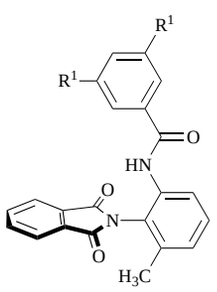
Synthesis of a clathrate host for formamides, *N*-[2-(3,5-dinitrobenzoylamino)-6-methylphenyl]phthalimide, and analysis of the interactions in the host–guest complex

Keiki Kishikawa,*,† Ryota Takeuchi,† Shigeo Kohmoto,† Makoto Yamamoto,† Kentaro Yamaguchi‡ and Kazutoshi Yamada†

Department of Materials Science, Faculty of Engineering and Chemical Analysis Center, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263, Japan

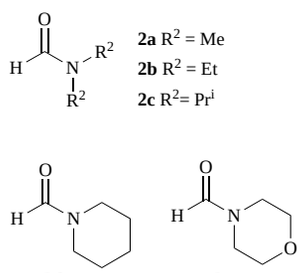
A clathrate host, *N*-[2-(3,5-dinitrobenzoylamino)-6-methylphenyl]phthalimide 1 is designed to achieve inclusion of *N*-substituted formamides. *N*,*N*-Dialkylformamides $HCONR_2$ of various sizes 2a–e [2a: R = Me; 2b: R = Et; 2c: R = Pr^i; 2d: $R_2 = -(CH_2)_5-$, 2e: $R_2 = -(CH_2)_2O(CH_2)_2-$] and dimethyl sulfoxide have been included as the guests in a clathrate host 1, in the ratio 1 : 1 in each case. The interaction between the host and guest has been investigated by X-ray analysis of complex 1·2c (1 : 1). The phthalimide plane and the *N*-phenyl group are orthogonal, which makes a suitable space for recognition of the formamides.

Study of clathrate compounds is an important field in supramolecular chemistry.[1,2] As the guests, organic compounds which have various functional groups such as hydroxy, carbonyl, carboxy, halogeno, amino, nitrile and nitro groups, have been included in clathrate compounds. Formamides, such as *N*,*N*-dimethylformamide **2a** (DMF),[3] *N*-methylformamide,[4] *N*,*N*-diethylformamide[5] **2b** and *N*-butyl-*N*-methylformamide,[6] have been reported to form clathrate compounds. However, to the best of our knowledge, there is no report on a host molecule capable of the inclusion of formamides of various sizes. In this paper, we prepared *N*-[2-(3,5-dinitrobenzoylamino)-6-methylphenyl]phthalimide (**1**, R = NO_2) as the clathrate host to demonstrate its inclusion ability toward formamides, and we investigated the interaction in the clathrate compound by X-ray crystallography. In order to include *N*-formamides the host molecule **1** has the following features; (1) the 3,5-dinitrobenzoyl group increases the acidity of the amide proton which can create strong hydrogen bonding with the electron-rich carbonyl oxygen of the *N*-formyl group of the guest, (2) the phthalimide moiety is orthogonal to the π-plane of the *N*-phenyl group due to steric repulsion between the methyl group and the two imide carbonyls, which makes a sufficient opening of the phthalimide π-plane for molecular recognition to occur, (3) the above mentioned twisted structure prohibits intramolecular hydrogen bonding between the amide proton and the imide-carbonyl oxygens, (4) the π-plane of the phthalimide interacts with the formyl O=C–N bond of the guest.



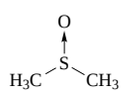
1 (R^1 = NO_2)

1' (R^1 = H)



2a R^2 = Me
2b R^2 = Et
2c R^2 = Pr^i

2d **2e**



2f

Results and discussion

The host **1** was prepared as follows. Condensation of 2-amino-3-nitrotoluene and phthaloyl chloride in the presence of triethylamine gave *N*-(2-methyl-6-nitrophenyl)phthalimide **3**. Hydrogenation of nitro compound **3** produced *N*-(2-amino-6-methylphenyl)phthalimide **4**. Reaction of amine **4** with 3,5-dinitrobenzoyl chloride in the presence of triethylamine generated the corresponding benzamide **1**.

The host **1** forms adducts on recrystallisation from a solution of a guest compound **2a**–**f** in chloroform with the host-to-guest ratio of 1 : 1 measured by ^{1}H NMR spectroscopy and elemental analysis. Inclusion of ethers [tetrahydrofuran (THF), diethyl ether], esters (ethyl acetate, methyl benzoate), amines (butylamine, diethylamine, triethylamine, aniline), alcohols (methanol, ethanol, propanol, propan-2-ol, butan-1-ol), acids (acetic acid, propionic acid, benzoic acid), aldehydes (propionaldehyde, benzaldehyde, *p*-tolualdehyde, *p*-anisaldehyde), ketones (acetone, acetophenone, benzophenone) and other amides (*N*,*N*-dimethylacetamide, acetanilide, benzamide) was not observed. Formamides and dimethyl sulfoxide (DMSO) were included selectively, possibly through hydrogen bonding between their electron-rich oxygens with the NH group of host **1**.

The X-ray analysis of complex **1·2c** (1 : 1) was achieved in order to confirm the molecular structure as shown in Fig. 1. The phthalimide π-plane is nearly orthogonal to the *N*-phenyl group [C8–N1–C9–C14, 112°], which makes a suitable space for recognition of the formyl group. The guest **2c** forms an inclusion complex within the gap in the L-shaped host molecule. The amide NH of the host forms a hydrogen bond with the formyl oxygen of the guest [H11···O8* 1.97 Å, N2–O8* 2.92 Å, N2–H11···O8* 178.6°]. The distance of 1.97 Å for H11···O8* is a typical value for an NH···O hydrogen bond.[1,7] The formyl carbonyl (O8*=C26*) lies on the phthalimide π-plane [O8*···C8 2.90; O8*···N1 3.10; O8*···C7 3.14; O8*···O1 3.31; O8*···C1 3.40; C26*···O2 3.27; C26*···C8 3.27; C26*···C7 3.59 Å]. The formyl double bond

† Department of Materials Science, Faculty of Engineering, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263, Japan.
‡ Chemical Analysis Center, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263, Japan.

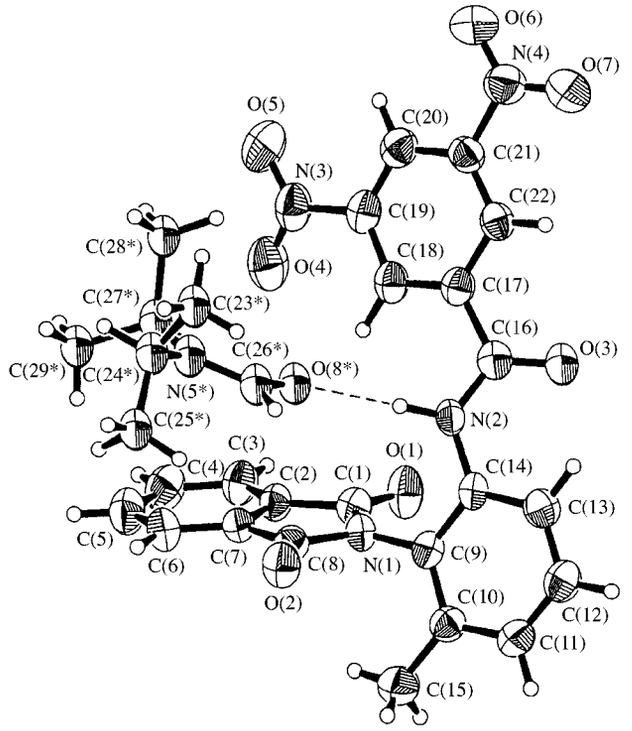
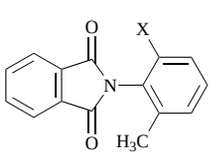


Fig. 1 X-ray structure of the inclusion compound **1**·**2c**, with crystallographic numbering scheme

interacts with the π-system of the phthalimide. In particular, O8* and C8 are a short interatomic distance apart; this distance is shorter than the sum of the van der Waals radii of C (1.7 Å) and O (1.5 Å) (3.2 Å).[8] Electrostatic forces are believed to interact between the electropositive and electronegative atoms to generate this effect. The methyl (C25*) hydrogens interact with C6 of the phthalimide [C25* · · · C6 3.53 Å] and the distance is shorter than the sum (3.7 Å) of the van der Waals radii of a methyl group (2.0 Å) and an aromatic carbon (1.7 Å).[9] The methyl hydrogens of the isopropyl group in guest **2c** has a CH/π interaction with the phthalimide π-plane. The complex is stabilised by these weak interactions, NH · · · O=C hydrogen bonding, the π–π interaction and the CH/π interaction.

In $CDCl_3$, the binding constant of the host toward DMF **2a** was unmeasurable in titration experiments monitored by ^1H NMR spectroscopy, due to the weak host–guest interaction. During the crystallisation process, some lipophilic space made by aggregation of several molecules would include the guest using those weak interactions. In recrystallisation of the benzamide **1′** (R^1 = H) with the guests under similar conditions, no inclusion was observed. This result showed the importance of the two nitro groups. These nitro groups increase the acidity of the amide hydrogen, which makes the hydrogen bonding strong.

According to previous reports, pyridino macrocycles[10] and carcerands[11] formed inclusion complexes with DMF in their cavities which showed high selectivity depending on the size of the guest molecule, due to their cyclic structures. In contrast, the L-shaped host **1** shows a wide spectrum of ability in inclusion of formamides, because the opening above the phthalimide π-plane can include longer and bulkier molecules than can cavities in those former host molecules.



3 X = NO_2
4 X = NH_2

Experimental

General

Mps were measured on a Yanaco MP-53 and are uncorrected. IR spectra were measured on a Hitachi I-2000 spectrometer, and UV spectra were measured on a Hitachi U-2000 spectrophotometer. NMR spectra were taken on a JEOL EX90 spectrometer; *J*-values are given in Hz. Microanalyses were performed on a Perkin-Elmer 2400. Silica gel for column chromatography was Fuji Gel BW-200 (150–350 mesh).

Synthesis of *N*-(2-methyl-6-nitrophenyl)phthalimide 3

A solution of 2-amino-3-nitrotoluene (1.00 g, 6.57 mmol), phthaloyl dichloride (1.48 g, 1.05 cm^3, 7.28 mmol) and triethylamine (1.48 g, 2.03 cm^3, 14.6 mmol) in toluene (20 cm^3) was refluxed for 19 h. After cooling, the solution was washed successively with three 20 cm^3 portions of 1 M hydrochloric acid and with four 20 cm^3 portions of saturated aq. sodium hydrogen carbonate. The organic phase was dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. The residual products were separated by column chromatography on silica gel with hexane–ethyl acetate (4:1) as eluent to give nitroimide **3** (1.394 g, 75.2%), R_f 0.23 (hexane–ethyl acetate, 4:1); plates, mp 174.5–176 °C (from $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3092 (CH), 1710 (C=O), 1606 (C–C), 1526 (NO), 1384 (NO) and 882 (CN); δ_H(90 MHz; $CDCl_3$) 2.32 (s, 3 H), 7.54 (t, *J* 7.7, 1 H), 7.63 (d, *J* 2.6, 1 H) and 7.7–8.1 (m, 5 H) (Found: C, 63.83; H, 3.34; N, 9.93. Calc. for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N. 9.93%).

Synthesis of *N*-(2-amino-6-methylphenyl)phthalimide 4

A solution of compound **3** (1.082 g, 3.83 mmol) in ethanol (20 cm^3) was hydrogenated in the presence of 5% palladium–carbon. After removal of the catalyst by filtration the solution was concentrated and separated by silica gel column chromatography with hexane–ethyl acetate (2:1) as eluent to give amine **4** (0.682 g, 70.5%), R_f 0.28 (hexane–ethyl acetate, 2:1); yellow plates, mp 203–204 °C (from $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3448 (NH), 3348 (NH), 1708 (C=O), 1622 (NH), 1374 (CH) and 1104 (CN); δ_H(90 MHz; $CDCl_3$) 2.10 (s, 3 H), 3.07 (br, 2 H), 6.69 (d, *J* 2.3, 1 H), 6.78 (d, *J* 2.3, 1 H), 7.18 (t, *J* 7.5, 1 H) and 7.80–8.1 (m, 4 H) (Found: C, 71.56; H, 4.63; N, 11.21. Calc. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11%).

Synthesis of *N*-[2-(3,5-dinitrobenzoylamino)-6-methylphenyl]-phthalimide 1

A solution of 3,5-dinitrobenzoyl chloride (101 mg, 0.436 mmol) in THF (5 cm^3) was added dropwise to a solution of compound **4** (100 mg, 0.396 mmol) and triethylamine (40.0 mg, 0.396 mmol) in THF (10 cm^3). The solution was stirred at room temp. for 3 h. The THF was evaporated off and replaced by ethyl acetate (10 cm^3). The solution was washed successively with three 20 cm^3 portions of 1 M hydrochloric acid and three 20 cm^3 portions of saturated aq. sodium hydrogen carbonate, and dried over anhydrous $MgSO_4$. The products were separated by column chromatography on silica gel with hexane–ethyl acetate (2:1) as eluent to give amide **1** (143 mg, 80.9%), R_f 0.30 (hexane–ethyl acetate, 2:1), needles, mp 253.5–256.5 °C (from $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3452, 3096, 1784 (C=O), 1718 (C=O), 1542, 1472, 1376, 1346, 1212, 1164, 1084, 882, 786, 720 and 532; λ_{max}(CH_3CN)/nm (ε_{max}/dm^3 mol^{-1} cm^{-1}) 239 (16 100) and 287 (sh, 5300); δ_H(90 MHz; $CDCl_3$) 2.24 (s, 3 H), 7.34 (d, *J* 7.6, 1 H), 7.48 (t, *J* 7.6, 1 H), 7.70–8.13 (m, 7 H), 8.17 (br, 1 H) and 9.11 (t, *J* 2.2, 1 H) (Found: C, 58.92; H, 2.89; N, 12.56. Calc. for $C_{22}H_{14}N_4O_7$: C, 59.19; H, 3.16; N, 12.55%).

***N*-[2-(Benzoylamino)-6-methylphenyl]phthalimide 1′.** R_f 0.23 (hexane–ethyl acetate, 2:1), plates; mp 217.5–219 °C (from $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3356, 3036, 2912, 1782 (C=O), 1682 (C=O), 1604, 1518, 1496, 1384, 1210, 1172, 1122, 882, 786, 706

and 530; λ_{max}(CH_3CN)/nm (ε_{max}/dm^3 mol^{-1} cm^{-1}) 242 (15 400); δ_H(90 MHz; $CDCl_3$) 2.21 (s, 3 H), 7.13–7.58 (m, 4 H) and 7.60–8.12 (m, 9 H) (Found: C, 74.03; H, 4.33; N, 7.84. Calc. for $C_{22}H_{16}N_2O_3$: C, 74.14; H, 4.53; N, 7.86%).

Recrystallisation of the clathrate compounds

Host compounds **1** (10 mg, 0.0174 mmol) and a guest compound **2a**–**f** (0.0869 mmol) were dissolved in chloroform (1 cm^3) and the solution was slowly concentrated under atmospheric pressure at room temp. (20 °C) to obtain crystals of the clathrate compounds. Mps of all clathrate compounds were measured; however, in all cases the crystals gradually changed to white solids, and each solid melted in the range 255–260 °C (mp of compound **1**: 253.5–256.5 °C).

***N*-[2-(3,5-Dinitrobenzoylamino)-6-methylphenyl]phthalimide/DMF 1:1 complex 1·2a.** Yellow plates (Found: C, 57.36; H, 3.86; N, 13.41. Calc. for $C_{25}H_{21}N_5O_8$: C, 57.80; H, 4.07; N, 13.48%).

***N*-[2-(3,5-Dinitrobenzoylamino)-6-methylphenyl]phthalimide/*N*,*N*′-diethyl formamide 1:1 complex 1·2b.** Plates (Found: C, 58.98; H, 4.38; N, 12.90. Calc. for $C_{27}H_{25}N_5O_8$: C, 59.23; H, 4.60; N, 12.79%).

***N*-[2-(3,5-Dinitrobenzoylamino)-6-methylphenyl]phthalimide/*N*,*N*′-diisopropyl formamide 1:1 complex 1·2c.** Prisms (Found: C, 60.43; H, 4.91; N, 12.24. Calc. for $C_{29}H_{29}N_5O_8$: C, 60.51; H, 5.08; N, 12.17%).

***N*-[2-(3,5-Dinitrobenzoylamino)-6-methylphenyl]phthalimide/*N*-formylpiperidine 1:1 complex 1·2d.** Plates (Found: C, 59.36; H, 4.27; N, 12.40. Calc. for $C_{28}H_{25}N_5O_8{\cdot}0.5H_2O$: C, 59.15; H, 4.61; N, 12.32%).

***N*-[2-(3,5-Dinitrobenzoylamino)-6-methylphenyl]phthalimide/*N*-formylmorpholine 1:1 complex 1·2e.** Plates (Found: C, 57.59; H, 3.92; N, 12.43. Calc. for $C_{27}H_{23}N_5O_9$: C, 57.75; H, 4.13; N, 12.47%).

***N*-[2-(3,5-Dinitrobenzoylamino)-6-methylphenyl]phthalimide/DMSO 1:1 complex 1·2f.** Needles (Found: C, 54.83; H, 3.68; N, 10.63. Calc. for $C_{24}H_{20}N_4O_8S$: C, 54.96; H, 3.84; N, 10.68%).

Crystal data for complex 1·2c

$C_{29}H_{29}N_5O_8$, M = 575.58. Triclinic, a = 11.152(7), b = 13.37(1), c = 10.667(9) Å, α = 111.08(5)°, β = 104.36(5)°, γ = 84.02(5)°, volume = 1437(1) Å^3, space group $P\bar{1}$ (No. 2), Z = 2, D_x = 1.329 g cm^{-3}. Crystal dimensions 0.40 × 0.23 × 0.30 mm, μ(Mo-Kα) = 0.99 cm^{-1}. Data collection and processing: Rigaku RAXIS II imaging plate area detector with graphite-monochromated Mo-Kα (λ = 0.710 69 Å) radiation; 2712 reflections measured, giving 1915 with $I > 4.00\sigma(I)$.

Structure analysis and refinement. The structure was solved by direct methods using SHELXS86[12] and was refined by full-matrix least-squares techniques using DIRDIF94.[13] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final residuals for reflections with $I > 4.00\sigma(I)$ were R = 0.056, wR = 0.064.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web pages (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/187.

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