Hydrogen Bond Directed Cocrystallization and Molecular Recognition Properties of Diarylureas

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Abstract: The hydrogen bond directed molecular recognition properties of a series of diarylurea (DAU) compounds have been studied using cocrystallization to probe hydrogen bond donor and acceptor selectivity of the host and guest molecules. Diarylureas with meta-substituted electron-withdrawing groups on the aryl rings are capable of forming cocrystal complexes with a wide variety of hydrogen bond acceptors. One particular DAU, 1,3-bis(*m*-nitrophenyl)urea, behaves primarily as a proton donor, one of the few organic molecules known to have this property. Its hydrogen bond accepting ability is drastically reduced, possibly because of two very weak CH···O interactions occurring in response to the presence of guest acceptor molecules and effectively negating the powerful proton-accepting ability of the urea carbonyl group. Only DAU compounds with meta-substituted electron-withdrawing groups have this property. The crystal structures of four DAU compounds and six of their cocrystal structures are reported. In addition, 19 other DAU cocrystals were prepared and characterized by chemical and spectroscopic means, and their hydrogen bond patterns were assigned based on spectroscopic analogies to those with known crystal structures. From this data hydrogen bond rules for diarylureas have been derived for use in predicting hydrogen bond patterns in related structures.

Introduction

Intermolecular interactions between molecules are the basis for molecular recognition. Most intermolecular forces such as van der Waals' interactions are weak and nondirectional. When a strong directional noncovalent interaction such as a hydrogen bond forms between two molecules, however, it determines the configuration of the pair or set of molecules with almost as much control as covalent bonds. This hydrogen bond set takes on new molecular recognition properties and new chemical properties of its own. Crystal structure analyses are useful for studying the structures of ensembles of molecules after association has taken place, while cocrystallization studies are useful for monitoring competitive interactions that determine the selectivity of recognition processes.[1]

Ducharme and Wuest have recently demonstrated how dimeric hydrogen bond interactions of pyridones are reliable enough to direct molecules with multiple pyridone sites into predictable aggregate structures.[2] A similar idea can be applied to heteroconjugate hydrogen bond pairs where two or more different molecules participate in complementary hydrogen bond interactions. Rebek has demonstrated this concept with his remarkable series of Kemp's acid derivatives.[3,4] These structures, which are models for studying molecular recognition at receptor sites, have a rigid U-shaped structure with proton-donating and -accepting groups converging onto the opening of the U. Guest molecules that are topologically complementary may be trapped into the opening with or without hydrogen bonding, but specific directional hydrogen bonds impart extra binding strength to the host-guest pair.[5,6] Hamilton,[7] Bell,[8] and Reinhoudt[9] have also designed complementary host-guest pairs where multiple hydrogen bond sites serve to strengthen the stability of a complex containing a small molecule trapped in a cavity or at the surface of a large molecule. Hydrogen bond interactions have also been used to stabilize crown ether complexes.[10]

Alternatively, hydrogen bond interactions may be used as key stabilizing interactions in the host structure itself. The host could be composed of multiple hydrogen-bonded subunits that aggregate to create pockets trapping topologically compatible guest molecules. This principle has been demonstrated for cyclamers made from 1,3-cyclohexanedione,[11,12] for hosts composed of phenols and benzylic alcohols[13] and for hosts composed of carboxylic acids hydrogen bonded to other small molecules such as alcohols.[14,15] In the latter cases the host molecules are purposely designed with large bulky groups either flanking a smaller rigid segment or situated adjacent to the hydrogen-bonding functional groups that form rigid segments. These designs promote formation of cavities with specific geometry. Hydrogen bonding is present as an additional force that either stabilizes the complex or stabilizes the host structure.

In the present work, we have purposely chosen systems where steric constraints are kept to a minimum and where the primary controlling feature of intermolecular association is the hydrogen bond interaction. In this way the independent contributions of intermolecular hydrogen bonding to molecular recognition can be evaluated, and hydrogen bond specificity and competitions can be studied. The process of evaluating intermolecular hydrogen bonds as tools for controlling molecular self-assembly has been discussed in a recent review,[1] as well as in our work on nitroanilines.[16] The use of intermolecular hydrogen bonds for designing cocrystals has also been discussed for aminopyrimidines with

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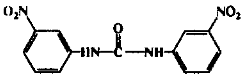
Table I. Urea Designators

$ArHN-\overset{O}{\overset{\|}{C}}-NHAr'$

	Ar	Ar′		Ar	Ar′
1	phenyl	phenyl	7	*p*-anisoyl	phenyl
2	*m*-nitrophenyl	*m*-nitrophenyl	8	*o*-anisoyl	phenyl
3	*o*-anisoyl	*o*-anisoyl	9	*o*-nitrophenyl	*o*-nitrophenyl
4	*m*-nitrophenyl	phenyl	10	*p*-nitrophenyl	*p*-nitrophenyl
5	*m*-nitrophenyl	*p*-nitrophenyl	11	*m*-tolyl	*m*-tolyl
6	*p*-anisoyl	*p*-anisoyl	12	*m*-trifluorotolyl	*m*-trifluorotolyl

Cocrystals of **2**



	guest		guest
13	2-butanone	21	cyclohexanone
14	tetrahydrofuran	22	cyclopentanone
15	triphenylphosphine oxide	23	dimethyl sulfoxide
17	diethyleneglycol	24	dioxane
18	*N*,*N*-dimethyl-*p*-nitroaniline	25	diethyl ether
19	acetone	26	polyethylene oxide
20	benzophenone	28	*p*-nitroaniline

Other Cocrystals

	host:guest		host:guest
16	5:dimethyl sulfoxide	30	12:triphenylphosphine oxide
27	4:triphenylphosphine oxide	31	12:dimethyl sulfoxide
29	10:dimethyl sulfoxide		

carboxylic acids,[17] for heteroconjugate carboxylic acids,[18] and for triphenylphosphine oxide cocrystals.[19]

The hydrogen bond directed cocrystallization properties of 1,3-diarylureas (DAU) are presented here.[20] Hart has previously reported that many diaryl-, dialkyl-, and monoaryl- or alkylureas readily form cocrystals.[21] In his compounds, the urea functionality is used as a rigid spacer between large bulky substituents such as trityl groups. These molecules do not hydrogen bond to one another because the urea groups are sterically inaccessible to one another, but they do associate by van der Waals' contacts into clathrates with large cavities formed by two or more of the urea host molecules. These cavities fill with small molecules, which may or may not hydrogen bond to the urea function. Hydrogen bonding is not essential to the complexation process for diarylureas with bulky groups.

In our work, the DAU molecules have flat planar aromatic substituents which provide little or no steric hindrance to hydrogen bonding by the urea functional groups. The urea proton-donating groups (–NH hydrogens) and accepting groups (C═O) are free from steric constraints, so they can interact with intramolecular or intermolecular hydrogen bond donors and acceptors. The role of competing intra- and intermolecular hydrogen bonds in determining the molecular recognition properties of DAU molecules is analyzed by competitive cocrystallization of DAU molecules with guests and then by correlating hydrogen bond pattern differences between their homomolecular and their cocrystal forms. It is shown that a very weak CH···O intramolecular interaction, not detectable by routine spectroscopic and crystallographic methods, may be responsible for dramatic changes in the molecular recognition properties of DAU molecules. This interaction apparently causes the urea carbonyl groups to become very weak intermolecular hydrogen bond acceptors. DAU molecules behave as intermolecular proton donors and acceptors in the absence of this weak interaction but behave primarily as donors in the presence of this interaction. Implications about the role of weak interactions in dictating molecular recognition properties and about the use of cocrystallization for studying molecular recognition are discussed.

Experimental Section

Preparation of Diarylureas. Urea **1** was purchased from Aldrich and purified by recrystallization from ethanol. Ureas **2–12**, Table I, were prepared by a standard method involving the reaction of the arylisocyanate (0.25 mol in 100 mL of benzene or other suitable solvent) with the appropriate aniline (0.25 mol in 100 mL of benzene). The solution was stirred overnight at room temperature under nitrogen and then filtered to give the product. Recrystallization from ethanol gave the final product in yields of about 95%. Analyses of the products are given below. Crystal structures of **2**α, **3**α and -β, and **13–18** were also done and are reported in the next section.

Experimental Data. (Key: compound name, number; crystal color and morphology, solvent(s) of recrystallization; mp; IR (Nujol mulls) (cm^{-1}); ^{1}H NMR; ^{13}C solution NMR (frequency) (solvent) chemical shift (ppm) multiplicity, integral, coupling in Hz; ^{13}C CP/MAS NMR chemical shift.)

1,3-Bis(phenyl)urea (Carbanilide) (1): white needles, acetic acid, acetone, acetone (with TPPO present in 1 and 10 molar quantities), acetonitrile, benzene, DMSO, 95% ethanol, ethanol, ethylene glycol, MEK. THF, or tetramethylene sulfoxide; mp 234–236 °C; IR 3330, 3280, 1650; ^{1}H NMR 300 MHz [$(CD_3)_2SO$] 6.97, t, 2 H, 7.29, t, 3 H, 7.50, d, 3 H, 8.69, s, 2 H; ^{13}C NMR 300 MHz [$(CD_3)_2SO$] 118.2, 121.8, 128.8, 139.7, 152.6; ^{13}C CP/MAS NMR 121.6, 124.2, 130.3, 136.9, 139.7, 140.9, 156.9.

1,3-Bis(*m*-nitrophenyl)urea, α Polymorph (2α): yellow prisms; acetic acid, benzene, chloroform, dichloromethane, 95% ethanol, ethanol, or ethylene glycol; mp 256–258 °C; IR 3391, 1697; ^{1}H NMR 300 MHz [$(CD_3)_2SO$] 7.59, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H, 8.56, t, 2 H, 9.40, s, 2 H; ^{13}C NMR 300 MHz [$(CD_3)_2SO$] 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4; ^{13}C CP/MAS NMR 113.4, 117.4, 126.3, 130.1, 135.8, 143.1, 147.6.

1,3-Bis(*m*-nitrophenyl)urea, β Polymorph (2β): white needles, acetic acid, 95% ethanol, or ethanol; transforms to α form then melts at 256–258 °C; IR 3325, 1658; ^{1}H NMR 300 MHz [$(CD_3)_2SO$] 7.59, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H, 8.56, t, 2 H, 9.40, s, 2 H; ^{13}C NMR 300 MHz [$(CD_3)_2SO$] 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4.

1,3-Bis(*o*-anisoyl)urea, α Polymorph (3α): white needles; acetonitrile or 95% ethanol saturated with KI; mp 190–191 °C; IR 3320, 1650; ^{1}H NMR 300 MHz [$(CD_3)_2SO$] 3.87, s, 6 H, 6.86–7.02, multiplet, 6 H, 8.10–8.13, dd, 2 H, 8.70, s, 2 H; ^{13}C NMR 300 MHz [$(CD_3)_2SO$] 55.7, 110.8, 119.1, 120.4, 121.9, 129.8, 148.1, 152.7; ^{13}C CP/MAS NMR 55.9, 112.8, 119.2, 124.4, 125.3, 127.0, 129.3, 151.7.

1,3-Bis(*o*-anisoyl)urea, β Polymorph (3β): white needles; acetic acid/water 1/1, benzene, or 95% ethanol saturated with KI; crystal shatters at 145 °C and then melts at 190–191 °C; IR 3340, 1680; ^{1}H NMR 300 MHz [$(CD_3)_2SO$] 3.87, s, 6 H, 6.86–7.02, multiplet, 6 H, 8.10–8.13, dd, 2 H, 8.70, s, 2 H; ^{13}C NMR 300 MHz [$(CD_3)_2SO$] 55.7, 110.8, 119.1, 120.4, 121.9, 129.8, 148.1, 152.7; ^{13}C CP/MAS NMR 55.8, 112.5, 119.2, 123.8, 126.7, 128.9, 130.2, 151.5.

Solid-State Conversion of 3β to 3α. Melting point studies show that both the α and β polymorphs melt at 190–1 °C. On heating **3**β shatters at ≈145 °C to give a material which melts at 190–1 °C. When the **3**β is heated to above 145 °C but not allowed to melt, the resulting material analyses as the α polymorph. DSC studies show an endotherm of 1.91 kcal/mol for this transformation.

1-(*m*-Nitrophenyl)-3-phenylurea (4): yellow needles; benzene, 95% ethanol, ethanol, or THF; mp 209–211 °C; IR 3316, 3286, 1642; ^{1}H NMR 300 MHz [$(CD_3)_2SO$] 7.05, t, 1 H, 7.5 Hz, 7.31, t, 2 H, 8.1 Hz, 7.47–7.61, t and d, 3 H, 7.70–7.86, 2 dd, 2 H, 8.58, t, 1 H, 2.2 Hz, 8.85, s, 1 H, 9.23, s, 1 H; ^{13}C NMR 200 MHz [$(CD_3)_2SO$] 111.7, 115.8, 118.2, 121.9, 123.9, 128.4, 129.6, 138.8, 140.6, 147.7, 152.0.

1-(*m*-Nitrophenyl)-3-(*p*-nitrophenyl)urea (5): yellow needles; acetone, acetone/DMSO (99/1), benzene, or 95% ethanol; mp >300 °C; IR 3352, 3317, 1720; ^{1}H NMR 300 MHz [$(CD_3)_2SO$] 7.61, t, 1 H, 8.5 Hz, 7.75, d, 2 H, 9.7 Hz, 7.70, dd, 1 H, 7.89, dd, 1 H, 8.23, d, 2 H, 9.7 Hz, 8.58, d, 1 H, 2 Hz, 9.60, s, 2 H.

1,3-Bis(*p*-anisoyl)urea (6): white needles; benzene, ethanol, or ethanol with 1 equiv of TPPO; mp 240–241 °C; IR 3300, 1634; ^{1}H NMR 300 MHz [$(CD_3)_2SO$] 3.73, s, 6 H, 6.86, d, 4 H, 9 Hz, 7.39, d, 4 H, 9 Hz, 8.36, s, 2 H; ^{13}C NMR 300 MHz [$(CD_3)_2SO$] 54.7, 113.7, 119.6, 133.1, 152.7, 154.3.

1-*p*-Anisoyl-3-phenylurea (7): white needles; benzene, 95% ethanol, ethanol, DMSO, or THF; mp 196.6 °C; IR 3300, 1630; ^{1}H NMR 300

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MHz [(CD$_3$)$_2$SO] 3.71, s, 3 H, 6.67, d, 2 H, 9.0 Hz, 6.95, t, 1 H, 7.3 Hz, 7.27, t, 2 H, 7.8 Hz, 7.37, d, 2 H, 8.9 Hz, 7.45, d, 2 H, 8.0 Hz, 8.48, s, 1 H, 8.59, s, 1 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 55.2, 114.0, 118.1, 120.0, 121.6, 128.8, 132.7, 140.0, 152.7, 154.5.

1-*o*-Anisoyl-3-phenylurea (8): white needles; benzene; mp 198.7 °C; IR 3335, 3290, 1645; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 3.88, s, 3 H, 6.89–7.02, multiplet, 4 H; 7.30, t, 2 H, 7.6 Hz, 7.50, d, 2 H, 8.5 Hz, 8.19, dd, 1 H, 3.9 Hz, 1.4 Hz, 8.28, s, 1 H, 9.35, s, 1 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 55.7, 110.7, 117.9, 118.3, 120.6, 121.74, 121.76, 128.7, 128.8, 139.9, 147.6, 152.4.

1,3-Bis(*o*-nitrophenyl)urea (9): yellow needles; acetonitrile, benzene, or ethanol; mp 241–243 °C; IR 3360, 1630; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 7.30, t, 2 H, 7.8 Hz, 7.71, t, 2 H, 7.8 Hz, 7.96, d, 2 H, 8.1 Hz, 8.04, d, 2 H, 8.1 Hz, 10.07, s, 2 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 123.7, 123.9, 125.3, 133.1, 134.5, 140.0, 151.9; ^{13}C CP/MAS NMR 125.8, 127.8, 131.5, 134.9, 140.2.

1,3-Bis(*p*-nitrophenyl)urea (10): yellow needles (very fine); acetic acid, acetone, acetone (with either a 1 molar quantity of TPPO, NNDMPNA, or PNA), acetonitrile, benzene, 95% ethanol, ethanol, or THF; mp >300 °C; IR 3369, 3343, 3323, 1735; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 7.74, d, 4 H, 9.2 Hz, 8.24, d, 4 H, 9.8 Hz, 9.2, s, 2 H; ^{13}C NMR 200 MHz [(CD$_3$)$_2$SO] ^{13}C CP/MAS NMR 116.9, 123.8, 125.5, 131.6, 141.8, 153.0.

1,3-Bis(*m*-tolyl)urea (11): white needles; acetic acid, 95% ethanol, ethanol, or THF; mp 225 °C; IR 3299, 1635; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 2.29, s, 6 H, 6.79, d, 2 H, 7.12–7.38, m, 6 H, 8.58, s, 2 H; ^{13}C NMR 200 MHz [(CD$_3$)$_2$SO] 20.8, 114.9, 118.2, 122.1, 128.2, 137.5, 139.2, 152.1.

1,3-Bis(*m*-α,α,α-trifluorotolyl)urea (12): white needles; acetonitrile, benzene, or chloroform; mp 198.9 °C; IR 3325, 3311, 1661; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 7.34, d, 2 H, 7.57, t, 2 H, 7.57, d, 2 H, 8.04, s, 2 H, 9.20, s, 2 H; ^{13}C NMR 200 MHz [(CD$_3$)$_2$SO] 114.0, 117.9, 121.0, 121.7, 126.5, 128.8, 129.5, 139.8, 152.1; ^{13}C CP/MAS NMR 106–140 (br), 131.

Preparation of Cocrystals. A typical cocrystallization experiment involves dissolving about 5 mmol of the urea and the guest compounds in stoichiometric amounts in a mutually miscible solvent (e.g., acetone, chloroform, acetonitrile) either at room temperature or with mild heating until dissolution is complete. When the guest molecule is itself a liquid, it can be used as the solvent. The solutions are allowed to evaporate from a covered crystallization dish at room temperature until crystals begin to form. These are removed from the solution immediately. Crystals that form subsequently from the mother liquor are also isolated and compared to those from other crops to test homogeneity. Chemical and spectroscopic analyses of cocrystals prepared in this way are given below with the same experimental key used previously. We also found that cocrystals could frequently be prepared simply by grinding the DAU host with the guest compounds as previously reported for other organic cocrystals.[17,22] Cocrystals prepared in this manner are so indicated.

1,3-Bis(*m*-nitrophenyl)urea/2-Butanone 1:1 Complex (13): yellow prisms; MEK; clouds at 50 °C and then melts at 256–258 °C; IR 3390, 1730, 1710; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 0.90, t, 3 H, 9 Hz, 2.06, s, 3 H, 2.42, q, 2 H, 7.59, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H, 8.56, t, 2 H, 9.40, s, 2 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 7.7, 29.3, 35.8, 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4; ^{13}C CP/MAS NMR 7.2, 29.6, 38.2, 111.2, 118.9, 122.5, 122.7, 126.2, 129.2, 131.7, 139.1, 143.7, 146.0, 146.4, 148.2, 152.6, 211.1.

1,3-Bis(*m*-nitrophenyl)urea/THF 1:1 Complex (14): yellow prisms; THF; clouds at 60 °C and then melts at 256–258 °C; DSC shows an endotherm of 7 kcal/mol at approximately 60 °C; IR 3330, 3305, 1720; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 1.78, t, 4 H, 3.63, t, 4 H, 7.59, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H, 8.56, t, 2 H, 9.40, s, 2 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 26.5, 68.4, 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4; ^{13}C CP/MAS NMR 27.1, 68.4, 112.9, 115.7, 117.6, 123.6, 124.6, 125.3, 128.7, 139.6, 143.7, 146.1, 147.4, 148.6, 153.7.

1,3-Bis(*m*-nitrophenyl)urea/TPPO 1:1 Complex (15): yellow prisms; acetone or ethyl acetate; clouds at 65 °C and then melts at 256–258 °C; IR 3340, 3320, 3300, 1715; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 7.59, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H, 8.56, t, 2 H, 9.40, s, 2 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4; ^{13}C CP/MAS NMR 112.9, 117.2, 121.7, 123.8, 127.2, 127.7, 130.7, 132.0, 134.4, 135.9, 139.3, 141.1, 146.0, 149.8, 155.0. This cocrystal was also prepared via solid-state methods by grinding the host and the guest in a 1:1 ratio for 10 min in a Wig-L-Bug dental amalgamator. The resulting compound gave the same spectroscopic results as the cocrystal formed in solution. Conversion of the starting materials to the cocrystal by this technique was close to 100%.

1-(*m*-Nitrophenyl)-3-(*p*-nitrophenyl)urea/DMSO 1:1 Complex (16): brown-yellow prisms; DMSO; clouds at ≈110 °C and then melts >300 °C; IR 3343, 3298, 3263, 3222, 3218, 1715, 1024; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 7.60, t, 1 H, 7.64–7.76, 2d, 3 H, 7.86, dd, 2 H, 8.19, d, 2 H, 8.57, s, 1 H, 9.60, s, 1 H, 9.75, s, 1 H; ^{13}C CP/MAS NMR 39.1, 111.0, 116.7, 121.6, 126.3, 131.4, 137.7, 142.6, 149.7.

1,3-Bis(*m*-nitrophenyl)urea/Diethylene Glycol 1:1 Complex (17): yellow prisms; diethylene glycol/95% ethanol 1/1; drops of liquid appear on the surface of the crystals between 95 and 115 °C, after which the crystals melt at 256–258 °C; IR 3440, 3410, 3370, 3330, 1700; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 3.41–3.53 ppm, m, 8 H, 4.58, m, 2 H, 7.59, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H, 8.56, t, 2 H, 9.40, s, 2 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 60.3, 72.3, 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4; ^{13}C CP/MAS NMR 62.4, 66.3, 72.6, 111.4, 116.3, 118.4, 124.7, 127.9, 131.0, 138.0, 141.2, 141.7, 144.9, 146.8, 148.6, 154.7.

1,3-Bis(*m*-nitrophenyl)urea/*N*,*N*-Dimethyl-*p*-nitroaniline (DMPNA) 1:1 Complex (18): red-orange needles; acetone or ethyl acetate; crystal turns yellow at 200 °C and then melts at 256–258 °C; IR 3346, 3309, 3300; 1722.

1,3-Bis(*m*-nitrophenyl)urea/Acetone 1:1 Complex (19): yellow prisms; acetone; clouds at 30 °C and then melts at 256–258 °C; IR 3440, 3410, 3370, 3330, 1700; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 2.12, s, 6 H, 7.59, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H, 8.56, t, 2 H, 9.40, s, 2 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 30.6, 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4, 205.7; ^{13}C CP/MAS NMR 30.4, 112.7, 116.2, 125.0, 131.1, 139.8, 147.8, 152.6, 203.6.

1,3-Bis(*m*-nitrophenyl)urea/Benzophenone 1:1 Complex (20). This cocrystal was prepared only by grinding in the solid state as described for **15**. The host was ground with a slight excess of the guest to give close to 100% conversion to the cocrystal after 10 min. The cocrystal has a carbonyl frequency at 1715 cm^{-1}. Two additional peaks were observed in the carbonyl region; one at 1648 cm^{-1} and the other at 1667 cm^{-1} which are, respectively, due to hydrogen-bonded and non-hydrogen-bonded carbonyls on the benzophenone molecule.

1,3-Bis(*m*-nitrophenyl)urea/Cyclohexanone 1:1 Complex (21): yellow prisms; cyclohexanone; clouds at 50 °C and then melts at 256–258 °C; IR 3390, 1730, 1710; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 25.1, 27.2, 41.7, 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4, 210.8; ^{13}C CP/MAS NMR 15.8, 28.6, 41.3, 42.5, 111.9, 117.8, 123.0, 123.8, 124.8, 128.4, 128.8, 140.0, 142.8, 143.1, 147.0, 149.2, 224.0.

1,3-Bis(*m*-nitrophenyl)urea/Cyclopentanone 1:1 Complex (22): yellow prisms; cyclopentanone; clouds at 50 °C and then melts at 256–258 °C; IR 3390, 1730, 1710; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 0.95, t, 4 H, 2.10, t, 4 H, 7.59, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H, 8.56, t, 2 H, 9.40, s, 2 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 23.5, 37.8, 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4, 216.2; ^{13}C CP/MAS NMR 29.7, 41.5, 43.1, 112.4, 116.4, 123.5, 124.6, 125.0, 128.1, 129.7, 139.5, 142.7, 143.0, 146.8, 147.4, 149.1, 226.1.

1,3-Bis(*m*-nitrophenyl)urea/DMSO 1:1 Complex (23): clear prisms; DMSO; clouds at 125 °C and then melts at 256–258 °C; IR 3330, 3290, 1735, 1015; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 2.52, s, 6 H, 7.59, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H; 8.56, t, 2 H, 9.40, s, 2 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 39.5, 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4.

1,3-Bis(*m*-nitrophenyl)urea/Dioxane 2:1 Complex (24): yellow prisms; dioxane; clouds at ≈80 °C and then melts at 256–258 °C; IR (grating) 3340, 3300, 1718; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 3.61, s, 8 H, 7.59, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H, 8.56, t, 2 H, 9.40, s, 2 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 67.4, 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4; ^{13}C CP/MAS NMR 67.1, 112.8, 116.9, 123.3, 124.7, 129.4, 139.9, 142.9, 147.2, 149.1.

1,3-Bis(*m*-nitrophenyl)urea/Ethyl Ether 1:1 Complex (25): yellow prisms; crystals lose solvent rapidly when removed from solution; ethyl ether; clouds at ≈30 °C and then melts at 256–258 °C; IR (grating) 3330, 3300, 1720; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 1.13, t, 6 H, 3.42, q, 4 H, 7.59, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H, 8.56, t, 2 H, 9.40, s, 2 H; ^{13}C NMR 300 MHz [(CD$_3$)$_2$SO] 17.1, 67.4, 112.5, 116.7, 124.7, 130.1, 140.6, 148.1, 152.4.

1,3-Bis(*m*-nitrophenyl)urea/Polyethylene Oxide (26): white powder; the urea was synthesized in the presence of polyethylene oxide (MW 300000, Aldrich) and the complex precipitated out of benzene; very broad, 150–260 °C; IR 3320, 1720; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 3.51, s, ≈4 H, 7.60, t, 2 H, 7.80, dd, 2 H, 7.85, dd, 2 H, 8.57, t, 2 H, 9.45, s, 2 H.

1-(*m*-Nitrophenyl)-3-phenylurea/TPPO 1:1 Complex (27): clear prisms; acetone; mp 200–201 °C; IR 3333, 3287, 3251, 1713, 1200, 1166, 1124; ^{1}H NMR 300 MHz [(CD$_3$)$_2$SO] 7.05, t, 1 H, 7.5 Hz, 7.31, t, 2 H, 8.1 Hz, 7.47–7.61, t and d, 3 H, 7.70–7.86, 2 dd, 2 H, 8.58, t, 1 H, 2.2 Hz, 8.85, s, 1 H, 9.23, s, 1 H; ^{13}C NMR 200 MHz [(CD$_3$)$_2$SO] 111.7, 115.8, 118.2, 121.9, 123.9, 128.4, 129.6, 138.8, 140.6, 147.7, 152.0; ^{13}C CP/MAS NMR 111.1, 112.8, 115.6, 122.7, 125.4, 128.2, 129.6,

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[22] Etter, M. C.; Frankenbach, G. M. *Chem. Mater.* **1989**, *1*, 10–12.

132.0, 138.8, 141.0, 144.6, 148.0, 155.5, 150.0.

1,3-Bis(*m*-nitrophenyl)urea/*p*-Nitroaniline (PNA) 1:1 Complex (28): red-orange needles; acetone, or ethyl acetate; crystal turns yellow at ≈200 °C and continuously turns yellow until it melts at 254 °C; IR 3401, 3353, 3300; 1706; ^{1}H NMR 300 MHz [$(CD_3)_2SO$] 3.36, s, 2 H, 6.62, d, 2 H, 6.73, s, 2 H. 7.59, t, 2 H, 7.75–7.97, m, 4 H, s, 2 H, 9.41, s, 2 H; ^{13}C NMR 300 MHz [$(CD_3)_2SO$] 111.6, 111.8, 115.9, 123.9, 125.4, 129.3, 139.8, 147.3, 151.6, 154.9.

1,3-Bis(*p*-nitrophenyl)urea/DMSO 1:1 Complex (29): yellow needles; DMSO; clouds at ≈100 °C and then melts >300 °C; IR 3366, 3324, 3285, 1740, 1021, 1012; ^{1}H NMR 200 MHz [$(CD_3)_2SO$] 2.52, s, 6 H, 7.74, d, 4 H, 9.2 Hz, 8.24, d, 4 H, 9.8 Hz, 9.2, s, 2 H; ^{13}C NMR 300 MHz [$(CD_3)_2SO$] 30.8, 38.4, 38.8, 39.3, 39.7, 40.1, 40.5, 40.9, 118.1, 125.3; ^{13}C CP/MAS NMR 39.8, 116.6, 124.4, 127.5, 137.0, 141.6, 151.4.

1,3-Bis(*m*-α,α,α-trifluorotolyl)urea/TPPO 1:1 Complex (30): white needles; acetone; mp 200–201 °C; IR 3339, 3307, 3258, 1716, 1177, 1158, 1124: ^{1}H NMR 200 MHz [$(CD_3)_2SO$] 7.34, d, 2 H, 7.50–7.80, m, 19 H, 8.05, s, 2 H, 9.20, s, 2 H.

1,3-Bis(*m*-α,α,α-trifluorotolyl)urea/DMSO 1:1 Complex (31): white needles: acetone; mp 200–201 °C; IR 3348, 3310, 3268, 1716, 1026; ^{1}H NMR 300 MHz [$(CD_3)_2SO$] 2.52, s, 6 H, 7.34, d, 2 H, 7.57, t, 2 H, 7.57, d, 2 H, 8.04, s, 2 H. 9.20, s, 2 H; ^{13}C NMR 200 MHz [$(CD_3)_2SO$] 39.5, 114.0, 117.9, 121.0, 121.7, 126.5, 128.8, 129.5, 139.8, 152.1; ^{13}C CP/MAS NMR 36.8, 38.7, 100–150 (br), 120.4, 129.7, 137.1, 146.0.

Selective Complexation of 2. Solutions comprised of equal volumes of THF/MEK and THF/ethyl ether were used for cocrystallizations of **2**. In both experiments the urea/THF complex (**14**) was formed exclusively. Also, solutions of **2** in acetone-containing TPPO produce exclusively the urea/TPPO complex (**15**), whereas, in the absence of TPPO, a cocrystal with acetone is formed. The formation of **14** and **15** was verified by melting point, solid-state IR, and solution ^{1}H NMR.

Instrumentation. IR, 5DXB FTIR Nicollet spectrometer or on a Beckman 5280 grating spectrometer; NMR, IBM NR200AF or NR300AF; melting point, Fischer-Johns; ^{13}C CP/MAS NMR, NR100AF with Doty solid-state probe; DSC, Mettler FP800.

Crystal Structure Analyses. The experimental details for the X-ray analysis of eight urea structures are listed in Table II. An Enraf-Nonius CAD4 diffractometer was used for data collection (Mo Kα radiation). All N–H protons were found from difference Fourier maps (thermal parameters refined isotropically), and scattering factors were taken from standard tables.[23] ORTEP drawings of unit cells, structure factors, intra- and intermolecular bond distances and angles, positional parameters, and esd's for each structure are supplied as supplementary material.

Results

The crystal structures of each diarylurea and their cocrystals are discussed in turn. The focus in this section is the relationship between molecular structure and hydrogen bond patterns. Selected intra- and intermolecular bond lengths and angles are given in Table III.

Graph sets are employed to facilitate comparison of hydrogen bond patterns with those of related structures. This method has been discussed in detail in several recent publications.[24,25] The pattern type is indicated (D = diad, R = ring, C = chain, and S = intramolecular), and the degree or "size" of a pattern is given in parentheses. The number of proton donors and acceptors are indicated in the notation as sub- and superscripts, respectively. It is not necessary to understand the intricacies of the assignment in order to use graph sets for hydrogen bond comparisons, but it is helpful to recognize that each unique hydrogen-bonding proton in the structure has its own independent graph set. Graph sets typical of compounds discussed here are illustrated in Figure 1.

1,3-Bis(*m*-nitrophenyl)urea (2α). This crystal form is one of three polymorphs of **2**.[26] In the absence of guest molecules, good crystals of the host molecule are difficult to obtain. Form **2α** was the only one that gave crystals suitable for X-ray crystal structure analysis. The crystal structure shows that the molecule has dihedral angles of 23.6° and 9.5° between the N–CO–N group and the aromatic rings. The twisted conformation is also seen in the urea portion itself with the –NH protons spaced 2.32 Å apart as compared to about 2.05 Å for a planar urea group. The *m*-nitro groups are oriented anti to the urea carbonyl groups. In all of the cocrystal structures of **2** the nitro groups are syn to the carbonyl oxygen. In addition, this is one of two structures, from all of the compounds and cocrystals reported here, in which the nitro group from **2** participates in the hydrogen bond pattern (the other is **13**). As shown in Figure 2a, both urea protons participate in hydrogen bonding as proton donors, and the carbonyl oxygen and nitro groups on the B ring participate as hydrogen bond acceptors, in graph set C(7)C(4).

The hydrogen bond chain formed by the carbonyl and the –NH group of the A ring is a typical amide pattern (C(4)). The O···N distance is 2.995 (3) Å. The remaining urea proton bonds to a nitro group, similar to the amine hydrogen bond patterns of nitroanilines,[16] but contacts only one of the two nitro oxygens (one N–H···O distance is 2.27 Å, and the other is 3.71 Å).

1,3-Bis(*o*-anisoyl)urea (3). This compound exists in two polymorphic forms, **3α** (orthorhombic) and **3β** (tetragonal). **3β** is the metastable crystal form, converting to **3α** at 145 °C via an endothermic transformation of 1.9 kcal/mol. The molecules lie on crystallographic symmetry axes in both structures (a 2-fold axis for **3α** and on a 4_2 axis for **3β**), Figure 2b,c. In **3α**, the torsion angles between the phenyl ring and the N–CO–N group are ±45.9°, while the comparable angle is ±25.8° for **3β**. Both structures have the same hydrogen bond patterns involving intramolecular hydrogen bonds from the urea –NH donors to the *o*-methoxy acceptor groups and, in addition, intermolecular hydrogen bonds from the same –NH donors to carbonyl acceptors on neighboring molecules. Thus, the urea protons and the urea carbonyl oxygens are both involved in three-center interactions, as shown.

3α and **–β** differ in the relative strengths of their inter- and intramolecular hydrogen bonds. **3α** has the shortest intermolecular hydrogen bonds (N···O = 2.993 (2) and 3.145 (2) Å in **3α** and **3β**, respectively) but the longest intramolecular hydrogen bond (N···O = 2.664 (1) and 2.579 (2) Å in **3α** and **3β**, respectively). Steric overcrowding in **3α** resulting from its short intermolecular hydrogen bond is avoided by the twisting of the phenyl rings out of the plane of the molecule. In **3β** where the molecule is more planar, the intermolecular hydrogen bond contact is longer. The hydrogen bond chain of molecules in **3α** is nearly planar and stacks with neighboring chains such that the phenyl rings overlap with 3.4 Å interplanar spacing. In polymorph **3β**, however, alternating molecules in the hydrogen bond chains are oriented orthogonal to one another along the crystallographic 4_2 axis, Figure 3.

1,3-Bis(*m*-nitrophenyl)urea/2-Butanone 1:1 Complex (13). This structure is unique among the entire set of cocrystals studied here. The dominant feature of this structure is not the hydrogen bond pattern but rather the formation of an inclusion compound in which the guest (2-butanone) and the host are not hydrogen bonded to one another, Figure 2d. The only hydrogen bond in the structure is one between a urea N–H proton and a urea nitro group (N(2)···O(2) = 2.912 (6) Å). Butanone is trapped in the cavity where it is highly disordered. The cavity has no proton donors in it so the butanone is trapped by a coincidental steric fit rather than by any particular stabilizing intermolecular interaction. The solid-state IR pattern shows two carbonyl frequencies at 1730 and 1710 cm^{-1}, consistent with non-hydrogen-bonded ketone and non-hydrogen-bonded urea carbonyl groups, respectively. Despite the unique structure of this cocrystal pair the diarylurea molecule is still planar.

1,3-Bis(*m*-nitrophenyl)urea/THF 1:1 Complex (14). In this structure, as in all the cocrystal structures, the two nitro groups are coplanar with their phenyl rings and are syn to the carbonyl group. The entire molecule is nearly planar in **14** with torsion angles of 3.2 and 5.2° between N–CO–N and the phenyl rings. This geometry places the aromatic –CH protons that are ortho to the nitro and the urea groups (–C(2)–H(21), –C(9)–H(91)) only 2.23 (2) and 2.23 (1) Å away from the carbonyl oxygen, with –CH···O angles of 122 (1) and 119 (1)°, Figure 2e and Table III.

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(23) Cromer, D. T.; Waber, J. T. *International Tables for Crystallography*; The Kynoch Press: Birmingham, England, Vol. IV, p 1074, Table 2A.

(24) Bernstein, J.; Etter, M. C.; MacDonald, J. C. *J. Chem. Soc., Perkin Trans. II* **1990**, 695–698.

(25) Etter, M. C.; MacDonald, J. C.; Bernstein, J. *Acta Crystallogr.* **1990**, *B46*, 256–262.

(26) Groth, P. *An Introduction to Chemical Crystallography*; Wiley: New York. 1906; pp 29–30.

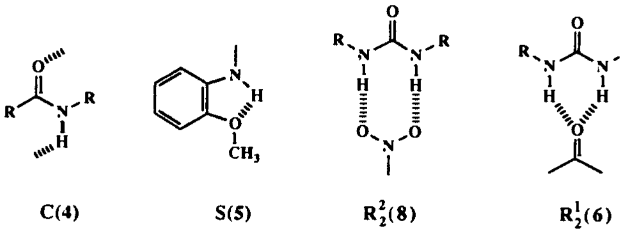


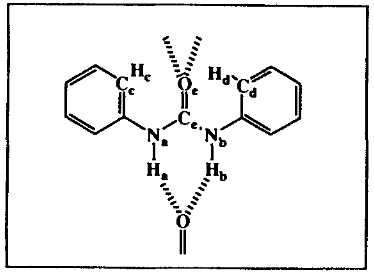
Figure 1. Common hydrogen bond motifs found in DAU crystal structures and DAU cocrystal structures. The motifs are identified by graph set notation as described in the text.

Table II. Crystallographic Data

	2α	**3α**	**3β**	**13**	**14**	**15**	**16**	**17**	**18**
crystal habit	prisms	needles	needles	prisms	prisms	prisms	prisms	needles	needles
guest molecule	none	none	none	2-butanone	THF	TPPO	DMSO	DEG	DMPNA
solvent	EtOH/abs EtOH	acetonitrile	ethanol	2-butanone	THF	acetone	DMSO	diethylene glycol	acetone
crystal size (mm^3)	0.16 × 0.30 × 0.35	0.15 × 0.25 × 0.50	0.20 × 0.30 × 0.50	≈0.2 × 0.3 × 0.5	0.35 × 0.40 × 0.20	0.39 × 0.39 × 0.13	0.21 × 0.39 × 0.13	0.20 × 0.30 × 0.45	0.07 × 0.22 × 0.50
emp formula	$C_{13}H_{10}N_4O_5$	$C_{15}H_{16}N_2O_3$	$C_{15}H_{16}N_2O_3$	$C_{17}H_{18}N_4O_6$	$C_{17}H_{18}N_4O_6$	$C_{13}H_{25}N_3O_6P$	$C_{15}H_{16}N_4O_6S$	$C_{17}H_{20}N_4O_8$	$C_{21}H_{20}N_6O_7$
radiation type λ = 0.71073 Å	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα
temp	rt[a]	rt[a]	rt[a]	rt[a]	rt[a]	rt[a]	rt[a]	rt[a]	rt[a]
a (Å)	11.495 (4)	11.030 (3)	11.826 (1)	16.20 (2)	9.586 (3)	12.34 (1)	9.635 (3)	11.247 (6)	20.002 (5)
b (Å)	13.816 (5)	12.551 (3)	11.826 (2)	13.44 (1)	11.636 (4)	15.136 (6)	10.07 (1)	12.029 (6)	15.414 (5)
c (Å)	8.307 (4)	4.754 (8)	9.833 (9)	14.41 (9)	8.289 (3)	8.311 (6)	10.195 (4)	7.54 (1)	7.165 (4)
α(deg)	90.00	90.00	90.00	90.0	107.24 (3)	101.93 (4)	68.93 (6)	103.98 (7)	90.00
β(deg)	91.92 (3)	90.00	90.00	90.0	93.94 (3)	91.22 (6)	78.05 (3)	102.30 (9)	107.61 (4)
γ(deg)	90.00	90.00	90.00	90.0	86.73 (3)	110.97 (4)	70.93 (5)	98.94 (4)	90.00
space group	$P2_1/c$	$P2_12_12$	$P4_2/n$	*Pnna*	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$C2/c$
Z	4	2	4	8	2	2	2	2	4
vol (Å^3)	1318 (2)	658 (1)	1375 (2)	3136 (9)	880 (1)	1412 (4)	868 (1)	944	2105 (3)
d_{calc} (g/cm^{-3})	1.52	1.37	1.31	1.586	1.41	1.36	1.46	1.44	1.48
measd reflcns	2585	1624	1829	3086	3400	3923	3405	3470	1847
reflcns used	1440	1268	984	1539	2210	2988	2633	2338	1069
R	0.050	0.042	0.049	0.077	0.041	0.035	0.041	0.037	0.058
R_w	0.056	0.048	0.045	0.095	0.049	0.043	0.060	0.051	0.059
θ_{max}(deg)	26	35	25	26	26	22	26	26	25
range of *h*,*k*,*l*	$-14 \leq h \leq 14$ $0 \leq k \leq 17$ $0 \leq l \leq 10$	$-4 \leq h \leq 17$ $0 \leq k \leq 20$ $0 \leq l \leq 7$	$-14 \leq h \leq 14$ $-14 \leq k \leq 14$ $0 \leq l \leq 11$	$0 \leq h \leq 19$ $0 \leq k \leq 20$ $0 \leq \; \leq 14$	$-11 \leq h \leq 11$ $-14 \leq k \leq 14$ $0 \leq l \leq 10$	$-13 \leq h \leq 13$ $-16 \leq k \leq 16$ $0 \leq l \leq 9$	$0 \leq h \leq 11$ $-12 \leq k \leq 12$ $-12 \leq l \leq 12$	$-13 \leq h \leq 13$ $-14 \leq k \leq 14$ $0 \leq l \leq 9$	$-25 \leq h \leq 23$ $0 \leq k \leq 18$ $0 \leq l \leq 8$
final Δelectron density (e$^-$/Å^{-3})	0.167	0.25	0.20	0.56	0.21	0.17	0.28	0.26	0.21
μ (cm^{-1})	1.13	0.90	0.87	1.10	1.02	1.42	2.16	1.08	1.06
(shift/error)$_{max}$	0.11	0.50	0.04	3.6	0.32	0.14	0.02	0.04	0.05
H bond graph set	C(7)C(4)	$N_1 = C(4)[R_2^1(6)]$ $N_2 = S(5)$	$N_1 = C(4)[R_2^1(6)]$ $N_2 = S(5)$	C(8)	$R_2^1(6)$	$R_2^1(6)$	$R_2^1(6)$	$N_1 = R_2^1(6)$ $N_2 = R_2^2(16)C(12)$	$R_2^2(8)$

[a] Room temperatures is denoted by rt.

Table III. Comparative Hydrogen Bond Geometries and Molecular Structures for Diarylureas and Their Cocrystals



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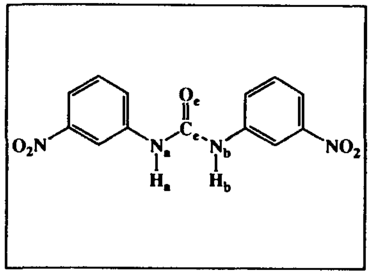
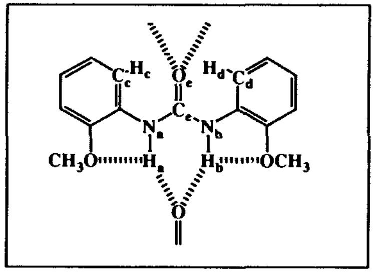
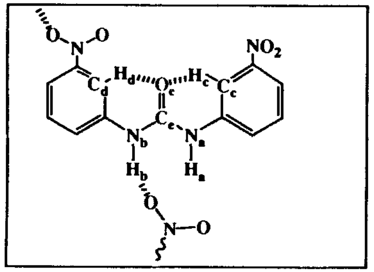


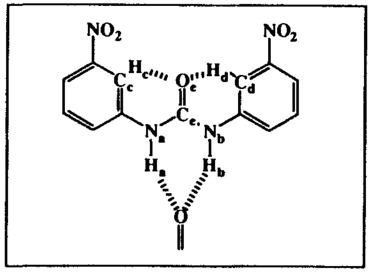
2α



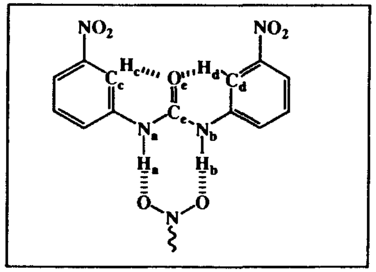
3α & β



13



14-17



18

	1[h]	2α	3α	3β	13[f]	14	15	16	17	18
					(2 + 2-butanone)	(2 + THF)	(2 + TPPO)	(5 + DMSO)	(2 + DEG)	(2 + DMPNA)
C_e=O_e (Å)	1.234 (4)	1.212 (3)	1.233 (2)	1.223 (3)	1.217	1.211 (2)	1.215 (2)	1.215 (2)	1.224 (2)	1.206 (5)
N_a–C_cO_c–N_b(deg)	114.6 (2)	113.3 (2)	113.2 (1)	112.4 (2)	112.7	112.0 (1)	112.2 (2)	111.4 (1)	113.0 (1)	111.7 (2)
C_e–$N_{a,b}$ (Å)	1.357 (3)	1.375 (3)	1.364 (1)	1.366 (2)	1.368	1.374 (2)	1.371 (3)	1.368 (2)	1.362 (2)	1.372 (3)
	1.340 (2)	1.349 (3)				1.372 (2)	1.365 (2)	1.377 (2)	1.361 (2)	
O_e=C_e–$N_{a,b}$	121.9 (2)	123.3 (2)	123.5 (6)	123.8 (1)	122.8	124.1 (1)	124.2 (2)	124.6 (1)	123.3 (1)	124.1 (2)
	123.5 (2)	123.5 (2)			124.4	123.9 (1)	123.7 (2)	124.0 (2)	123.7 (1)	
$H_a \cdots H_b$ (Å)	1.99	2.10	2.15	2.03 (4)	2.02	2.02 (2)	2.06	1.95	2.08 (2)	2.07 (5)
NC(O)N–Ar(deg)	43.0	9.5[a]	45.9	25.8	4.35	3.2	19.1	3.3[c]	6.4	2.3
(dihedral)	36.1	23.6[b]	−45.9	−25.8	−4.17	6.4	23.5	15.4[d]	9.1	−2.3
$N_{a,b} \cdots O$ (Å)	2.782	3.063[a]	2.993 (2)	3.145 (2)	3.363	2.995 (2)	2.860 (3)	2.842 (2)	2.880 (2)	3.003 (4)
	2.920	2.955 (3)[b]	2.664 (2)[e]	2.579 (2)[e]	2.912	2.918 (2)	2.969 (2)	2.866 (2)	3.100 (2)	
$H_{a,b} \cdots O$ (Å)	2.12	2.27[a]	2.24 (2)	2.33 (3)	2.54	2.21 (2)	2.06 (3)	2.00 (1)	2.11 (2)	−2.26 (3)
	1.88	2.30	2.43 (2)	2.19 (2)	2.05	2.10 (2)	2.21 (2)	2.11 (1)	2.38 (2)	
$N_{a,b}$–$H_{a,b} \cdots O$(deg)	161.3	157.8[a]	150 (1)	162 (2)	165	149 (2)	163 (2)	163.1 (2)	162 (2)	167 (3)
	154.1	142.5[b]	97 (1)[e]	108 (2)	154	157 (2)	154 (2)	156.9 (2)	143 (1)	
C_e=$O_e \cdots H_{c,d}$(deg)	154.6	[g]	89.4	98.7 (5)	104.5	103.3 (4)	101.8 (6)	101.8 (4)	102.3 (4)	101.5
	142.4				102.2	102.2 (4)	100.8 (7)	100.3 (4)	101.2 (4)	
$C_{c,d} \cdots O_e$ (Å)	2.67		2.58 (2)	2.34 (2)	2.19	2.23 (1)	2.23 (2)	2.25 (2)	2.25 (1)	2.28
	2.49				2.27	2.23 (2)	2.26 (2)	2.30 (2)	2.29 (2)	
$C_{c,d}(H) \cdots O_e$(deg)	−105.7		−101.1	120 (1)	119.5	122 (1)	126 (2)	121 (2)	119	120.7
	105.1				119.0	119 (1)	118 (2)	119 (2)	120	

[a] Values corresponding to the hydrogen bond between the urea NH and the nitro oxygen. [b] Values corresponding to the hydrogen bond between NH groups and urea carbonyl. [c] Torsion angles formed by the urea group and the *m*-nitrophenyl ring. [d] Torsion angles formed between the urea group and the *p*-nitrophenyl ring. [e] Values for the intramolecular hydrogen bond to the methoxy oxygen atom. [f] All hydrogen bonds in this structure are NH···O contacts. [g] The proton in the 2 position is anti to the urea carbonyl. [h] Values taken from ref 28.

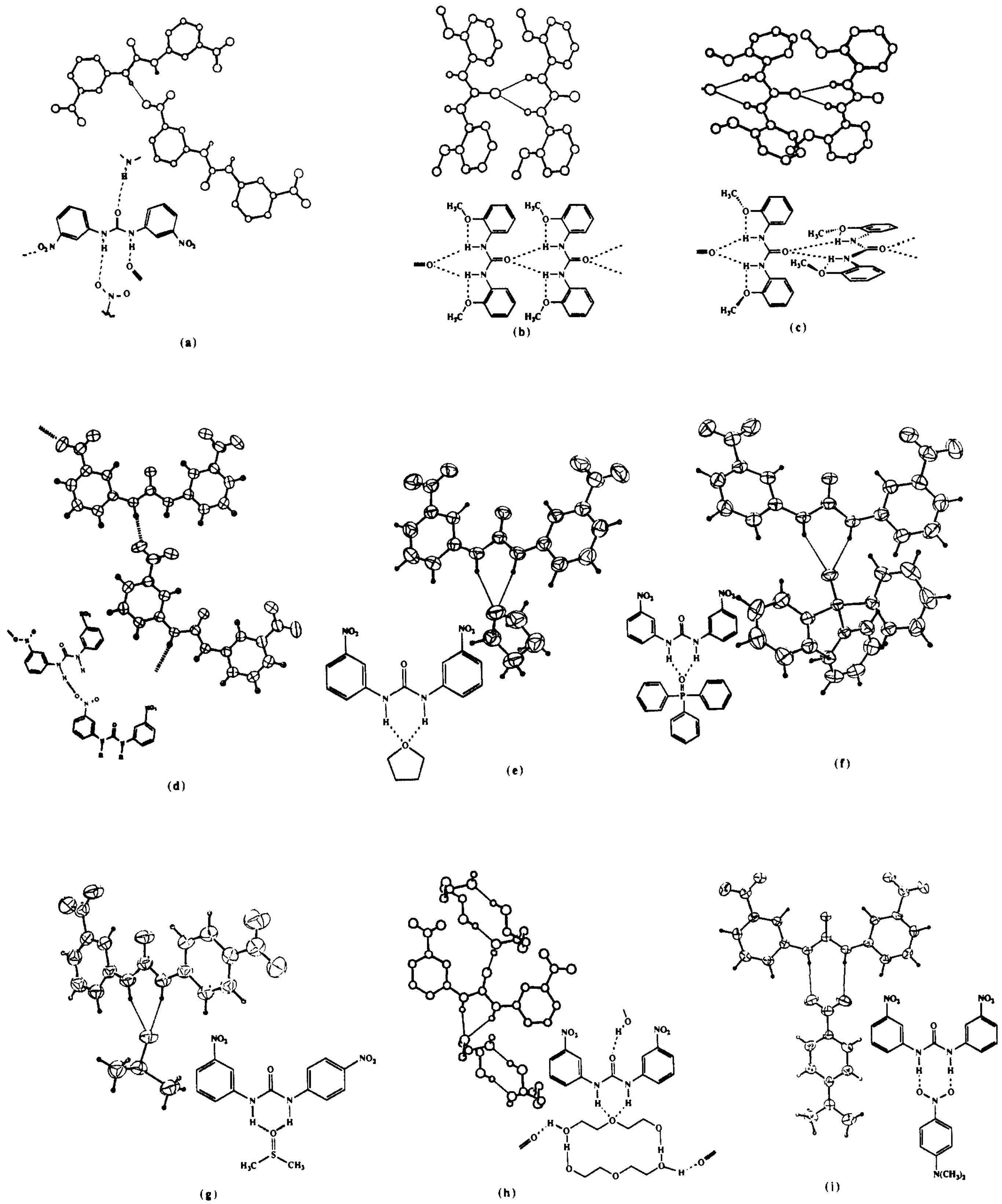


Figure 2. These pictures show the hydrogen bond patterns of urea hosts with their guest acceptors, as found in their respective cocrystal structures. Schematic diagrams of the hydrogen bond patterns are also shown: (a) One of the urea –NH groups of **2***α* is bonded to one of the nitro oxygens, while the other –NH group bonds to the urea carbonyl in a pattern similar to that found in secondary amides. (b) and (c) These two polymorphs have the same hydrogen bond connectivity patterns but different secondary structures. (d) The 2-butanone clathrate structure, **13**, showing a single $-NH\cdots O_2N$ hydrogen bond. The guest molecule is disordered and does not form hydrogen bonds to the host molecule. (e) The THF cocrystal, **14**, showing a three-center hydrogen bond between the THF acceptor oxygen and the two chelating urea –NH groups. (f) The TPPO cocrystal, **15**, showing the typical three-center intermolecular hydrogen bond between the urea host and the guest acceptor. (g) The DMSO cocrystal, **16**, also showing the three-center host–guest hydrogen bond pattern. (h) The DEG cocrystal, **17**, showing participation of the urea carbonyl oxygen in the hydrogen bond pattern. The DEG molecules bond to one another via $OH\cdots O$ hydrogen bonds and form a dimeric bridge between the urea molecules. The urea still forms the common three-center hydrogen bond to the guest molecule. (i) The *N*,*N*-dimethyl-*p*-nitroaniline cocrystal, **18**, showing two-center hydrogen bonds between each –NH group and one of the nitro oxygens. As in all other cocrystal structures, except **17**, the urea carbonyl is not involved in the intermolecular hydrogen bond pattern.

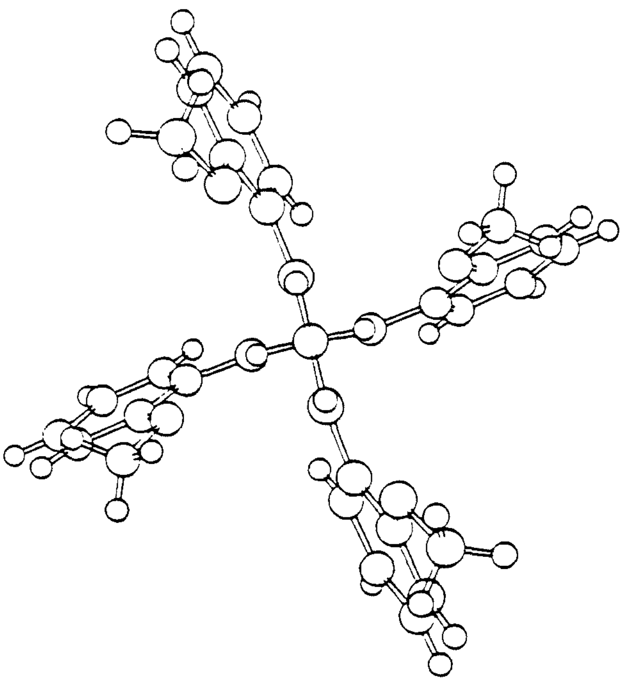


Figure 3. Compound 3β viewed down the 4_2-axis of the hydrogen bond chain.

The THF guest molecule is hydrogen bonded to the urea protons by two short contacts (N···O = 2.995 (2) and 2.918 (2) Å) to give a hydrogen bond pattern with graph set $R_2^1(6)$. The carbonyl bond length is very short (1.211 (2) Å) consistent with the absence of intermolecular hydrogen bonds.

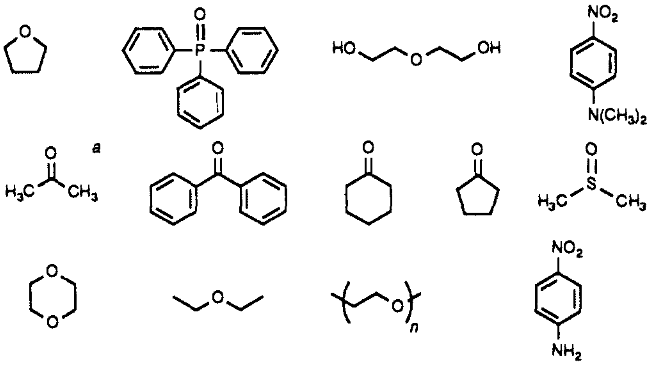
1,3-Bis-(*m*-nitrophenyl)urea/Triphenylphosphine Oxide (TPPO) 1:1 Complex (15). This cocrystal has the same type of hydrogen bond pattern as found for **14**. The nitro groups are coplanar with their phenyl rings (torsion angles 1.7 and 1.2°) and are syn to the carbonyl groups. The urea molecule is less planar than for **14** with phenyl ring torsion angles of 19.1 and 23.5°, placing the ortho -CH protons 2.26 and 2.23 Å from the carbonyl oxygen, Figure 2f. The phosphoryl oxygen is an unsymmetrical bifurcated acceptor, accepting both -NH donors (2.962 (2) and 2.860 (3) Å for -N···O) with one of the -N···O bond lengths shorter than for the comparable bond lengths in **14**. The phosphoryl P=O bond length is 1.499 (1) Å, typical of hydrogen-bonded phosphoryl groups,[19] and the carbonyl C=O distance is short (1.215 (2) Å), as expected, since it does not participate in any intermolecular hydrogen bonds.

1-(*m*-Nitrophenyl)-3-(*p*-nitrophenyl)urea/DMSO 1:1 Complex (16). This compound has only one *m*-nitro group, but it is syn to the carbonyl oxygen like the *m*-nitro groups of other cocrystals of **2**. The *m*-nitrophenyl ring has a smaller torsion angle with the N-CO-N plane (3.3°) than that of the *p*-nitrophenyl ring (15.4°). Both urea -NH protons bond to the oxygen of the DMSO guest, as shown in Figure 2g. The hydrogen bonds are unsymmetrical and short (N···O = 2.886 (2) and 2.842 (2) Å). This structure is isographic with **14** and **15**. The DMSO molecule is slightly disordered in the structure. The occupancy of the S atom refined to 94% at the major site.

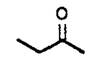
1,3-Bis(*m*-nitrophenyl)urea/Diethylene Glycol (DEG) 1:1 Complex (17). This cocrystal is the only one of the series that has an intermolecular hydrogen bond to the urea carbonyl group. This hydrogen bond is from one of the DEG protons, and it occurs in addition to, not in exclusion of, the expected urea host-guest interaction with the ether oxygen. The nitro groups are syn to the carbonyl oxygen, Figure 2h. The urea molecule is nearly planar (torsion angle 6.4 and 9.1° for N-CO-N and phenyl ring planes). The N···O distances from the urea proton to the DEG ether oxygen are 3.100 (2) and 2.880 (2) Å, and the closest intramolecular contacts between the aromatic -CH protons and the urea carbonyl oxygen are 2.25 (1) and 2.29 (2) Å. After the DEG molecule has formed this contact between the urea -NH donors and the DEG ether oxygen ($R_2^1(6)$), there are still two unused proton donors (the DEG -OH protons) and three unused acceptors (the two DEG -OH oxygens and the urea carbonyl). One DEG proton forms a hydrogen bond to a DEG -OH oxygen on an i-related molecule to form a 16-membered ring with graph set $R_2^2(16)$ (O···O = 2.831 (2) Å). The remaining DEG -OH proton chooses the urea carbonyl oxygen over the unused DEG -OH oxygen (C(12)). This hydrogen bond, C=O···HO is reasonably strong since the O···O distance is short (2.737 (2) Å) and the carbonyl C=O distance is slightly lengthened (1.224 (2) Å).

Table IV. Summary of Cocrystallization Properties of **2**

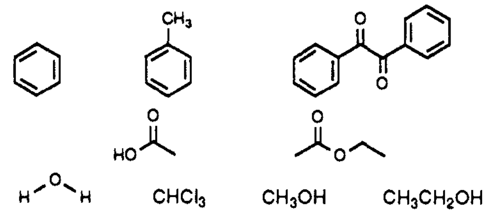
Guest Molecules That Cocrystallize with and Hydrogen Bond to 2



Guest Molecules That Cocrystallize with, but Do Not Form Hydrogen Bonds to, 2



Compounds That Did Not Cocrystallize with **2**

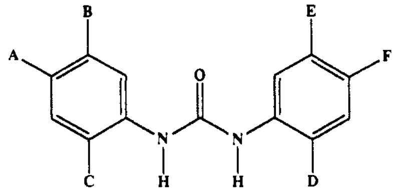


[a] For this compound, IR and NMR data clearly confirm the formation of a 1:1 crystal, but without a crystal structure the exact hydrogen-bonding pattern cannot be assigned.

1,3-Bis(*m*-nitrophenyl)urea/*N*,*N*′-Dimethyl-*p*-nitroaniline (DMPNA) 1:1 Complex in (18). This structure is like the complexes **14** and **15** in that the *m*-nitro groups are syn to the carbonyl oxygen and the urea protons are used in intermolecular hydrogen bonds to the guest molecule. The carbonyl oxygen of the urea group is also free of intermolecular hydrogen bonds, Figure 2i. The urea molecule is nearly planar with torsion angles between the N-CO-N and the phenyl rings of ±2.3°. There is a crystallographic 2-fold axis in the complex so the two intermolecular hydrogen bonds are identical. An unusual feature of this structure involves the nitro groups of the guest molecule. Each oxygen of the nitro group accepts one urea proton to form an eight-membered ring with graph set $R_2^2(8)$. Most nitroanilines form four-membered ring hydrogen bond patterns where one aniline proton is positioned between the two nitro oxygen atoms.[16] The hydrogen bond N···O distance in **18** (3.003 Å) indicates a moderately strong hydrogen bond. A typical nitroaniline hydrogen bond distance (N···O) is 3.05 Å. The O-N-O nitro angle (127°) is about the same as the comparable angle for non-hydrogen-bonded nitro groups and is considerably larger than for nitro groups that hydrogen bond to one proton donor in a four-membered ring pattern (120.1°).

Other Cocrystal Structures and Methods of Characterization. Several 1:1 cocrystals of 1,3-bis(*m*-nitrophenyl) urea, **2**, were prepared and characterized by chemical and spectroscopic means rather than by crystallography. Guest molecules are listed in Table IV. Several cocrystals of diarylureas other than **2** were prepared and listed in Table V as class II.

Table V. Diarylurea Cocrystallization Classes



compd	A	B	C	D	E	F
Class I: Diarylureas That Will Not Complex Guest Acceptors						
1	H	H	H	H	H	H
3α,β	H	H	OCH_3	OCH_3	H	H
6	OCH_3	H	H	H		OCH_3
7	OCH_3	H	H	H	H	H
8	H	H	OCH_3	H	H	H
9	H	H	NO_2	NO_2	H	H
11	H	CH_3	H	H	CH_3	H
Class II: Diarylureas That Complex the Very Strong Guest Acceptors TPPO and/or DMSO						
4	H	NO_2	H	H	H	H
5	H	NO_2	H	H	H	NO_2
10	NO_2	H	H	H	H	NO_2
12	H	CF_3	H	H	CF_3	H
Class III: Diarylureas That Complex Strong and Moderate Acceptors (Ketones, Ethers, Nitroanilines)						
2	H	NO_2	H	H	NO_2	H

Equally important in determining host–guest selectivity in these systems are the host–guest combinations that did not give rise to the formation of cocrystals. Compound **2** would not cocrystallize with solvents that were weak proton acceptors (benzene, toluene, chloroform, alcohols, ethyl acetate, acetic acid, water). Except for **10**, none of the other diarylureas lacking an electron-withdrawing group (EWG) in the meta position cocrystallized with any acceptors. These cocrystallization properties are summarized in Table V.

Characterization of cocrystals was based on chemical analysis of stoichiometry by solution NMR, determination of rigid or entrapped solvent molecules by solid-state ^{13}C CP/MAS NMR, solid-state IR, and thermal analyses. The IR analyses proved to be particularly useful. Carbonyl stretching frequencies are very sensitive to hydrogen bonding, varying from 1630 cm^{-1} in **7** to 1735 cm^{-1} in **10**. The low-frequency bands occur in homomolecular structures where the urea carbonyl oxygen forms two strong hydrogen bonds to the –NH protons of a neighboring urea molecule ($R_2^1(6)$). This assignment is confirmed by the hydrogen bond pattern found in the crystal structures of **1**, **3**α, and **3**β, which have carbonyl stretching frequencies of 1650, 1650, and 1680 cm^{-1}, respectively. Similar low-frequency bands of this type also occur for compounds for which crystal structures have not been done. These structures most likely have hydrogen bond patterns like that of carbanilide (**1**), with graph set $N_1 = C(4)[R_2^1(6)]$.

Only two structures are available having just a single intermolecular hydrogen bond to the urea carbonyl oxygen (**2**α and **17**), and they have intermediate frequencies (1697 and 1700 cm^{-1}). When the carbonyl oxygen of the diarylurea host molecule has no intermolecular hydrogen bonds, its frequency occurs at or above 1700 cm^{-1}, much like the carbonyl bands of ketones.

Solid-state NMR was also useful in providing confirming evidence that **21** and **22** were cocrystals with guest molecules hydrogen bonded to the urea groups. The carbonyl ^{13}C chemical shifts of the guest moved downfield by about 10 ppm in their cocrystals as compared to solution, consistent with deshielding by hydrogen bond interactions.[27] For the acetone cocrystals (**19**) no such shift was observed ($\Delta\sigma = -2.1$ ppm). The IR and NMR data for **19** do not unambiguously determine the hydrogen bond pattern of this cocrystal.

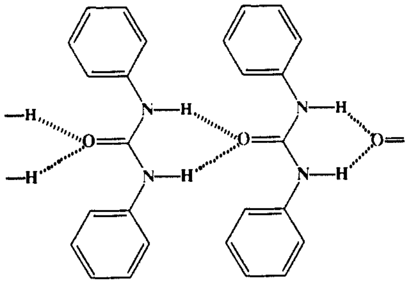


Figure 4. The hydrogen bond pattern found in *N*,*N'*-diphenylurea, showing use of all the donors and acceptors in a hydrogen bond chain with the three-center hydrogen bonds at the carbonyl oxygen atoms.[28]

The melting point behavior of the cocrystals was also characteristic. Cocrystals usually turned cloudy or cracked at lower temperatures (below 200 °C) and then melted at the melting point of the host urea molecule, 256–258 °C. All of the guest molecules have much lower melting points than 256 °C, and most of them even have lower boiling points than 256 °C, so they vaporize out of the cocrystals during heating.

Other Diarylurea Compounds. Several diarylureas were prepared as host molecules and were characterized chemically and spectroscopically (**2**, **3**α and -β, **5**, **6**, and **8**–**12**). With the exception of 1,3-bis(*p*-nitrophenyl) urea (**10**) as discussed above, their solid-state carbonyl IR stretching frequencies vary from 1630 to 1661 cm^{-1} suggesting that they all form the normal diarylurea pattern $C(4)[R_2^1(6)]$. Upon complexation and conversion to $R_2^1(6)$ each of these ureas gives a carbonyl frequency of 1700 cm^{-1} or above. In addition, the β polymorph of **2** was characterized. It is metastable relative to the α polymorph. **2**β has an IR pattern much more like that of **1** than like that of **2**α and a carbonyl frequency at 1658 cm^{-1}, so it almost certainly has the normal diarylurea hydrogen bond pattern.

Discussion

Diarylurea molecules have two proton donors and one proton acceptor that can participate in hydrogen bond interactions. Whether all or some of these groups are actually used for hydrogen bonding in solution or in the solid state depends on competition with proton donors and acceptors present on solvent molecules, on guest molecules in solution, and on neighboring molecules in the solid state. We have observed that certain diarylureas readily form cocrystals with proton acceptor guest molecules, while other diarylureas do not. In the present study this chemical information is coupled to crystallographic studies of diarylureas and their cocrystals as a way to evaluate competitive intermolecular self-assembly processes and as a way to predict the intra- and intermolecular hydrogen-bonding properties of this class of compounds.

We have developed empirical hydrogen bond rules for several classes of organic molecules, the simplest of which states that all available proton donor and acceptor groups will be used in the hydrogen bond patterns of most organic molecules in the crystalline state.[1] This principle suggests that a preferred hydrogen bond pattern for DAU compounds would have the single urea carbonyl group positioned between the two –NH hydrogens of a neighboring molecule, as shown in Figure 4 for 1,3-bis(phenyl)urea.[28]

The Anomalous Complexation Dilemma. One way to affect hydrogen bond competition is to introduce competitive acceptor groups (A) on guest molecules. Such acceptors could interfere with the normal hydrogen bond pattern of a DAU compound in several different ways, depending on their relative proton-accepting abilities. If A were a better acceptor than the carbonyl group of the DAU compound, it might take the place of the carbonyl group, as in Scheme I (part 1) below. If A had about the same accepting ability as the carbonyl group, it could bond to one of the proton donors, while the carbonyl group bonded to the other, Scheme I (part 2). If A were a poorer acceptor than either a "free" or a once hydrogen-bonded DAU carbonyl group, it should not

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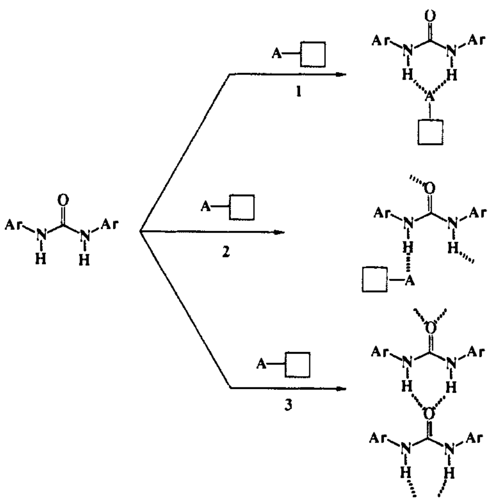
[27] Etter, M. C.; Hoye, R. C.; Vojta, G. M. *Cryst. Rev.* **1988**, *1*, 281.

[28] Dannecker, W.; Kopf, J.; Rust, H. *Cryst. Struct. Comm.* **1979**, *8*, 429–432.

Scheme I

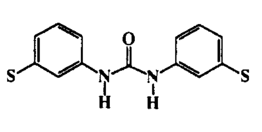


be incorporated into a complex at all, as shown in Scheme I (part 3).

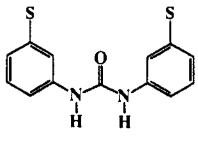
To test these different possibilities DAU compounds have been cocrystallized with guest molecules containing various proton-acceptor groups. For example, 1,3-bis(*m*-nitrophenyl) urea **2**, was cocrystallized with very good acceptors like phosphine oxides and much poorer acceptors like esters, ethers, and aromatic compounds, Table IV. To our surprise, guest molecules with the best acceptor groups as well as those with the moderately good acceptor groups formed complexes with **2**. In addition, moderate-to-weak acceptors were not incorporated into any other DAU host except for **2**. Compound **2** appeared to be an all-purpose cocrystallizing agent, crystallizing even with compounds that were expected to be poorer acceptors than the urea carbonyl, while some of the other very closely related diarylureas (like **12**, with *m*-CF_3 substituents) would cocrystallize only with the strongest acceptors. Others (like **11**, with *m*-CH_3 substituents) would not incorporate guest molecules at all (Scheme I) (part 3).

Differential complexing properties of diarylurea hosts cannot be explained from simple analyses of pK_a or steric properties. For example, –NH acidity does not correlate with complexation behavior since the *p*-NO_2 derivatives should have more acidic –NH protons than the *m*-NO_2 derivatives, but the *p*-NO_2 derivatives are less effective as proton donors during cocrystallization. Intramolecular steric hindrance to formation of the particular conformer needed for guest complexation is not a likely factor since the nitro group is about the same size as –CF_3, –CH_3, or –OCH_3 groups, yet the nitro derivatives complex most easily with guest molecules.

When guest molecules are bulky, or when host–guest hydrogen bonds are very short, intermolecular steric hindrance to guest complexation or to host self-association could be a contributing factor in differential complexation behavior. Ortho substituents oriented syn to the –NH groups would be the most likely substituents to interfere with guest complexation. Since the –OCH_3 groups in **3** are locked into such a position through intramolecular hydrogen bonding, such steric hindrance might contribute to their poor complexation behavior. On the other hand, the relatively small meta substituents tested in this study should cause little or no steric hindrance to guest incorporation at the –NH sites on the urea molecule regardless of whether they are syn or anti to the carbonyl group of DAU.

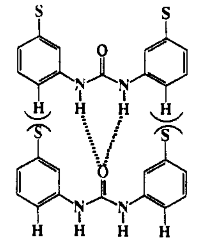


anti



syn

The role of intermolecular steric interference on self-association should also be small for the particular aryl substituents studied here since many DAU compounds do self-associate in the absence of guest molecules (**1**, **2**, **3α**, **3β**, **6**, **8**, **9**, **11**, and **12**) including some with *m*-nitro substituents (**2α** and **2β**). Groups that are syn to the carbonyl groups would interfere the most with approach of a neighboring molecule in a coplanar orientation, as shown. The strain could be relieved by rotation of the aryl rings or by approach of the second molecule along a plane that is twisted relative to that of the first molecule (as found for **3β**, Figure 4).



In other words, DAU compounds with *m*-nitro groups behave just like DAU compounds with other meta substituents with regard to self-association. It is only with regard to association with guest molecules that the *m*-nitro derivatives have unique properties. Thus, we are left with the anomaly that *the only DAU compound which is a generally good complexing agent for proton acceptors is the m-nitro-substituted diarylurea, 2*.

A Solution to the Anomaly? Upon comparison of the molecular structures of DAU molecules in their cocrystal forms with those in their self-assembled forms, a reasonable solution to the anomalous cocrystallization behavior of **2** is seen. The homomeric structures (**1**, **2α**, **3α**, **3β**) have dihedral angles between their aromatic rings and their urea –N–(CO)–N planes of 43.6 and 36.1 (meta substituent = H), ±45.9 (meta substituent = OCH_3), ±25.8 (meta substituent = OCH_3), and 9.5 and 23° (meta substituent = NO_2). For the cocrystal structures, the dihedral angles for the *m*-nitro aromatic rings in increasing order are ±2.3, 3.2, 3.3, 5.2, 6.4, 9.1, 19.1, and 23.5. The two highest values are for the triphenylphosphine oxide (TPPO) cocrystal (**15**) which has a very short hydrogen bond and considerable intermolecular steric strain. For TPPO in particular, the guest molecule is also very bulky so the DAU molecule has apparently relieved intermolecular steric hindrance by adopting a twisted conformation. Except for this case (**15**), the other compounds have no apparent intermolecular steric strain associated with complexation and have nearly planar conformations.

There are two structures, **2α** and **13**, in which the *m*-nitro DAU molecule is not involved in hydrogen bond interactions with a guest molecule. Structure **13** is a true clathrate,[29] since the butanone guest is incorporated as a topologically complementary molecule with no hydrogen bond interactions to the DAU host. The DAU host in this case has only one single hydrogen bond contact, between a nitro group and one of the –NH protons, Figure 2d.

In all the cocrystal structures, including **13**, the intramolecular (C)H···O distances between the ortho proton nearest the carbonyl group and the carbonyl oxygen are 2.30 Å or less, as shown. This distance is within the 2.40 Å limit suggested by Kennard as an indicator for C(H)···O hydrogen bonds.[30] For structure **1**, with no *m*-nitro groups, the comparable C(H)···O distances are 2.49 and 2.66 Å, and for **2α**, which has its *m*-NO_2 groups syn to the carbonyl, one C(H)···O is longer and the other is shorter than 2.30 Å.

These data suggest that a weak stabilizing intramolecular CH···O interaction may be forming in DAU molecules when meta electron-withdrawing substituents are present. This interaction leads to an effective decrease in the *intermolecular* hydrogen-bonding ability of the carbonyl oxygen. To test this idea *m*-CF_3 groups were substituted for the NO_2 groups, as alternative good electron-withdrawing substituents. These ureas complex with the best proton acceptors but not with the moderate-to-weak acceptors. A better choice might have been a *m*-CN group (relative inductive effects (σ_I) of *m*-NO_2, *m*-CN, and *m*-CF_3 are 0.65, 0.56, and 0.45,

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[29] Weber, E. *Top. Curr. Chem.* **1987**, *140*, 2–20.

[30] Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063–5070.

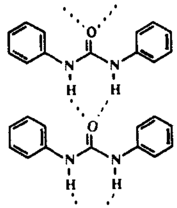
Table VI. Correlation of Hydrogen Bond Pattern and IR Carbonyl Frequencies

compd	hydrogen bond pattern involving the carbonyl group[a]	hydrogen bond pattern involving –NH protons	urea carbonyl frequency (cm^{-1}) (C=O length, Å)
	I. Diarylureas		
1	C(4)	$R_2^1(6)$	1650 (1.232 (4))
2α	C(4)	C(7)	1697 (1.212 (3))
3α	C(4)	$R_2^1(6)$	1650 (1.223 (3))
3β	C(4)	$R_2^1(6)$	1680 (1.223 (3))
2β, **4**, **6**, **8**, **9**, **11**, **12**	unknown[b]	unknown	1630–1661
	II. Diarylurea Cocrystals		
13[c]	none	C(8)	1730, 1710 (1.217 (5))
14	none	$R_2^1(6)$	1720 (1.211 (2))
15	none	$R_2^1(6)$	1715 (1.215 (2))
16	none	$R_2^1(6)$	1715 (1.206 (5))
17[d]	C(12)	$R_2^1(6)$	1700 (1.224 (2))
18	none	$R_2^2(8)$	1727 (1.206 (5))
19, **20–28**, **30**, **31**	unknown	unknown	1700–1735

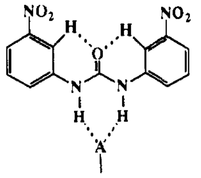
[a] Hydrogen bond patterns are indicated by graph sets as described in the text.[1c] [b] Patterns are indicated as unknown when the crystal structure has not been determined. [c] This is the only cocrystal that has a guest molecule (2-butanone) which is not hydrogen bonded to the urea host. [d] This cocrystal is the only one in which the guest molecule acts as a proton donor to the carbonyl group of the urea host.

respectively).[31] Theoretical studies would be useful here to help determine the role of the CH···O interactions in these host–guest complexes.

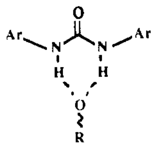
Hydrogen Bond Pattern Analysis. There are certain hydrogen bond patterns that occur frequently in DAU compounds and in their cocrystals, primarily as a consequence of the number and relative strengths of the proton donors and acceptors present in these systems. These patterns were derived from the DAU cocrystal structures presented here and from three 1,3-disubstituted urea crystal structures in the literature (1,3-bis(cyclohexyl)urea,[32] 1,3-bis(α-tosylbenzyl)urea,[33] and 1,3-bis(β,β,β-trinitroethyl)urea[34]). Other urea and urea cocrystal structures from the literature were not used since they were either unsubstituted or monosubstituted ureas or the urea functionality was only one of many other kinds of competing functional groups so the independent role of the urea group could not be evaluated easily. The rules listed below are to be used as guidelines for predicting hydrogen bond patterns and are useful as a baseline against which other intermolecular and steric interactions can be evaluated. The "rules" are the most likely patterns of self-association in the absence of steric and ionic interactions. They are not necessarily the only possible patterns for DAU compounds. The first three rules apply in general to all small organic molecules and have been discussed previously. 1. All good donors and acceptors are used in hydrogen bonding. 2. Six-membered ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds. 3. The best proton donors and acceptors, after cyclic intramolecular hydrogen bonds have formed, form intermolecular hydrogen bonds to one another. 4. The NH hydrogens prefer to adopt an anti relationship to the carbonyl group and form three-center bonds to urea carbonyl groups (C(4)[$R_2^1(6)$]).



5. Cocrystals form when there are strong meta-substituted electron-withdrawing substituents (like $-NO_2$) on the aryl rings, and when the guest molecules have acceptor groups (A) that are stronger than the internally hydrogen-bonded urea carbonyl oxygen.



6. In cocrystals, the –NH protons form three-center bonds to acceptor groups on guest molecules ($R_2^1(6)$).



7. Acceptor groups in the ortho positions on aromatic rings form intramolecular hydrogen bonds to the –NH protons. This interaction takes place in addition to rule no. 4 above. 8. Nitro groups of *m*-nitro-substituted DAU compounds are used as hydrogen bond acceptors for urea protons in the absence of guest molecules with good proton acceptors.

Hydrogen Bond Patterns of Other Urea Cocrystals. Of the many cocrystal complexes that Hart made from bulky disubstituted urea hosts, like 1,3-ditrityl urea (DTU), those that formed hydrogen bonds to the guest molecules usually did so by using the same graph set that we observed for most of our cocrystals, namely, $R_2^1(6)$. Hart's complexes do not have intramolecular hydrogen bonds to the urea carbonyl groups, so their carbonyl oxygen atoms are still strong intermolecular proton acceptors. These oxygens are sterically hindered, however, which prevents them from engaging in hydrogen bonding to bulky guest molecules. Secondary amides can act as a bridge between two DTU molecules by donating their –NH hydrogens to the urea carbonyl group and inserting their carbonyl oxygen between the –NH protons of a neighboring urea molecule, as shown.[35] This situation is analogous

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(31) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New York, 1975.

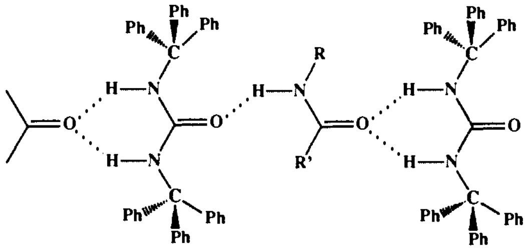
(32) Coiro, V. M.; Giacomello, P.; Giglio, E. *Acta Crystallogr.* **1971**, *B27*, 2112–2119.

(33) Tel, R. M.; Engberts, B. F. N. *J. Chem. Soc., Perkin Trans. II* **1976**, 483–488.

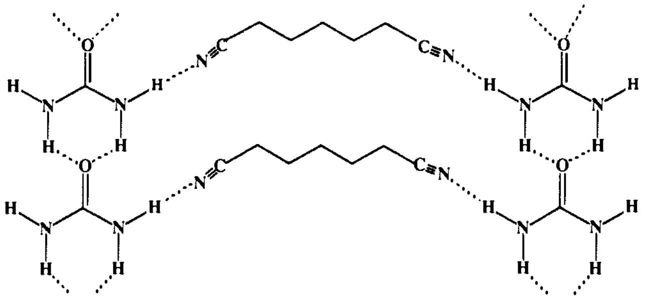
(34) Lind, M. D. *Acta Crystallogr.* **1970**, *B26*, 590–596.

(35) The graph set of the 1:1 cocrystals between DTU and a secondary amide is describable using graph set notation with first- and second-order networks. The first-order network describes the hydrogen bond motif for each individual hydrogen bond type, as if this one hydrogen bond type were the only one present in the structure. Thus, $N_1 = R_2^1(6)D$ since there is one dimeric hydrogen bond and one cyclic intermolecular hydrogen bond with two donors, one acceptor, and a six-membered ring. The second-order network designation refers to hydrogen bond patterns that include more than one type of hydrogen bond. The chain pattern apparent in these structures is formed by two different kinds of hydrogen bonds and the repeat pattern involves eight atoms, so $N_2 = C(8)$. These designations may seem complicated for such a simple structure, but they explicitly show how subsets of the hydrogen bond patterns of our DAU host–guest complexes are the same as subsets of Hart's DTU complexes. For further details on how to make and use these assignments, see a recent publication on graph sets.[25]

to our DEG complex (**17**) which bridges neighboring urea molecules. Hart's complexes show that intramolecular C(H)···O hydrogen bonding in a disubstituted urea is not a necessary condition for complexing guest molecules. In his complexes a different factor, topology, is promoting complexation. In either case, preferred hydrogen bond patterns are formed when the balance of other forces either promotes complexation (through enclathration) or prevents other competitive hydrogen bonds from forming (by steric interference in Hart's compounds and by intramolecular hydrogen bonding in the DAU complexes presented here).



Recently an interesting application of our hydrogen bond rules to predicting the structure of a urea cocrystal with a dicyanoalkyl guest molecule was presented. Hollingsworth[36] showed that a simple nonsubstituted urea cocrystal also followed our hydrogen bond rules. Urea has four proton donors and only one acceptor oxygen. By tying up the two anti -NH proton donors in the predicted $R^1_2(6)$ pattern, two syn -NH hydrogens remain to form hydrogen bonds to guest molecules. He found that α,ω-dicyanoalkyl molecules bridge between two urea chains by bonding to the syn -NH hydrogens on neighboring chains. Other patterns would also have been consistent with our rules. For example the cyano groups could have bonded to the anti hydrogens and left the syn hydrogens to form cyclic dimers to neighboring urea molecules. Nevertheless, all the proton donors and acceptors were used, and the rules presented above were not violated.



Molecular Recognition Properties of DAU Compounds. By cocrystallizing **2** with more than a dozen different guest molecules and by comparing the cocrystal structures to those of **2** itself, we have mapped out the molecular recognition properties of **2** as it is perturbed by a variety of neighboring molecules. In the absence of guest molecules, **2** seeks ways to use both its proton donors and its carbonyl oxygen in hydrogen bond interactions, as discussed above for **2***β*. In **2***α* one of the nitro groups is also used. When guest acceptors are present, molecules of **2** respond by preferentially selecting guest acceptors as hydrogen bond partners, rather than other molecules of **2**. Since such selectivity occurs primarily for **2**, and not for DAU compounds with other substituents, **2** must have a special ability to respond to the presence of guest acceptors. This ability involves stabilization of a planar conformation with the *m*-NO_2 groups oriented syn to the carbonyl oxygen. In this conformer the carbonyl group becomes an ineffective hydrogen bond acceptor which can freely donate its -NH hydrogens to guest acceptors. These subtle interactions are only apparent from the combined use of cocrystallization studies on a large number of DAU compounds and by having available a comparably large number of crystal structures for definitively assigning hydrogen bond patterns.

The use of guest molecules as a probe during cocrystallization to study the structural response of a receptor molecule is, thus, a promising new approach to understanding the intermolecular chemistry of small organic molecules.

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Supplementary Material Available: Tables of positional parameters, anisotropic thermal parameters, and intra- and intermolecular bond lengths and angles and ORTEP drawings of unit cells for nine crystal structures (150 pages); tables of observed and calculated structure factors (83 pages). Ordering information is given on any current masthead page.

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[36] Hollingsworth, M. Private communication.