

The Mechanism of the Enantioselective Photocyclization of 2-Piperidone in the Clathrate Crystal

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The achiral molecules of *N*-(arylcarbonylmethyl)-2-piperidones form 1:1 host–guest complexes with the chiral host molecule derived from tartaric acid. The guest molecules in the clathrate crystals are converted into the chiral 7-aryl-7-hydroxy-1-azabicyclo[4.2.0]octan-2-one derivatives with high optical yields on exposure to a high pressure Hg lamp. The crystal structures and absolute configurations of the clathrate compound (**5a**), which consists of (–)-(2*R*,3*R*)-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.5]decane (**4**) and *N*-(*p*-bromophenylcarbonylmethyl)-2-piperidone (**1a**), and of the chiral product of (–)-(6*S*,7*S*)-7-hydroxy-1-azabicyclo[4.2.0]octan-2-one (**2a**) were determined by X-rays. (**5a**) C₃₄H₃₄O₄·C₁₃H₁₄NO₂Br, fw=802.81, monoclinic *C*2, *a*=24.186(3), *b*=9.550(3), *c*=19.711(3) Å, β=116.18(1)°, *V*=4086(2) Å³, *Z*=4, final *R* became 0.047. (**2a**) C₁₃H₁₄NO₂Br, fw=296.16, orthorhombic, *P*2₁2₁2₁, *a*=7.047(2), *b*=31.151(3), *c*=5.696(2) Å, *V*=1250.3(5) Å³, *Z*=4, final *R* became 0.039. The enantioselectivity of the photocyclization is clearly explained by the two structures if we assume that the reaction proceeds topochemically.

The asymmetric induction can be performed with high chemical and optical yields in a chiral crystal environment.¹⁾ The achiral α-oxoamides included in chiral clathrate crystals are converted to the chiral β-lactams with very high optical yield.²⁾ Moreover, the chiral β-lactams are obtainable from the achiral α-oxoamide without any host molecules if the crystal of oxoamide has a chiral space group.³⁾

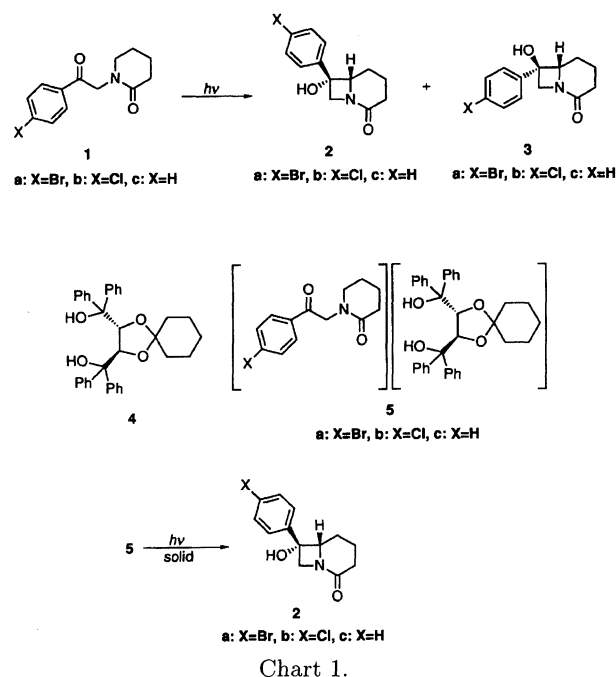
In the synthetic studies of diastereomeric 7-hydroxy-1-azabicyclo[4.2.0]octan-2-one, **2** and **3** respectively, the photocyclization of *N*-(arylcarbonylmethyl)-2-piperidone, **1**, in *t*-BuOH solution was found to be a very useful method, although the reaction proceeds non-stereoselectively.^{4,5)} Such low stereoselectivity probably results from the rotational freedom around the exocyclic C–N bond in the reactant molecule.

Recently it was found that the reactant molecule, **1**, easily forms a clathrate complex, **5**, with the host molecule, **4**,⁵⁾ which is prepared from tartaric acid (Chart 1).^{6,7)} On exposure to a high pressure Hg lamp at room temperature, the powdered sample of the clathrate crystals gave **2** with high optical yield.⁵⁾

In order to elucidate the reason why such high stereoselectivity can be obtained, the single crystals of a clathrate complex, **5a**, and the product, **2a**, were prepared. This paper reports the crystal structures and absolute configurations of these two crystals and discusses the mechanism of the asymmetric photocyclization.

Results and Discussion

Figure 1 shows the crystal structure of **5a** viewed along the *b*-axis. The guest molecule is hydrogen bonded to the host molecule through O(2)⋯H(103)–O(3). The distances and angle of O(2)⋯H(103), O(2)⋯O(3), and O(2)⋯H(103)–O(3) are 1.72 Å, 2.747(6) Å, and 159°, respectively. The host molecule also forms an intramolecular hydrogen bond, through O(3)⋯H-

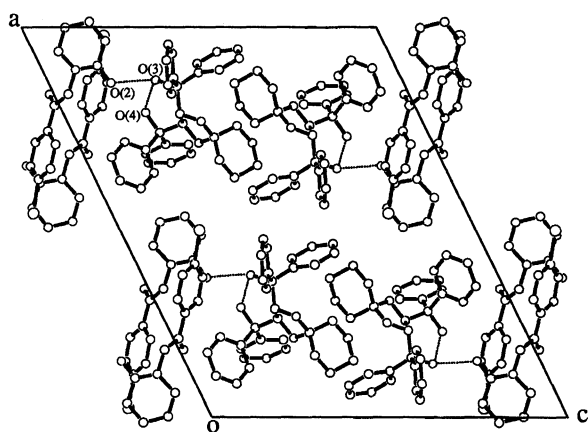


(104)–O(4). The distances and angle of O(3)⋯H(104), O(3)⋯O(4), and O(3)⋯H(104)–O(4) are 1.74 Å, 2.693(6) Å and 155°, respectively.

The molecular structure of **5a** with the numbering of the atoms is shown in Fig. 2. Some selected bond distances and angles of **5a** are listed in Table 1. The structure of the host molecule is very similar to that of the host molecule in the clathrate crystal with the same host molecule reported in the previous work.⁸⁾ The torsion angles of the diol moiety are as follows: C(16)–C(14)–C(15)–C(17); –96.6(6)°, C(15)–C(14)–C(16)–O(3); 60.5(7)°, and C(14)–C(15)–C(17)–O(4); 73.3(6)°, the corresponding values of the previous work are –93.5(3), 60.6(3), and 72.5(3)°, respectively.

Table 1. Selected Bond Distances ($\text{\AA}$) and Angles ($^\circ$) of **5a** and **2a**

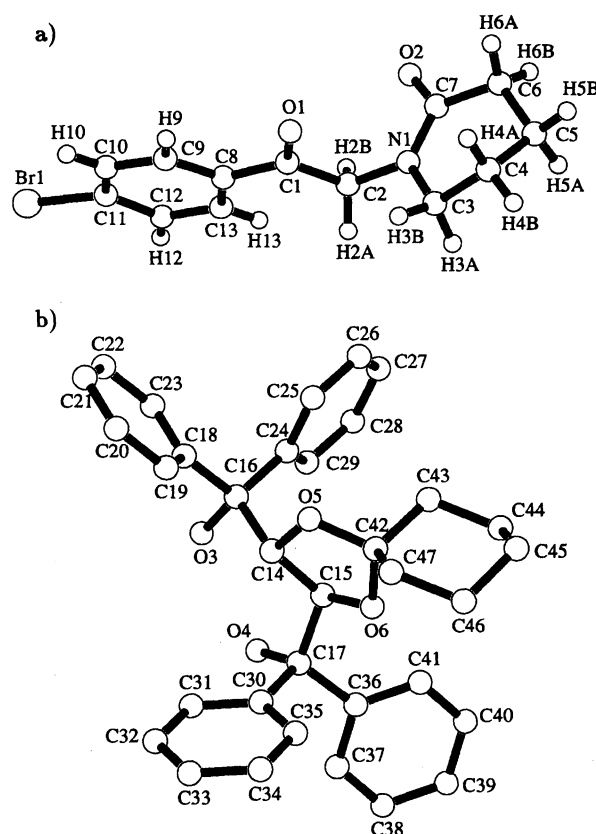
	5a	2a		5a	2a
O(1)–C(1)	1.212(9)	1.418(5)	C(2)–N(1)–C(3)	116.1(6)	94.1(3)
O(2)–C(7)	1.245(8)	1.229(6)	C(2)–N(1)–C(7)	119.2(6)	130.0(5)
N(1)–C(2)	1.446(8)	1.471(5)	C(3)–N(1)–C(7)	124.7(6)	127.9(4)
N(1)–C(3)	1.458(9)	1.472(6)	O(1)–C(1)–C(2)	121.5(8)	107.2(4)
N(1)–C(7)	1.346(9)	1.328(6)	O(1)–C(1)–C(3)	—	111.0(4)
C(1)–C(2)	1.496(11)	1.570(6)	O(1)–C(1)–C(8)	121.2(9)	111.9(4)
C(1)–C(3)	—	1.557(6)	C(2)–C(1)–C(3)	—	87.1(3)
C(1)–C(8)	1.495(10)	1.483(6)	C(2)–C(1)–C(8)	117.2(8)	119.5(4)
C(3)–C(4)	1.488(12)	1.494(6)	C(3)–C(1)–C(8)	—	117.6(4)
C(6)–C(7)	1.477(9)	1.494(7)	N(1)–C(2)–C(1)	113.1(7)	87.5(3)
O(3)–C(16)	1.444(7)	—	N(1)–C(3)–C(1)	—	87.9(3)
O(4)–C(17)	1.440(7)	—	N(1)–C(3)–C(4)	111.9(7)	112.5(4)
O(5)–C(14)	1.431(7)	—	C(1)–C(3)–C(4)	—	124.0(4)
O(5)–C(42)	1.429(7)	—	O(2)–C(7)–N(1)	119.8(6)	122.5(6)
O(6)–C(15)	1.434(6)	—	N(1)–C(7)–C(6)	119.6(7)	115.4(5)
O(6)–C(42)	1.411(7)	—	O(5)–C(14)–C(15)	104.7(4)	—
C(14)–C(15)	1.539(9)	—	O(5)–C(14)–C(16)	109.6(4)	—
C(14)–C(16)	1.555(8)	—	C(15)–C(14)–C(16)	116.8(5)	—
C(15)–C(17)	1.548(8)	—	O(6)–C(15)–C(14)	101.6(5)	—
			O(6)–C(15)–C(17)	107.7(4)	—
			C(14)–C(15)–C(17)	117.6(5)	—
			O(3)–C(16)–C(14)	105.6(5)	—
			O(4)–C(17)–C(15)	107.3(4)	—

Fig. 1. Crystal structure of **5a** viewed along the *b*-axis. Broken lines indicate the hydrogen bonds.

The benzoyl moiety is almost planar, within 0.18 $\text{\AA}$, and the lactam moiety is almost perpendicular to the benzoyl moiety. The torsion angles of C(3)–N(1)–C(2)–C(1) and C(7)–N(1)–C(2)–C(1) are 85.7(9) and $-94.6(9)^\circ$, respectively.

The above conformation of the guest molecule allows some intramolecular short contacts. The distances of C(1)···C(3) and O(1)···H(3B) are 3.24(1) and 2.82 $\text{\AA}$, respectively. These distances are significantly shorter than the sum of the van der Waals radii of the corresponding atoms, 3.50 and 2.95 $\text{\AA}$.

Figure 3 shows the crystal structure of **2a** viewed along the *c*-axis. The hydrogen bonds are formed between O(2)···H(101)–O(1). The distances and angle of O(2)···H(101), O(2)···O(1), and O(2)···H(101)–O(1)

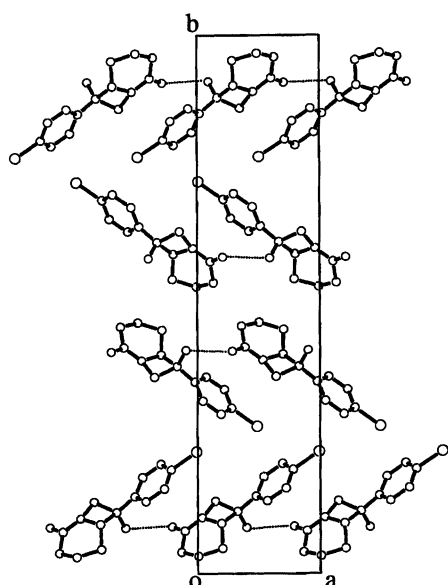
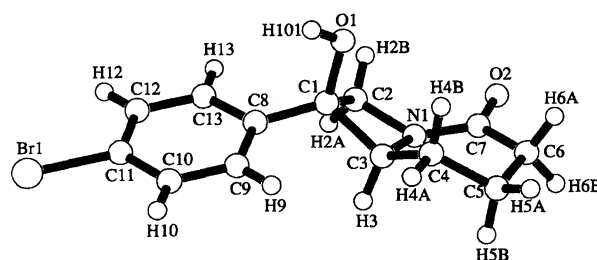
Fig. 2. Molecular structures of a) the guest molecule and b) the host molecule in **5a**.

are 1.91 $\text{\AA}$, 2.718(5) $\text{\AA}$ and 171° , respectively.

Figure 4 shows the molecular structure of **2a** with the

Table 2. Crystal Data and Experimental Conditions

	5a	2a
Chemical formula	$C_{34}H_{34}O_4 \cdot C_{13}H_{14}NO_2Br$	$C_{13}H_{14}NO_2Br$
Formula weight	802.77	296.16
Crystal system	Monoclinic	Orthorhombic
Space group	$C2$	$P2_12_12_1$
Z	4	4
$a/\text{\AA}$	24.186(3)	7.047(2)
$b/\text{\AA}$	9.550(3)	31.151(3)
$c/\text{\AA}$	19.711(3)	5.696(2)
$\beta/^\circ$	116.18(1)	—
$V/\text{\AA}^3$	4086(1)	1250.3(5)
$D_x/\text{Mg m}^{-3}$	1.305	1.573
Diffractometer	AFC-7S	AFC-7S
Radiation	Mo $K\alpha$	Mo $K\alpha$
$\lambda/\text{\AA}$	0.71073	0.71073
$\mu(\text{Mo } K\alpha)/\text{mm}^{-1}$	1.056	3.277
$F(000)$	1680	600
Crystal description	Plate-like	Plate-like
Crystal dimensions/ mm^3	$0.3 \times 0.3 \times 0.5$	$0.1 \times 0.5 \times 0.5$
T/K	296	296
$2\theta_{\text{max}}/^\circ$	50	55
Range of h , k , and l	$-28 \leq h \leq 23$ $0 \leq k \leq 10$ $0 \leq l \leq 23$	$0 \leq h \leq 9$ $0 \leq k \leq 40$ $0 \leq l \leq 7$
Scan technique	$\omega/2\theta$	ω
Scan width/ $^\circ$	$1.26 + 0.35 \tan \theta$	$0.94 + 0.35 \tan \theta$
Scan rate/ $^\circ(\omega) \text{ min}^{-1}$	8	16
Independent reflections	3350	1709
Observed reflections [$F_o^2 > 0$]	2849	1461
$R(F)(I > 2\sigma I)$	0.047	0.039
$wR(F^2)(I > 2\sigma I)$	0.093	0.068
S	1.007	1.031
Extinction coefficient	0.0020(3)	0.0034(7)
$(\Delta/\sigma)_{\text{max}}$	0.000	0.001
$\Delta\rho/\text{e } \text{\AA}^{-3}$	-0.24, 0.22	-0.23, 0.27

Fig. 3. Crystal structure of **2a** viewed along the c -axis. Broken lines indicate the hydrogen bonds.Fig. 4. Molecular structure of **2a**.

numbering of the atoms. The absolute configurations of the two chiral carbons, C(1) and C(7), are *S*. Some selected bond distances and angles of **2a** are listed in Table 1.

Let us consider from the structure of the guest molecule in **5a**: the H(3B) atom is abstracted by O(1) to form a hydroxyl group if the photoreaction occurs as observed in *t*-BuOH solution.^{4,5} H(3B) is closer with O(1) than H(3A), the corresponding distances of O(1)···H(3A) and O(1)···H(3B) being 4.01 and 2.82 Å, respectively. The C(3) atom seems to attack to C(1)

Table 3. The Final Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($B_{eq}/\text{\AA}^2$) for **5a**

Atom	<i>x</i>	<i>y</i>	<i>z</i>	B_{eq}
Br(1)	4781(1)	367	2225(1)	10.7
O(1)	1721(3)	-1007(8)	134(3)	7.1
O(2)	1429(2)	121(7)	-1773(3)	5.8
O(3)	1359(2)	-1158(5)	6944(2)	3.4
O(4)	2190(2)	-3175(5)	7668(2)	4.0
O(5)	2420(2)	165(5)	6228(2)	3.2
O(6)	2982(2)	-1836(5)	6601(2)	3.2
N(1)	1092(3)	912(7)	-950(3)	5.0
C(1)	2007(4)	38(11)	142(4)	5.1
C(2)	1718(4)	1209(10)	-405(5)	5.6
C(3)	614(4)	1231(13)	-712(5)	8.8
C(4)	12(4)	594(18)	-1225(6)	10.9
C(5)	-141(4)	716(25)	-2003(6)	12.0
C(6)	348(3)	97(12)	-2193(4)	6.8
C(7)	988(3)	377(10)	-1627(4)	5.1
C(8)	2673(4)	188(11)	685(4)	4.8
C(9)	2963(5)	-848(11)	1198(5)	6.2
C(10)	3583(5)	-799(13)	1667(5)	7.1
C(11)	3915(4)	309(15)	1616(5)	6.6
C(12)	3643(4)	1420(11)	1134(5)	6.2
C(13)	3014(4)	1339(11)	654(4)	5.7
C(14)	2222(2)	-553(7)	6720(3)	2.6
C(15)	2471(3)	-2053(8)	6771(3)	2.8
C(16)	1514(3)	-391(7)	6420(3)	2.8
C(17)	2716(3)	-2801(7)	7546(3)	3.2
C(18)	1303(2)	1133(5)	6407(3)	3.2
C(19)	1708(2)	2255(6)	6679(2)	3.8
C(20)	1482(2)	3600(5)	6658(3)	4.6
C(21)	851(3)	3824(5)	6365(3)	5.3
C(22)	445(2)	2703(6)	6092(2)	5.1
C(23)	671(2)	1357(6)	6113(2)	3.9
C(24)	1170(2)	-1054(6)	5633(2)	3.4
C(25)	1099(2)	-282(5)	5002(3)	4.1
C(26)	796(2)	-865(7)	4285(2)	5.4
C(27)	563(2)	-2219(8)	4198(3)	6.2
C(28)	634(2)	-2990(6)	4829(4)	5.8
C(29)	937(2)	-2408(6)	5547(3)	4.7
C(30)	3157(2)	-1851(5)	8183(2)	3.1
C(31)	2957(2)	-1198(7)	8665(3)	5.1
C(32)	3353(3)	-323(6)	9236(3)	7.3
C(33)	3949(3)	-100(6)	9325(3)	7.7
C(34)	4149(2)	-753(7)	8843(3)	6.6
C(35)	3753(2)	-1628(6)	8272(3)	4.7
C(36)	3022(2)	-4219(5)	7550(3)	3.4
C(37)	3259(2)	-4932(6)	8235(2)	4.7
C(38)	3498(2)	-6272(6)	8285(2)	5.6
C(39)	3500(2)	-6899(5)	7649(3)	5.8
C(40)	3263(2)	-6186(6)	6964(3)	5.1
C(41)	3024(2)	-4847(6)	6915(2)	3.9
C(42)	2834(2)	-715(7)	6083(3)	3.1
C(43)	2533(3)	-1243(8)	5271(3)	3.2
C(44)	2981(3)	-2106(9)	5081(3)	4.0
C(45)	3560(3)	-1256(9)	5240(3)	4.4
C(46)	3874(3)	-781(8)	6066(3)	3.9
C(47)	3427(2)	89(8)	6252(3)	3.4

from the side of *re*-face of the carboxyl group which includes C(1), if we consider from the topochemical point of view. The two generated asymmetric carbons, C(1) and C(3), have the configurations of *S*, as shown in Fig. 5. That is in good agreement with the observed configuration of **2a**.

Since the O(2) atom is hydrogen bonded with the hydroxyl group of the host molecule, it cannot rotate freely around the C(2)–N(1) bond. This is one reason why such a high enantioselectivity is obtained in this clathrate crystal.

Experimental

The crystal data and experimental details are summarized in Table 2. The Lorentz, polarization, absorption, de-

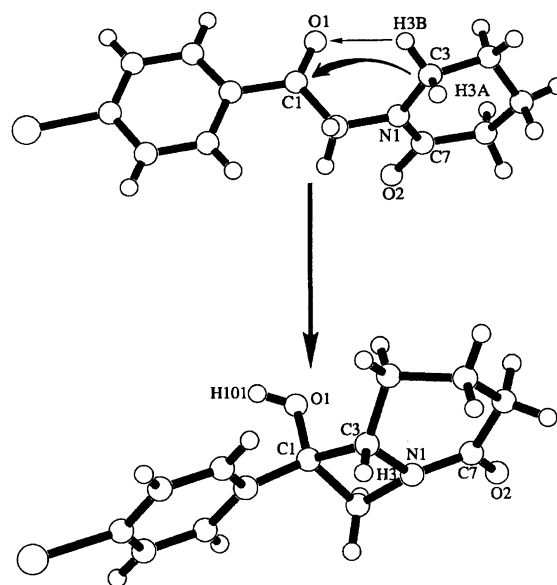


Fig. 5. The process of photocyclization.

Table 4. The Final Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($B_{eq}/\text{\AA}^2$) for **2a**

Atom	<i>x</i>	<i>y</i>	<i>z</i>	B_{eq}
Br(1)	-4915(1)	7731(1)	4289(1)	6.2
O(1)	956(5)	9143(1)	-957(7)	4.3
O(2)	7112(5)	9122(1)	-1322(7)	5.1
N(1)	4625(5)	8955(1)	958(7)	3.6
C(1)	1692(6)	8840(1)	666(9)	3.0
C(2)	3538(6)	8646(2)	-453(10)	3.9
C(3)	3012(6)	9063(2)	2490(9)	3.3
C(4)	2934(7)	9530(2)	3069(12)	4.5
C(5)	4927(8)	9668(2)	3808(10)	5.2
C(6)	6344(8)	9595(2)	1833(11)	5.1
C(7)	6078(7)	9203(2)	358(11)	3.9
C(8)	198(7)	8549(1)	1574(8)	3.1
C(9)	-717(7)	8641(2)	3675(8)	3.4
C(10)	-2230(7)	8404(1)	4495(9)	3.6
C(11)	-2817(7)	8058(2)	3176(9)	3.6
C(12)	-1954(7)	7952(2)	1102(10)	4.0
C(13)	-447(7)	8194(1)	323(9)	3.8

cay, and extinction corrections were applied for both crystals. The structures of **5a** and **2a** were solved by the Patterson method with the program SAPI 91⁹⁾ and by the direct method with the program SIR 92,¹⁰⁾ respectively. The structures were refined by the full-matrix least-squares method with program SHELXL-93.¹¹⁾ The weighting schemes were $w = [\sigma(F_o^2)^2 + (0.0463P)^2]^{-1}$ for **5a** and $w = [\sigma(F_o^2)^2 + (0.0253P)^2]^{-1}$ for **2a**, where $P = (F_o^2 + 2F_c^2)/3$. Positions of several hydrogen atoms were obtained on difference maps and those of the others were calculated geometrically. The phenyl groups of the host molecule in **5a** was constrained to have regular hexagonal geometry with C–C distances of 1.39 Å, and were refined as a rigid group. The anisotropic and isotropic temperature factors were applied to non-hydrogen atoms and hydrogen atoms in the final refinement, respectively. The positional parameters of hydrogen atoms were constrained to have the C–H distances of 0.96 Å for primary, 0.97 Å for secondary, 0.98 Å for tertiary, and 0.93 Å for aromatic and the O–H distances of 0.82 Å. Atomic scattering factors were taken from International Tables for Crystallography.¹²⁾ The absolute structures of **5a** and **2a** were determined by the Flack parameter¹³⁾ and anomalous scattering of X-rays, respectively. The final atomic coordinates are listed in Tables 3 and 4 for **5a** and **2a**, respectively.[#]

[#]The tables of the anisotropic temperature factor for non-hydrogen atoms, bond distances and angles, the parameters of hydrogen atoms, and the $F_o - F_c$ are deposited as Document No. 67049 at the Office of the Editor of Bull. Chem. Soc. Jpn.

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