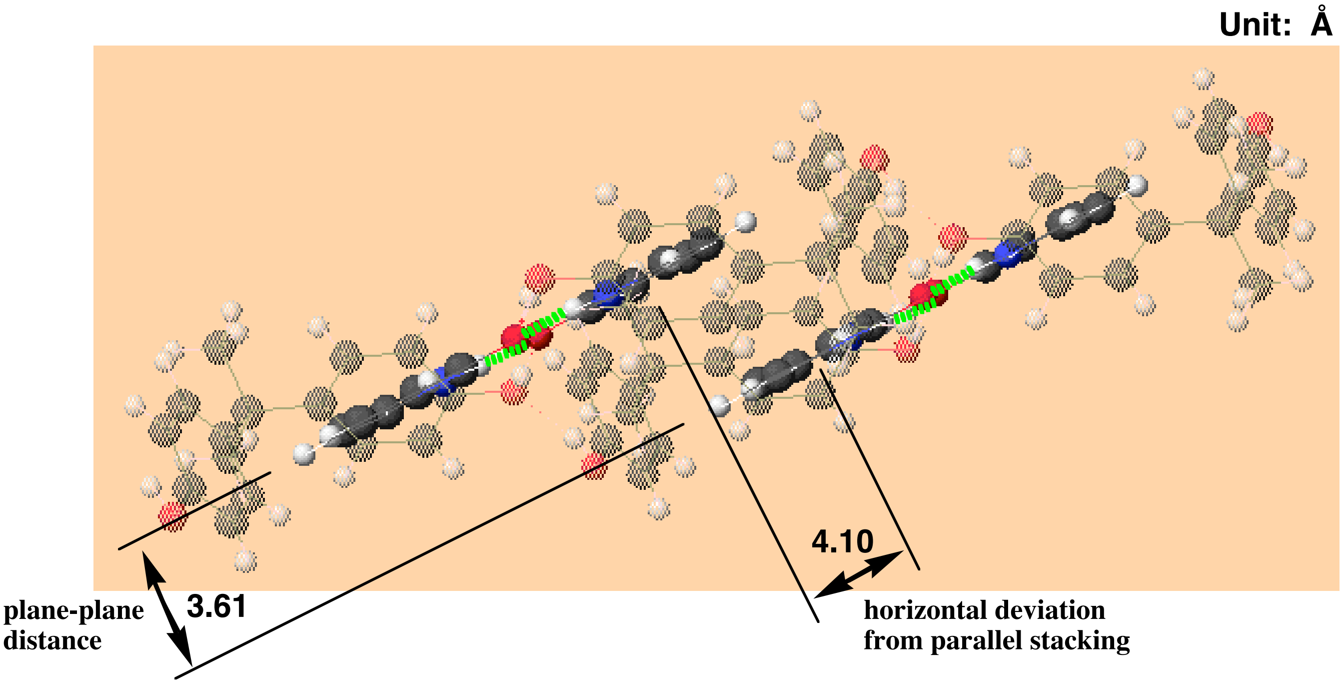

Figure 3. Side view of the complex between 2-pyridone and bisphenol A

Our results would provide a tacit device in the quick characterization of a series of molecular complexes in terms of a sole compound (2-pyridone in the present work) whenever other dependable indices are difficult to reach. Further investigations using parameters obtained by regression analysis are now in progress in our laboratories.

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