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CAPTURE OF PHENOLIC ENDOCRINE DISRUPTORS WITH 2-PYRIDONE†

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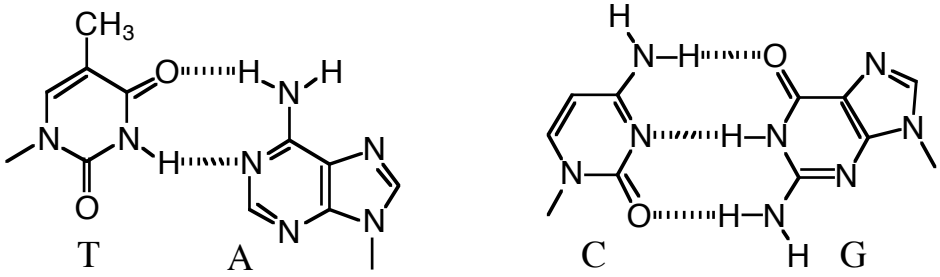
Abstract — Crystalline molecular complexes between phenolic endocrine disruptors and 2-pyridones were prepared in fairly good isolated yields through simple procedures. Crystal structure of a complex between bisphenol A and 2-pyridone (1:1 molar ratio) is also described.

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]



A decade ago, in due course of a study on the reaction of *p*-nitrophenol with 2-trifluoroacetoxypyridine, our colleague Keumi by chance isolated crystalline material which was proved to be a molecular crystal, containing *p*-nitrophenol and 2-pyridone in 1:1 ratio.[2]

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†Dedicated to Professor Yuichi Kanaoka on his 75th birthday.

The continuous search was, however, unavoidably stopped due to Keumi's untimely death. In addition, lack of motivation for capturing of phenol at that time deprived us of chance for further study. The recent success in solving the crystal structure of a complex between *p*-nitrophenol and 2-pyridone triggered a reinvestigation of the subject described above.[3] We thus focused our attention on phenolic endocrine disruptors.[4] In this paper, we wish to report the molecular compounds formed from phenolic endocline disruptors and 2-pyridones.

Preparation of molecular crystals was examined with commercially available materials. General procedure is as follows: to a stirred suspension of 2-pyridone (2-PyOH; 5 mmol) in ether (25 mL) was added phenol (5 mmol) over a few minutes, and the mixture was further stirred overnight; the mixture was either filtrated (for suspension, method A) or evaporated *in vacuo* (for clear solution, method B) to give a complex. When method A provided merely the recovered small quantity of 2-pyridone owing to the high solubility of the complex, both 2-pyridone and phenol (5 mmol each) were either dissolved in chloroform (25 mL) and evaporated *in vacuo* (method C) or directly ground for a few minutes using a mortar and a pestle (method D). The samples possessing "narrow range" melting point were adopted as molecular crystals in the present study. Ratios of the components in the samples were checked by ^{1}H NMR spectra. Results are shown in Table 1.

2-Pyridone turns out to be surprisingly useful "captor" for a variety of phenols including well-known endocrine disruptors such as pentachlorophenol (Run 1), 2,4,6-trichlorophenol (Run 2), 3,4-dichlorophenol (Run 4), *p*-*n*-nonylphenol (Run 6), diethylstilbestrol (Run 9) and bisphenol A (Run 10), complexes of which form crystalline materials with specific melting points. In the case of methyl *p*-hydroxybenzoate (Run 11) and 4-*tert*-butylphenol (Run 12), the use of chlorinated 2-pyridone analogues (5-Cl- or 6-Cl-2-PyOH, respectively) but not with 2-pyridone itself led to success, suggesting that the dipole-dipole interaction would play a crusial role in complexation.

Crystal structure of a complex composed of 2-pyridone and bisphenol A (Run 10) is depicted in Figure 1.[5] The molecular crystal possesses following four structural features. (a) Two 2-pyridone units, related through an inversion center, forms a dimer by hydrogen bonds [N(1)•••O(1)' at (2-*x*, -*y*, 1-*z*), 2.840 (7) Å; N(1) □ H(1)•••O(1)', 177(5)°]. (b) A 2-pyridone and a bisphenol connected through a hydrogen bond [O(3)•••O(1)" at (*x*, *y*, *z*+1), 2.659(7) Å; O(3) □ H(13)•••O(1)", 170(7)°] constitutes a structural unit of 1:1. In total, this crystal can be defined as a 2:2 complex around the inversion center, analogous to our previous work.[3] (c) The neighboring structural units linked through a hydrogen bond [O(2)•••O(3)"' at (*x*, *y*, *z*-1), 2.763(8) Å; O(2) □ H(6)•••O(3)"', 164(8)°] forms an infinite pillar structure through the entire crystal. In the crystal structure of bisphenol A, phenolic OH groups perform at once donors (hydrogens) and acceptors (oxygens), giving a three-dimensional intermolecular bisphenol network.[6] Different from the sole crystal, only one donor hydrogen and one acceptor oxygen are characteristically used in every molecule of bisphenol A of the complex.

Other materials possessing a molar ratio of 1:1 in the present study probably have the structures based on hydrogen-bonded dimeric pyridones. Further studies are currently underway.

Table 1. Formation of Molecular Crystals

Run	Phenol		Pyridone		Method	Complex		
	Compound	mp/℃	Compound	mp/℃		Yield/%	mp/℃	mol. ratio
1	C_6Cl_5OH	190	2-PyOH	107	A	85	175-178	1:1
2	2,4,6-Cl_3-C_6H_2OH	67	2-PyOH	107	A	84	152-154	1:1
3	2,4-Cl_2-C_6H_3OH	127	2-PyOH	107	B	quant.	80-84	1:1
4	3,4-Cl_2-C_6H_3OH	66	2-PyOH	107	A	91	75-83	1:1
5	2-NO_2-C_6H_4OH	45	2-PyOH	107	D	quant.	28-32	1:1
6	*p*-*n*-Nonylphenol	45	2-PyOH	107	B	quant.	43-46	1:1
7	Hydroquinone (HQ)	173	2-PyOH	107	D	quant.	118-121	1:1
8	2-^{t}Bu-HQ	127	2-PyOH	107	D	quant.	63-70	1:1
9	Diethylstilbestrol	169	2-PyOH	107	D	quant.	182-186	1:1
10	Bisphenol A	156	2-PyOH	107	C	quant.	112-115	1:1
11	4-MeO_2C-C_6H_4OH	126	5-Cl-2-PyOH	164	C	quant.	100-105	1:1
12	4-^{t}Bu-C_6H_4OH	99	6-Cl-2-PyOH	130	C	quant.	64-68	1:1

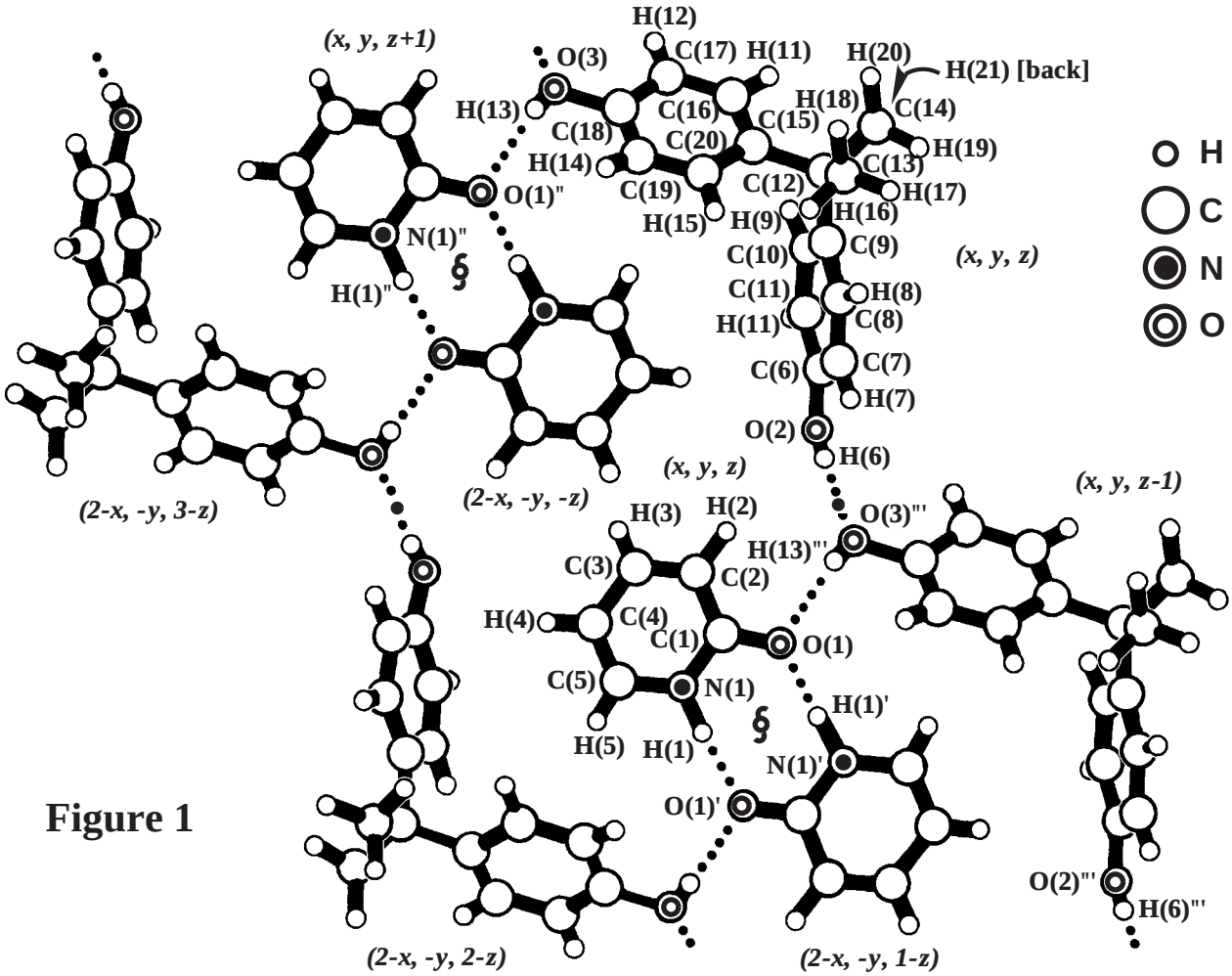

Figure 1

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5. A single crystal for an *X*-Ray study was obtained by slow evaporation of *n*-hexane-chloroform solution. $C_{20}H_{21}NO_3$, M = 323.39, space group $P2_1$, a = 10.420(2) Å, b = 15.817(2) Å, c = 10.671(1) Å, V = 1758.0(4) Å^3, Z = 4, D_c = 1.222 g/cm^3, $F(000)$ = 688, □(Cu K_a) = 1.54178 Å. Crystallographic data (excluding the structure factor) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-164219. Copies of the data can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+44)223-33603; e-mail: deposit@ccdc.cam.ac.uk].
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