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HYDROGEN BONDED COMPLEXES IV UREA-PHENOL COMPLEXES

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Abstract

A number of crystalline, hydrogen-bonded complexes of ureas and phenols are reported. The most commonly observed urea-phenol ratio is 1:1, but some complexes with ratios of 2:1, 1:2 and 1:3 were encountered. The structures of these complexes are discussed and one degradative reaction is described.

As in our earlier studies[1,2], our interest has been focused on those hydrogen-bonded complexes which can be isolated as crystalline solids and which can be recrystallized without change in composition. Most recent investigations of hydrogen-bonded complexes were carried out using spectroscopic measurements in solution. Such studies provide limited information about complexes with donor-acceptor ratios of 1:1 and no reliable information about complexes having ratios differing from 1:1. The observation of a large equilibrium constant for formation of a particular complex in solution provides no assurance that that complex will be isolable as a solid and will have a melting point above room temperature. Moreover, such measurements provide no physical properties other than the extinction coefficients for light absorption.

In previous studies[1,2] it was shown that phenols form solid, isolable hydrogen-bonded complexes with both amides and lactams and that these may occur with donor-acceptor ratios of 1:1, 1:2 or 1:3. Complex formation between phenols and ureas was first studied with melting point-composition curves[3-6] from which one can infer the existence of any complexes that may form and determine their melting points and stoichiometry. Such observations do not guarantee that the complex will be isolable and recrystallizable. An additional requirement is the availability of a solvent or solvent system with solubility characteristics for both the starting materials and complex which permit recrystallization of the complex. More recent studies[7-9] have all been with absorption spectroscopy in solution.

Our interest in the urea-phenol complexes was aroused by the fact that, unlike the previously studied complexes[1,2] where the donor-acceptor ratio was always one or less, the urea-phenol complexes may form with donor-acceptor ratios of one or greater[3,4,6,8]. In the present report we list those urea-phenol complexes which we were able to isolate as well defined solids. Complexes having donor-acceptor ratios of 1:1, 2:1 and 3:1 were encountered. Also included are a study of a pertinent reaction of these complexes and a discussion of their structures.

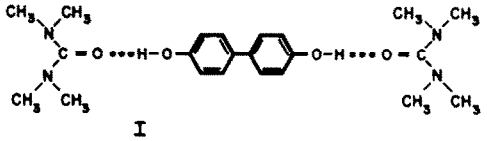
Results and Discussion

The successful preparations of urea-phenol complexes are assembled in Table 1. In every case the yield was good, and the complex could be recrystallized without changing its composition. In the large majority of cases the urea-phenol ratio is 1:1, but we did find one isolated case in which the ratio was 1:2, three cases in which the ratio was 2:1 and four cases in which the ratio was presumably 1:3.

To emphasize a point made earlier some unsuccessful attempts need to be indicated. Melting point-composition curves indicate that urea and p-nitrophenol form a 1:1 complex of m.p. 118° and that urea and phenol form a 1:2 complex of m.p. 60°[4]. Our efforts to obtain these two complexes from solution failed, probably because we did not find a suitable solvent system. Infrared spectrometry in carbon tetrachloride solution at 30° indicates that tetramethylurea forms both 1:1 and 1:2 complexes with phenols[8], with the equilibrium constant for formation of the 1:1 complex always much larger than the constant for formation of the 1:2 complex. Nevertheless, in one instance, the reaction between tetramethylurea and pentachlorophenol, we were able to obtain the 1:2 complex but not the 1:1 complex. With tetramethylurea and six other phenols we could prepare only the 1:1 complex. In the reaction with picric acid, we obtained the 1:1 complex with the initial molar ratio of tetramethylurea to picric acid at 2:1. With initial molar ratios of both 1:2 and 1:3 we failed to obtain the 1:2

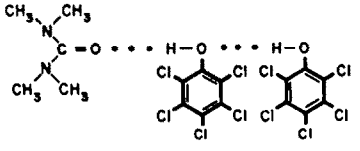
complex and recovered picric acid in 80% yield. Thus neither a melting point-composition curve nor absorption spectroscopy is a completely reliable guide to complexes that may be isolated as recrystallizable solids.

The urea and phenol in the 1:1 complexes are held together by a hydrogen bond, with the urea carbonyl oxygen as acceptor and the phenolic hydroxyl group as donor. This follows from the observed perturbations in the infrared of the carbonyl and hydroxyl vibrations on complex formation[7,8,9]. The structures of the three complexes with urea-phenol ratios of 2:1 [entries 5, 13, and 17 in Table I] are also straightforward. The phenols involved are in one case 4,4′-biphenol and in the other two cases hydroquinone. In both phenols the hydroxyl groups are well separated, and there is no steric constraint to formation of two hydrogen bonds with two urea molecules. For the tetramethylurea - 4,4′-biphenol complex the structure is I; the only surprising aspect is that in the three cases where we obtained 2:1 complexes we were unable to prepare the 1:1 complex, but this, too, may have been due to our failure to find an appropriate solvent system.



I

The one 1:2 complex that we prepared [entry no. 8 in Table I] is of special interest. Preparative experiments with the initial molar ratios of urea to pentachlorophenol at 3:2, at 1:1 and at 1:2 all gave only the 1:2 complex and in good yield in all three experiments. The structures of 1:2 urea-phenol complexes in solution have been discussed with one group[7] favoring structure III and the other group[8] favoring II. It is not clear why no consideration is given to a structure, IV, containing both an O··· H-O and an N··· H-O hydrogen bond.



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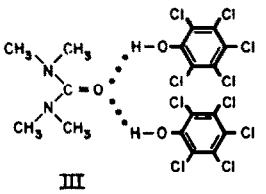

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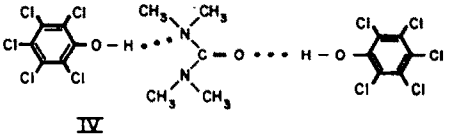


IV

The last four entries in Table I are for complexes of ureas and picric acid, all having urea-phenol ratios of 1:3. The first of these complexes that we prepared was from 1-piperidinecarboxamide and picric acid. It was reasonable to react to such a result with scepticism and to suspect that what in fact was obtained was a fortuitous mixture of either 1-piperidinecarboxamide and picric acid or the 1:1 complex and picric acid that provided, on titration, exactly the correct neutral equivalent for the 1:3 complex. However, when three other examples of 1:3 urea-phenol complexes were encountered, a detailed study, with the focus on the 1:3 piperidinecarboxamide-picric acid complex, was undertaken.

When 1-piperidinecarboxamide and 1.1 molar equivalents of picric acid are reacted in 2-propanol-hexane the 1:1 complex, m.p. 119-122°, is obtained in 95% yield. Recrystallization from the same solvent system results in an 87% yield; m.p. 120-123°; neutral equivalent [NE], 357. When 3.5 molar equivalents of picric acid in the same 2-propanol-hexane solvent are used, one obtains a quantitive yield of the presumed 1:3 complex; m.p. 103-108°; NE, 268 [calcd. for 1:3 complex, 272]. Recrystallization from the same solvents gave a 96% yield of the complex; m.p. 103-107°; NE, 272. Recrystallization from more dilute 2-propanol-hexane gave a 78% recovery of the complex; m.p. 103-107°; NE, 272.

When the above two experiments were repeated with acetone-hexane as the solvent system only the 1:1 complex was obtained even with the initial molar ratio of urea to phenol at 1:3.5. Not surprisingly, when an attempt was made to recrystallize the 1:3 complex from this

Table I
UREA-PHENOL COMPLEXES

	A UREA	B PHENOL	A-B RATIO	CRYSTALLIZING SOLVENTS	M.P. °C	YIELD %	ANALYSES CALCULATED C	H	N	NE	CALCULATED C	H	N	NE
1	Tetramethylurea	Resorcinol	1:1	Ether-hexane	46-48	92			12.38				12.10	
2	Tetramethylurea	o,o'-Biphenol	1:1	Ether-hexane	54-55	82			9.27				9.16	
3	Tetramethylurea	2,3-Naphthalenediol	1:1	Ether-hexane	65-66	91			10.14				9.83	
4	Tetramethylurea	Hydroquinone	1:1	Ether-hexane	57-60	79			12.38				12.26	
5	Tetramethylurea	4,4'-Biphenol	2:1	Acetone-hexane	98-100	86			13.39				13.09	
6	Tetramethylurea	2,4-Dinitrophenol	1:1	Ether-hexane	55-57	90				300				301
7	Tetramethylurea	Picric Acid	1:1	2-Propanol-ether	59-63	87				345				346
8	Tetramethylurea	Pentachlorophenol	1:2	Ether-hexane	92-99	89				324				324
9	1,3-Dimethylurea	2,3-Naphthalenediol	1:1	Ether-acetone-hexane	114-119	64			11.28				11.35	
10	1,3-Dimethylurea	o,o'-Biphenol	1:1	2-Propanol-hexane	62-65	54			10.21				10.02	
11	1,3-Dimethylurea	Picric Acid	1:1	2-Propanol	126-128	88				317				316
12	1,1-Dimethylurea	Picric Acid	1:1	Methanol	131-133	83				317				317
13	1-Piperidinecarboxamide	Hydroquinone	2:1	Acetone-hexane	116-119	95	59.00	8.25	15.29		59.08	8.23	15.18	
14	1-Piperidinecarboxamide	2,3-Naphthalenediol	1:1	Ether-hexane	71-76	88	66.65	6.99	9.72		66.58	7.15	9.90	
15	1-Piperidinecarboxamide	Picric Acid	1:1	2-Propanol-hexane	120-123	87				357				357
16	1-Piperidinecarboxamide	Pentachlorophenol	1:1	Acetone-hexane	114-115	86				394				394
17	4-Morpholinecarboxamide	Hydroquinone	2:1	Acetone-hexane	128-131	92			15.13				15.01	
18	4-Morpholinecarboxamide	2,4-Dinitrophenol	1:1	2-Propanol-hexane	114-117	76				314				314
19	4-Morpholinecarboxamide	Picric Acid	1:1	2-Propanol	106-110	100				359				357
20	4-Morpholinecarboxamide	Pentachlorophenol	1:1	2-Propanol-hexane	126-130	96				396				396
21	1-Pyrrolidinecarboxamide	Picric Acid	1:1	2-Propanol	125-128	87				343				339
22	Urea	Picric Acid	1:1	2-Propanol	153-155					289				290
23	Thiourea	Picric Acid	1:1	2-Propanol	135-138	91				305				300
24	Tetramethylthiourea	2,3-Naphthalenediol	1:1	Ether-hexane	59-61	79			9.58				9.52	
25	1,3-Dimethylurea	Picric Acid	1:3	2-Propanol	110-117	90				258				258
26	1-Piperidinecarboxamide	Picric Acid	1:3	2-Propanol-hexane	103-107	96				272				272
27	4-Morpholinecarboxamide	Picric Acid	1:3	2-Propanol	96-100	78				273				279
28	1-Pyrrolidinecarboxamide	Picric Acid	1:3	2-Propanol	102-108	85				267				272

solvent system, the only product obtained was the 1:1 complex. Similar results were obtained with acetonitrile as solvent, but with the initial molar ratio of reactants at 1:3.5 the yield of isolated 1:1 complex was poor.

When equivalent quantities of 1-piperidinecarboxamide and picric acid were reacted in concentrated chloroform solution the 1:1 complex, m.p. 120-122°, was obtained in 88% yield. When 1-piperidinecarboxamide and picric acid in a molar ratio of 1:3.6 were reacted in chloroform the product obtained was the 1:3 complex [81%]; m.p. 105-111°; NE, 268. However, on recrystallization from chloroform there was some deterioration in the product; m.p. 103-111°;NE, 283. The reaction of 1-pyrrolidinecarboxamide and 3 equivalents of picric acid in chloroform yielded the 1:3 complex in 78% yield; m.p. 101-104°; NE, 270. Recrystallization from chloroform gave 57% of product; m.p. 103-108°; NE, 270. Chloroform was also a suitable solvent for obtaining the 1:3 4-morpholine carboxamide-picric acid complex.

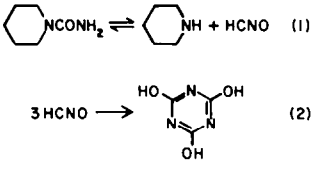
These results attached some credibility to the reality of these observed 1:3 complexes. Some scepticism still remained, in part because none of the systems that afforded 1:3 complexes gave any indication of 1:2 complexes being formed. From simple structural considerations we would have expected 1:2 complexes to be more probable than 1:3 complexes.

To resolve our doubts we set out to do a detailed melting point-composition curve for the 1-piperidinecarboxamide-picric acid system. The experimental technique involved melting mixtures of the two components, getting them to resolidify and then grinding the solid to a powder and determining the melting point. When the 1:1 1-piperidinecarboxamide-picric acid complex was subjected to this procedure irreversible chemical changes occured. It was apparent that results obtained by this classical method would be suspect, but we thought it, nevertheless, worthwhile to explore the nature of these irreversible changes.

When 5 g. of the 1-piperidinecarboxamide-picric acid complex was heated in a sealed tube at 125° for 20 hours, two products were obtained - one insoluble in methanol and one soluble in methanol. The methanol insoluble product, 0.3 g. [17%] was identified as cyanuric acid by comparison of its infrared spectrum with the spectrum of an authentic sample. The methanol soluble product was piperidinium picrate; [72% yield]; m.p. 150-153° and showed no depression on mix-melting with an authentic sample of the picrate. The same result was obtained on heating an equimolar mixture of 1-piperidinecarboxamide and picric acid.

This thermolysis reaction proved to have some generality for mixtures of equivalent quantities of ureas of the type, $RRNCONH_2$, and picric acid. With 4-morpholine-carboxamide the product was 79% morpholine picrate, m.p. 147-150°, and with 1,1-dimethylurea the product was 64% dimethylamine picrate, m.p. 158-160°. With 1,3-dimethylurea some decomposition occurred, but we did not succeed in isolating a pure product.

The isolation of cyanuric acid as well as the picrates indicates a reaction mechanism which is reminiscent of Wöhler's classical demonstration of the relationship between urea and ammonium cyanate[10]. The urea is in equilibrium with piperidine and cyanic acid [equation 1], cyanic acid polymerizes to cyanuric acid [equation 2], and picric aid and piperidine form the picrate. The equilibration in [1] will occur only with ureas having at least one unsubstituted nitrogen, and this may account for our inability to isolate a pure product from the thermolysis experiment with 1,3-dimethylurea.



A related transformation can be effected by refluxing either the 1:1 complex or equivalent quantities of the two starting materials in n-propanol. With 1-piperidinecarboxamide and picric acid the products were 92% piperidinium picrate and 89% n-propyl carbamate after 20 hours of refluxing. It is conceivable that this transformation also involves equilibrium [1], but it is more probable that the observed products result from a picric acid catalyzed alcoholysis of 1-piperidine-carboxamide. Refluxing the largely insoluble potassium cyanate in n-propanol for 70 hours resulted in the formation of only a trace of n-propyl carbamate.

Some support for the reality of the 1:3 1-piperidinecarboxamide-picric acid complex was obtained by applying the Kofler contact method[11] to 1-piperidinecarboxamide-picric acid mixtures. Coming from the picric acid side there is a first eutectic mixture at about 90°, followed by a very distinct molecular compound, melting at about 108°. Then there was a second eutectic mixture which did not crystallize even at room temperature, but no

second maximum to clearly indicate the presence of a second molecular compound was detected. However, the one definite molecular compound of m.p. about 108° is in good agreement with our isolated 1:3 complex of m.p. 103-107°[12].

Further evidence attesting to the reality of these 1:3 complexes was obtained from X-ray powder diffraction patterns. The pattern obtained with the 1:3 1-piperidinecarboxamide-picric acid complex is clearly different from the patterns obtained with the starting materials, the 1:1 complex and mechanical mixtures of the starting materials in a urea to phenol molar ratio of 1:3 and of the 1:1 complex and picric acid in the molar ratio of 1:2.

The crystal morphologies, examined in detail with scanning electron microscopy, provide additional support. The crystals of the 1:1 1-piperidinecarboxamide-picric acid complex grow as long hollow rods with a rectangular cross-section, while the 1:3 complex grows as fan-shaped crystal clusters with small solid crystals growing from a central nucleus. The two starting materials have crystal morphologies that are clearly distinguishable from those of the two complexes. Picric acid crystallizes as very thin platelets and 1-piperidinecarboxamide grows in long irregular strands without flat surfaces.

The available evidence, taken *in toto*, attaches a high degree of probability to the proposition that these 1:3 complexes are true molecular compounds even though it may fall somewhat short of guaranteeing absolute certainty. For the structures of these 1:3 complexes we would suggest either one in which two phenols are linked to the carbonyl oxygen as in II and III and the third phenol is hydrogen-bonded to a urea nitrogen or a structure in which a phenol molecule is hydrogen-bonded to each of the two urea nitrogens as well as to the carbonyl oxygen.

EXPERIMENTAL SECTION

Starting materials: Picric acid stabilized with water was crystallized from methanol to obtain the dry acid. Technical grade pentachlorophenol was crystallized two times from toluene; m.p. 189-191°. 4,4'-Biphenol was obtained from the Buffalo Color Corporation and used without purification. The remaining phenols were all reagent grade chemicals and were also used without purification.

1-Piperidinecarboxamide, 4-morpholinecarboxamide and 1-pyrrolidinecarboxamide were prepared by aminolysis of urea with the appropriate amines. The procedure was to reflux urea with excess amine until evolution of ammonia ceased. The excess amine was then removed at the water pump and the crude product was recrystallized. The details are given in Table II. The procedure has been described previously[13] and it was suggested that the reaction mechanism was that proposed by Davis and Underwood[10] and involves the equilibration of urea to ammonium cyanate. We would suggest that at the low temperatures involved in the reactions of Table II, especially in the reaction with pyrrolidine, b.p. 88°, that a true solvolysis reaction with the amine attaching at the carbonyl carbon atom is more probable. The remaining ureas were reagent grade chemicals and were used without further purification.

Table II
PREPARATION OF SUBSTITUTED UREAS BY AMINOLYSIS OF UREA

Amine	Reaction Temperature °C	Reaction Time Hours	Product	M.P. °C	Crystallizing Solvent	Yield %
Piperidine	106	40	1-Piperidine-carboxamide	105-107	Chloroform-hexane	82
Morpholine	126-130	45	4-Morpholine-carboxamide	112-115	Chloroform-hexane	94
Pyrrolidine	88	48	1-Pyrrolidine-carboxamide[14]	222-224	Methanol-ethanol	73

The following preparations of hydrogen-bonded complexes are typical.

2,3-Naphthalenediol-1,3-dimethylurea 1:1 complex: 2,3-Naphthalenediol [3.20 g.; 0.02 mole] and 1,3-dimethylurea [1.76 g.; 0.02 mole] were dissolved in warm ether containing a little acetone. The solution was filtered and hexane was added. This precipitated an oil which crystallized on scratching. The crude product was filtered and recrystallized from ether-acetone-hexane; yield 3.2 g. [64%]; m.p. 114-119°.

4-Morpholinecarboxamide-hydroquinone 2:1 complex: 4-Morpholinecarboxamide [5.2 g.; 0.04 mole] and hydroquinone [2.2 g.; 0.02 mole] were dissolved in a mixture of ether [100 ml.] and acetone [150 ml.]. The solution was filtered and hexane [150 ml.] was added. On cooling the product crystallized; yield 6.8 g. [92%]; m.p. 128-131°. Recrystallization from acetone-hexane gave 5.4 g. [73%]; m.p. 128-131°.

4-Morpholinecarboxamide-picric acid 1:3 complex: 4-Morpholinecarboxamide [0.65 g; 0.005 mole] and picric acid [3.44 g.; 0.015 mole] were dissolved in boiling 2-propanol. The solution was filtered and hexane was added. On cooling the product precipitated; yield 4.0 g. [97%] m.p. 95-105°. Recrystallization from 2-propanol-hexane yielded 3.2 g. [78%] of product; m.p. 96-100°.

Tetramethylurea-pentachlorophenol 1:2 complex: Tetramethylurea [1.74 g.; 0.015 mole] and pentachlorophenol [2.66 g.; 0.01 mole] were dissolved in ether [10 ml.] and hexane [50 ml.] was added. On cooling the crude product crystallized; yield 3 g.; m.p. 50-85°. Recrystallization from ether-hexane yielded 1.7 g. [89%]; m.p. 92-99°. For analyses of this complex and the others described above see Table I.

Alcoholysis of 1-Piperidinecarboxamide: A mixture of 1-piperidinecarboxamide [1.30 g.; 0.0101 mole] and picric acid [2.32 g.; 0.0101 mole] in n-propanol [50 ml.] was refluxed 18.5 hours. The solution was seeded with piperidinium picrate and cooled in the freezer, yielding 2.93 g. [92.4%] of piperidinium picrate;m.p. 150-153°. The filtrate was made up to a volume of 100 ml. with ethanol, and gas chromatography on this solution indicated the presence of 0.93 g. [89.4%] n-propylcarbamate.

Preparation of n-propylcarbamate: An authentic sample of n-propylcarbamate to serve as a standard in the gas chromatography was prepared as follows. A solution of urea[12.1 g.; 0.2 mole] in n-propanol [100 ml.] was refluxed 92 hours. Most of the n-propanol was distilled at atmospheric pressure. On cooling the residue solidified. The residue was boiled two times with toluene and the combined toluene extracts were cooled yielding 3.86 g. [18.7%] of white crystals;m.p. 54-57°. Recrystallization from hexane raised the m.p. to 58-60°.

Anal: Calcd. for $C_4H_9NO_2$: N, 13.59%; Fd N, 13.43%.

X-Ray Diffraction Patterns: The preparation of diffraction specimens was optimized by trial and error. The as-crystallized picric acid and 1:1 complex showed a high degree of preferred orientation but could be ground to sufficiently randomize the diffraction pattern. The 1:3 complex received little preparation since its fragile crystal structure was easily damaged. Mixtures were prepared by grinding appropriate molar ratios of two materials together. Diffractometer strip charts were visually compared to determine similarities and differences.

Crystal Morphologies: The crystal morphologies were examined with a scanning electron microscope (SEM). The SEM specimens were dispersed on slightly tacky films of carbon paint and were subsequently sputter coated with gold. The crystals were stable in a vacuum and could be scanned with a very low current electron beam without visible deterioration.

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