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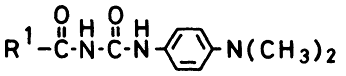
A NEW TYPE OF CRYSTALLINE 1:1 MOLECULAR COMPLEX FORMATION SPECIFIC FOR THE SHAPE OF NONPOLAR GROUPS

Tadashi ENDO,* Kazuhiro MIYAZAWA, Masayuki ENDO,
Akira UCHIDA,† Yuji OHASHI,† and Yoshio SASADA†
College of Science and Engineering, Aoyama Gakuin University,
Chitosedai, Setagaya-ku, Tokyo 157
†Laboratory of Chemistry for Natural Products, Tokyo Institute
of Technology, Nagatsuta, Midori-ku, Yokohama 227

The formation of crystalline 1:1 molecular complexes was examined between a pair of acylurea derivatives (1 and 2) having a wide variety of alkyl groups as nonpolar substituents (R^1 and R^2). The complex formation has been found to depend on the shapes of R^1 and R^2. This suggests the presence of specific weak interactions between the nonpolar groups.

A large number of reports have so far been published to describe the contribution of hydrogen bonding[1)] and/or charge-transfer interaction[2)] to the stabilization of crystalline molecular complexes between compounds having polar moieties and/or π-electron systems. Much attention has recently been focused on crown-type,[3)] inclusion,[4)] and intercalation complexes[5)]. As a continuing study on three-dimensional shape-specific weak interactions,[6)] we have investigated the formation of crystalline 1:1 molecular complexes between a pair of acylurea derivatives (1 and 2) with various alkyl groups as nonpolar substituents (R^1 and R^2) from an acetonitrile (MeCN) solution.

The model compounds[7)] 1 and 2 are each composed of the three sites —— "nonpolar site" (R^1 or R^2), "acylurea site" ($-\overset{O}{C}\overset{H}{N}\overset{O}{C}\overset{H}{N}-$), and "substituted benzene ring site" ($-C_6H_4NMe_2$-p or $-C_6H_4NO_2$-p).



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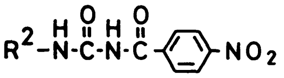
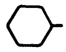
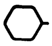


2

A typical procedure for complex formation is as follows. The two acylurea derivatives (1 and 2, 0.50 mmol each) were dissolved in pure MeCN mostly by heating and this solution was allowed to evaporate slowly at room temperature. The resulting crystal was identified as a 1:1 molecular complex according to the following criteria: (1) sharp melting point different from those of 1 and 2, (2) the presence of the two components in 1:1 molar ratio on the UV absorption spectrum

R^1									
	—	—	—	+ drp	+ drp	+ o	—	+ o	+ o
t-Bu	—	—	—	+ ro	+ ro	+ rb	+ rb	+ ro	+ drp
i-Pr	—	—	—	—	+ rb	+ ro	+ ro	+ drp	—
Et	—	—	—	+ db	+ ro	+ ro	+ ro	+ ro	+ drp
	Et	i-Pr	t-Bu	n-Pr	i-Bu	t-BuCH$_2$	n-Bu	i-Pen	n-Pen

R^2

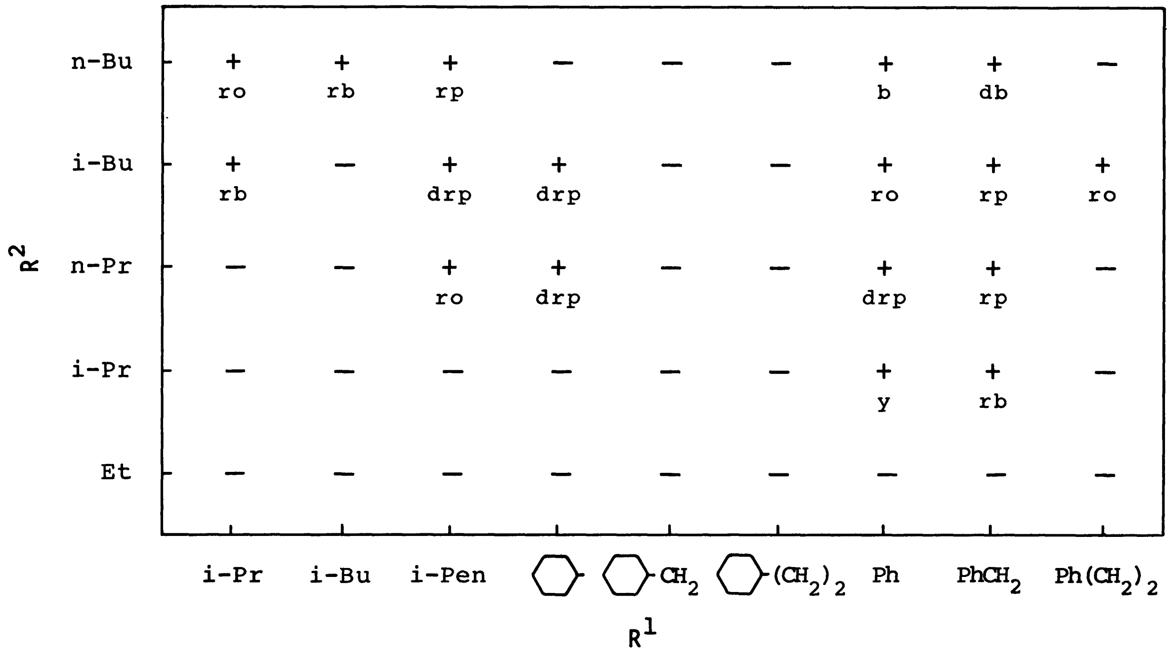
Fig. 1. Crystalline 1:1 molecular complex formation for various combinations of R^1 and R^2. The + indicates complex formation and the small letters below + indicate the color of the complexes: drp, dark reddish purple; ro, reddish orange; db, dark brown; rb, reddish brown; o, orange. The — indicates no complex formation; Pen and  represent the pentyl and cyclohexyl groups, respectively.

of a dilute MeCN solution of the crystal, (3) the existence of the two components in roughly equimolar amounts on thin-layer chromatogram.[8)]

Figure 1 shows the structure dependence of the crystalline 1:1 molecular complex formation. The number of carbon atoms (n) along the longest straight chains is 2 for the C_2H_5 (Et), i-C_3H_7 (i-Pr), and t-C_4H_9 (t-Bu) groups.[9)] The data in Fig. 1 indicate that the complex formation occurs only for $n_1 + n_2 \geq 5$ where n_1 and n_2 are the carbon numbers along the longest straight chains for R^1 and R^2, respectively, and that this rule could be applied to all combinations in Fig. 1 if the n value for the cyclohexyl group is also regarded as being 2.[10)]

It is evident from the data in Fig. 2 that among three sets of alkyl groups used as R^1 the phenylalkyl groups ($Ph(CH_2)_m$) afford the crystalline complexes with higher frequency than the branched alkyl groups ($Me_2CH(CH_2)_m$), particularly than cyclohexylalkyl groups ($C_6H_{11}(CH_2)_m$),[11)] m being 0 to 2. These results suggest that phenyl-alkyl interactions between R^1 and R^2 would contribute more largely to the stabilization of the complexes than alkyl-alkyl interactions. Further, comparison of the data for R^2 = Et and n-Pr with those for R^2 = i-Pr and i-Bu (Fig. 2),[9)] respectively, reveals that the probability of forming the complexes is higher for the branched alkyl groups than for the corresponding straight-chain alkyl groups. These findings together with the results[12)] obtained with R^1 = i-Pr in Fig. 1 would imply that branched alkyl and phenylalkyl groups tend to stabilize the crystalline complexes to a greater extent when paired with branched alkyl groups than when paired with straight-chain alkyl groups.

Of particular interest is the observation, made by X-ray crystallographic studies of the complex for R^1 = $PhCH_2$ and R^2 = i-Bu (Fig. 3),[13)] that these two



R^2 \ R^1	i-Pr	i-Bu	i-Pen	⬡	⬡-CH_2	⬡-$(CH_2)_2$	Ph	$PhCH_2$	$Ph(CH_2)_2$
n-Bu	+ ro	+ rb	+ rp	−	−	−	+ b	+ db	−
i-Bu	+ rb	−	+ drp	+ drp	−	−	+ ro	+ rp	+ ro
n-Pr	−	−	+ ro	+ drp	−	−	+ drp	+ rp	−
i-Pr	−	−	−	−	−	−	+ y	+ rb	−
Et	−	−	−	−	−	−	−	−	−

Fig. 2. Crystalline 1:1 molecular complex formation for various combinations of R^1 and R^2. The symbols and small letters are as in Fig. 1: rp, reddish purple; b, brown; y, yellow.

nonpolar groups —— the phenylalanine and leucine side chains —— are brought so close together.[14)]

The need of the acylurea site participating in intermolecular hydrogen bonding (Fig. 3) for the complex formation is exemplified by the fact that a 1:1 mixture of N-(p-dimethylaminophenyl)phenylacetamide and N-isobutyl-p-nitrobenzamide gives no crystalline complexes under the same conditions as with 1 and 2. The trend of the complex formation often changes, when the combinations of R^1 and R^2 are reversed

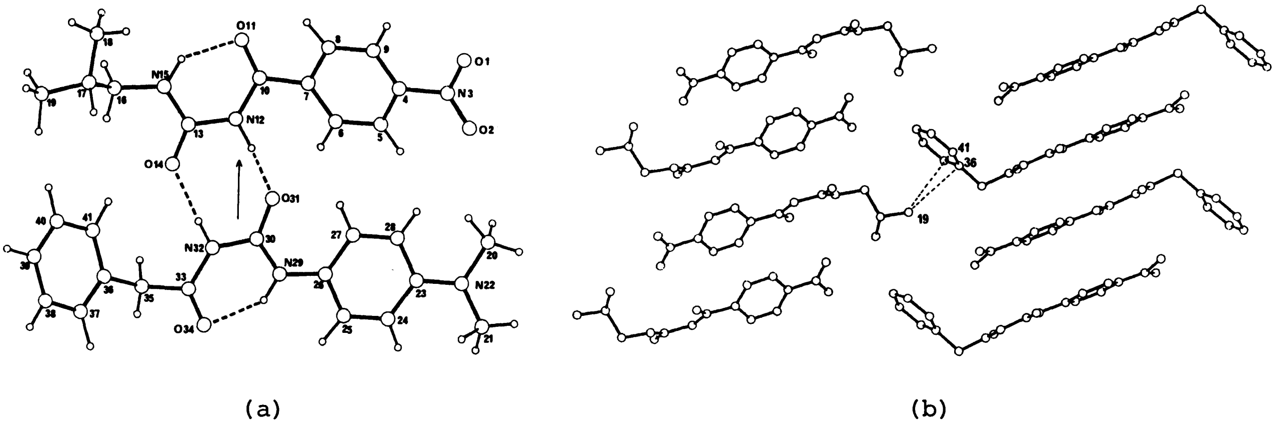


Fig. 3. (a) Pattern of hydrogen bond and (b) a view along an arrow in (a) showing the contacts between R^1 and R^2 in the crystalline 1:1 complex for $R^1 = PhCH_2$ and $R^2 = $ i-Bu.

(Figs. 1 and 2); this suggests that the interactions between the nonpolar site and the substituted benzene ring site play an important role in stabilizing the complexes.

The experimental evidence presented here leads us to conclude that the crystalline 1:1 molecular complex formation between **1** and **2** depends on the shapes of the nonpolar substituents R^1 and R^2. This suggests the presence of weak interactions specific for the shapes of these nonpolar groups.

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7) The acylurea derivatives were readily prepared in high yields by addition of amines to acyl isocyanates at 0 °C in dry MeCN as described before (T. Endo, S. Noguchi, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 44, 3424 (1971)). Satisfactory spectroscopic data were used to support the assignment of all new compounds.

8) In this connection, it has been found that (1) the color of the crystalline complexes alters markedly from yellow to reddish orange and to dark reddish purple with the structures of R^1 and R^2 (Figs. 1 and 2) in sharp contrast to their components (**1** and **2**) being colorless crystals except for **1** where $R^1 = Ph$ (pale yellow needles) and (2) solutions of the crystalline complexes in MeCN are colorless in most cases.

9) Similarly, the n values are 3 for the n-Pr, i-Bu, and t-BuCH$_2$ groups, and 4 for the n-Bu and i-Pen groups.

10) This rule also holds true for the data in Fig. 2.

11) The phenyl and cyclohexyl groups are similar in three-dimensional shape to each other, as indicated by CPK models.

12) Also in the case of $R^1 = \text{i-Pr}$ and $R^2 = \text{n-}C_6H_{13}$, complex formation has not been observed.

13) Crystal data: $C_{29}H_{34}N_6O_6$, $\underline{M} = 562.63$, triclinic, space group $P\bar{1}$, $\underline{a} = 11.413(3)$, $\underline{b} = 16.740(3)$, $\underline{c} = 8.569(2)$ Å, $\alpha = 91.76(3)$, $\beta = 108.24(3)$, $\gamma = 108.47(2)°$, $\underline{U} = 1459.3(7)$ Å^3, $\underline{Z} = 2$, $\underline{D}_c = 1.281$ g cm^{-3}. The structure was solved by direct method and refined by least-squares to the final $\underline{R}$ factor of 0.107. The hydrogen bond distances and angles are as follows: N(12)···O(31), 2.820(4) Å; O(14)···N(32), 2.895(4) Å; O(11)···N(15), 2.705(4) Å; O(34)···N(29), 2.690(4) Å; ∠N(12)-H(12)···O(31), 164(3)°; ∠N(32)-H(32)···O(14), 176(2)°; ∠N(15)-H(15)···O(11), 135(3)°; ∠N(29)-H(29)···O(34), 138(3)°.

14) The short interatomic distances between the PhCH$_2$ and i-Bu groups are as follows: C(19)···C(36), 3.602(9) Å; C(19)···C(41), 3.672(9) Å. Figure 3 exhibits that R^1 and R^2 cannot make effective van der Waals contacts with each other if $n_1 + n_2 \leq 4$.

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