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Clustering of a hydrogen-bonding complex between indole and isoquinoline

Correlation with nucleation of intermolecular compounds

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Upon crystallization from mixtures containing indole and isoquinoline, intermolecular compounds of 1 : 1 molecular ratio have been isolated as crystals. This crystallisation process, *i.e.*, molecules → clusters → nucleus was studied in a specially designed mass spectrometer. From the mass spectrometric analysis of clusters isolated from liquid droplets containing indole, isoquinoline and acetonitrile, clusters composed of equimolecular indole and isoquinoline, *i.e.* $(indole)_n(isoquinoline)_n$: $n = 1, 2, 3, \ldots$, were observed as prominent species. This suggested that the hydrogen-bonded complex of indole and isoquinoline works as a unit species for the nucleation of the intermolecular compounds.

Crystallization occurs when solid phases having ordered structures are formed from a random phase such as liquid, vapour, *etc*. Crystallization can be divided into two processes: a nucleation process followed by crystal growth. Crystal growth has been studied theoretically[1–3] and also experimentally.[4–6] For example, BCF theory describes crystal growth on the surface of a perfect crystal at the molecular level in terms of intermolecular interaction of nearest particles, temperature and incoming flux.[7] Additionally, the growth mechanism has been studied experimentally by measurement of the rate of crystal growth, with varying temperature.[4–6] However, the nucleation of crystals from the liquid phase (primary nucleation, appearance of embryo) has not been discussed at the molecular level. This is due to the experimental difficulty in observing the nucleation process.

Recently, it was proposed that solute molecules are already assembled in the liquid phase to form small clusters and primary nucleation should start from the growth of this cluster.[8]

We have reported that an indole and isoquinoline mixed solution forms an intermolecular compound crystal over a wide range of mixture ratios under atmospheric and also higher pressures.[9] In this intermolecular compound, the molecular ratio between indole and isoquinoline was 1 : 1, suggesting that the hydrogen-bonded complex works as a unit species.

In order to study the relation of the intermolecular interaction in the liquid phase to nucleation, mass spectrometric analysis of clusters isolated from liquid droplets was carried out using a specially designed mass spectrometer. Previously, we have measured the mass spectrum of clusters isolated from a pyrrole–pyridine–water three-component solution, and confirmed that the hydrogen-bonded complex between pyrrole and pyridine exist as a stable species.[10]

In this study, the mass spectra of clusters generated from indole–isoquinoline and *N*-methylindole–isoquinoline mixed solutions were measured and compared with the solid–liquid equilibrium property of these mixtures.

The nucleation mechanism of an intermolecular compound will be discussed with the distribution of clusters reflecting intermolecular interactions in this mixture.

Experimental

Measurement of solid–liquid phase diagram

Fig. 1 shows the schematic diagram of the apparatus for the measurement of solid–liquid phase diagram.[9] The sample mixture was inserted into the vessel (7), and compressed by an oil pump (8) to crystallize the solution perfectly. Then, while carefully observing the melting of crystal, the pressure of this vessel was slowly decreased, and the temperature and pressure when the crystal melted were measured. Phase equilibrium lines were determined by repeating this operation at different sample concentrations.
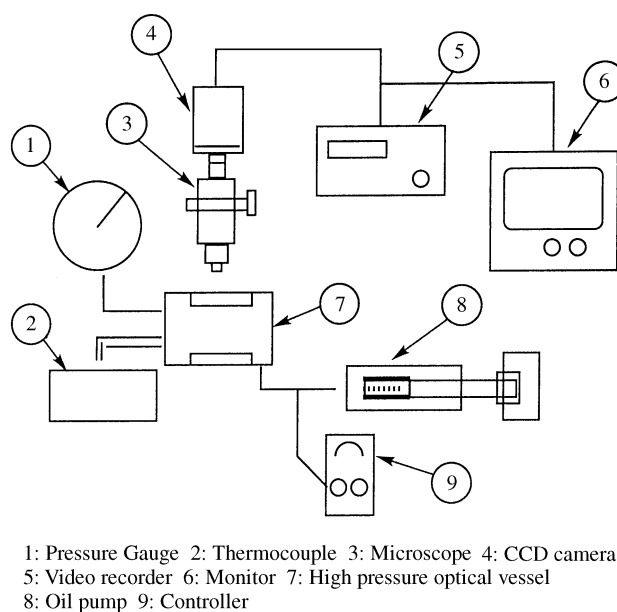

1: Pressure Gauge 2: Thermocouple 3: Microscope 4: CCD camera
5: Video recorder 6: Monitor 7: High pressure optical vessel
8: Oil pump 9: Controller

Fig. 1 Schematic diagram of the apparatus for the measurement of solid–liquid phase diagrams. (Reproduced from ref. 9, with permission.)

Measurement of clusters formed from liquid droplets

The mass spectra of clusters in solutions were measured by using the adiabatic expansion of liquid droplets. Detail of this apparatus have been given previously.[11] The sample solution was injected into a four-stage differentially pumped vacuum system through a heated nozzle. Mist particles (very small liquid droplets) were formed in the first chamber (0.2 Torr), and were disintegrated into clusters by adiabatic expansion in the second and third chambers. The resulting clusters were ionized by electron impact (30 eV) in the third chamber, and analysed with a quadrupole mass spectrometer in the fourth chamber.

Reagents

Commercially available indole (Tokyo Kasei, >99.0%), isoquinoline (Wako chemical, >97.0%), N-methylindole (Aldrich, >97%), m-cresol (Tokyo Kasei, >98.0%), [$^2H_8$]m-cresol(CD$_3$C$_6$D$_4$OD) (Aldrich, >99% atom%) and acetonitrile (Wako, >99.8%) were used. These compounds were carefully mixed and used after exposing to ultrasonic waves.

Results and Discussion

Solid–liquid phase diagrams

Indole–isoquinoline. We have already reported the solid–liquid phase diagram of an indole–isoquinoline solution.[8] As Fig. 2 shows, the equilibrium lines of indole–isoquinoline can be divided into three portions by two eutectic lines (a–a′ and b–b′). Pure isoquinoline will be crystallized when the concentration of indole is smaller than eutectic line a–a′, and pure indole can be crystallized when the concentration of indole is larger than b–b′. However, if the concentration of this mixture is in the region between a–a′ and b–b′, the intermolecular compound of 1:1 molar ratio of indole and isoquinoline is always crystallized over this wide range of mixing ratios.

As shown in Fig. 2, eutectic points were shifted with increase in pressure and the formation region of the intermolecular compound became narrower. Generally, high-density crystals are more favourable than low-density ones under high-pressure atmospheres. The narrowing of the intermolecular-compound region indicates that the crystal of the intermolecular compound has a more bulky structure than the

pure indole and isoquinoline crystals. This is reasonable, if the bulky hydrogen-bonded complex between indole and isoquinoline is the repeating unit of the lattice of the crystal of the intermolecular compound. Furthermore, we measured ^1H NMR spectra to study the interaction between indole and isoquinoline. It was observed that the peak intensity of H in the imino group is much stronger in an indole–isoquinoline equimolecular mixture than in pure indole. This suggests that strong intermolecular hydrogen bonding can exist between indole and isoquinoline molecules.

However, the maximum position of the eutectic curve is not changed even under a pressure of 2000 kg cm^{-2} which means that the molar ratio of indole to isoquinoline in this intermolecular compound is always 1:1.

N-methylindole–isoquinoline. Fig. 3 shows the solid–liquid phase diagram of N-methylindole–isoquinoline solution. It shows clearly that an intermolecular compound is not formed between them. Pressure around the sample does not have any effect on the phase diagram and the minimum point of the melting temperature is always at the same concentration (ca. 84 mol% indole).

Indole, which has an NH— group, can undergo hydrogen bonding with isoquinoline but for N-methylindole this is not possible. The intermolecular interaction in solution should be quite different between indole–isoquinoline and N-methylindole–isoquinoline. By means of the mass spectrometry study, this difference was found to be reflected in the clustering, and to be related to the crystallization.

Measurement of mass spectrum of clusters

Clusters in indole–isoquinoline system. Fig. 4 shows the mass spectrum of clusters generated from the solution containing indole, isoquinoline and acetonitrile (molar ratio 1:1:30); the paired numbers represent m, n for an (indole)$_m$(isoquinoline)$_n$ cluster. As we reported previously, relatively larger clusters were observed only after the removal of acetonitrile at higher nozzle temperatures. The larger clusters do not exist in the solution, but they form after the desolvation.[11]

As shown in Fig. 4, clusters which include the same number of indole and isoquinoline molecules such as 1–1, 2–2, 3–3, 4–4 etc. were formed predominantly. This suggests that the hydrogen-bonding complex of indole with isoquinoline forms a unit which aggregates to form larger clusters such as 2–2,
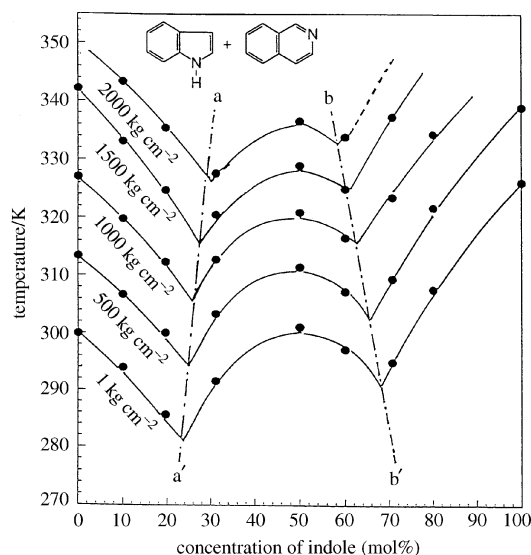
Fig. 2 Solid–liquid phase diagram of indole–isoquinoline mixed solution. (Reproduced from ref. 9, with permission.)
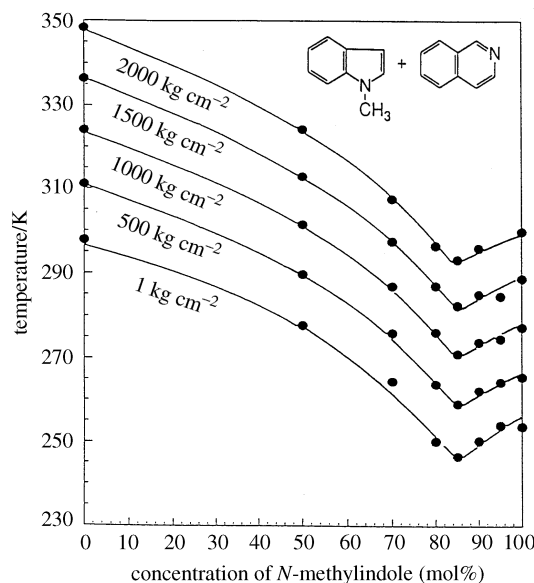
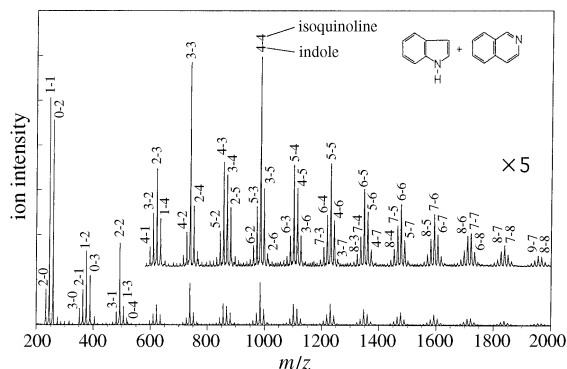**Fig. 3** Solid–liquid phase diagram of N-methylindole–isoquinoline mixed solution

Fig. 4 Mass spectrum of clusters generated from an indole–isoquinoline mixture in acetonitrile. Molar ratio of indole/isoquinoline/acetonitrile is 1 : 1 : 30, at nozzle temperature 230 °C. Paired numbers represent m, n for (indole)$_m$(isoquinoline)$_n$.

3–3, 4–4 *etc.* The primary nuclei should be generated from such spontaneous association of the hydrogen-bonding complex.

As we reported previously, the 1 : 1 pyrrole–pyridine complex can be formed over a wide range of mixing ratios in pyrrole–pyridine mixed solution, and clusters composed of equimolecular pyrrole and pyridine such as (pyrrole)$_2$(pyridine)$_2$, (pyrrole)$_3$(pyridine)$_3$ are formed predominantly.[10]

From these results, it is reasonable to assume that the crystal of the intermolecular compound 1 : 1 mole ratio can be formed through the stacking of the indole–isoquinoline hydrogen-bonding complex. Interestingly, such hydrogen-bonding complexes as indole–isoquinoline and pyrrole–pyridine readily aggregate with one another; this may be due to the dipole–dipole interaction induced along the hydrogen bond.

Clusters of *N*-methylindole with isoquinoline. Fig. 5 shows the mass spectrum of clusters generated from *N*-methylindole-isoquinoline mixture in acetonitrile. The molar ratio of *N*-methylindole/isoquinoline/acetonitrile is 1 : 1 : 30. In this figure, since the molecular weights of *N*-methylindole (131) and isoquinoline (129) are very close, clusters which include the same number of molecules overlap to give broad peaks. For example, in (*N*-methylindole)$_a$(isoquinoline)$_b$ clusters, 5–3, 4–4 and 3–5 clusters have m/z values: 1042, 1040 and 1038, respectively, and hence it is difficult to observe them as an isolated peak. Each peak in Fig. 5 corresponds to a group of clusters which include the same total number of molecules ($a + b$).
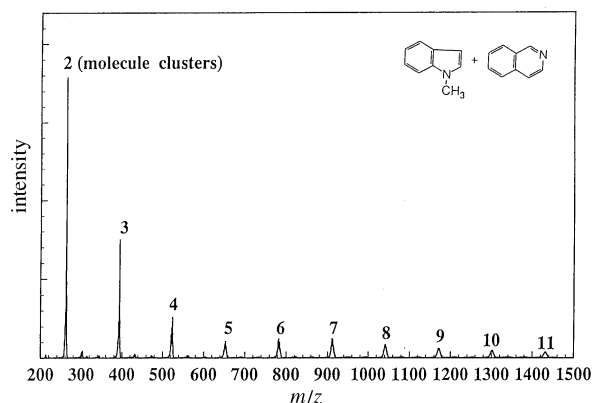
As shown in Fig. 5, the intensities of the peaks decrease monotonically with increasing mass number. Preferential clustering, as observed in the indole–isoquinoline system (Fig. 4), did not take place. Furthermore, the molecular composition in the (*N*-methylindole)$_a$(isoquinoline)$_b$ cluster was found to be dependent on the relative concentrations in the solution. In Fig. 6, the mass spectrum of clusters generated from an *N*-methylindole/isoquinoline 5 : 5 mixture is compared with that of a 3 : 7 mixture. The peak position for the 3 : 7 mixture is clearly shifted to lower mass number from the peak position for the 5 : 5 mixture. As for a cluster with $a + b = 10$, the most probable compositions for 3 : 7 and 5 : 5 mixtures are 3–7 and 5–5 cluster, respectively. The observed peak positions of the clusters $m/z = 1226$ and 1300 are in good agreement with the peaks of the 3–7 and 5–5 clusters, respectively. Other peak positions also agree with the probable composition determined by the initial concentration of the mixture. In contrast, for indole–isoquinoline systems with 3 : 7 and 5 : 5 mixing ratios, the resulting composition in the clusters was almost the same, independent of the mixing ratio.

The difference in the clustering between *N*-methylindole–isoquinoline and indole–isoquinoline indicates that hydrogen-bonding formation of N—H⋯N plays a key role in preferential clustering.

Cluster distribution of ideal mixture

Theoretical distribution of clusters for ideal mixture. In order to compare the preferential clustering between indole and isoquinoline with a random mixing clustering without any preference, the number of combinations for two kinds of molecules are plotted in Fig. 7. For a given cluster size, a, the existence ratio for possible molecular composition should follow the combination $_{\alpha}C_{\beta}$ where α and β represent $a + b$ and b for an A$_a$B$_b$ cluster, respectively. (A and B represent component molecules, and their intermolecular interactions in the solution: A⋯A, A⋯B and B⋯B are the same. a and b represent the numbers of A and B molecules in the cluster, respectively.) For example, clusters composed of 2 molecules,
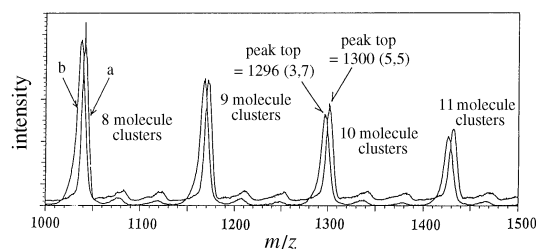

Fig. 6 Mass spectrum of clusters generated from *N*-methylindole-isoquinoline mixtures in acetonitrile, at nozzle temperature 200 °C. Molar ratios of *N*-methylindole/isoquinoline/acetonitrile are 5 : 5 : 150 in (a) and 3 : 7 : 150 in (b).
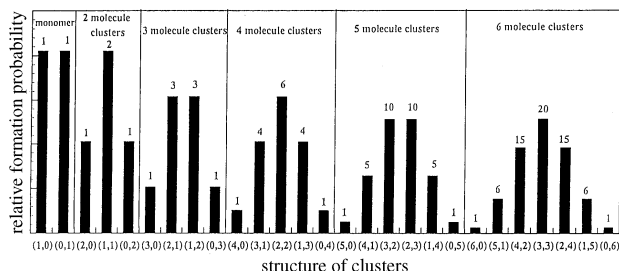

Fig. 5 Mass spectrum of clusters generated from *N*-methylindole–isoquinoline mixture in acetonitrile. Molar ratio of *N*-methylindole/isoquinoline/acetonitrile is 1 : 1 : 30, at nozzle temperature 200 °C. Each peak corresponds to a group of clusters which include the same number of molecules. The numbers on the peaks represent $a + b$ for (*N*-methylindole)$_a$(isoquinoline)$_b$.

Fig. 7 Ideal distribution of clusters of a given size which are formed through mixing of A and B molecules. If there is no preference for intermolecular interactions, the distribution of a given cluster size should be proportional to the ratio of the number of combination. (Cluster sizes are 2–6; no particular interaction between two compounds). Paired numbers represent m, n for (A)$_m$(B)$_n$.

$\alpha = 2$ are indicated by (2, 0), (1, 1) and (0, 2) in Fig. 7. The formation ratios for these three clusters are $_2C_0$, $_2C_1$ and $_2C_2$. (2, 0) and (0, 2) have the same probability where the concentrations of A and B are the same; therefore, $_2C_0$ appears equal to $_2C_2 = 1$. Similarly, four molecule clusters are indicated by (4, 0), (3, 1), (2, 2), (1, 3) and (0, 4). The ideal formation ratio of these clusters is $_4C_0 : _4C_1 : _4C_2 : _4C_3 : _4C_4 = 1 : 4 : 6 : 4 : 1$.

We could confirm such an ideal distribution for the mixture of m-cresol and $[^2H_8]$m-cresol.

Clusters of m-cresol and $[^2H_8]$m-cresol. Fig. 8 shows the mass spectrum of clusters generated from a mixture of m-cresol and deuteriated m-cresol ($CD_3C_6D_4OD$). In this mixture, the following intermolecular interactions: m-cresol–m-cresol, m-cresol–$[^2H_8]$m-cresol and $[^2H_8]$m-cresol–$[^2H_8]$m-cresol appear to be almost the same. Therefore, the resulting mass distribution should become close to the distribution determined by combination without any preference, as shown in Fig. 7.

Fig. 8 shows the mass spectrum of clusters generated from m-cresol–$[^2H_8]$m-cresol–acetonitrile (1 : 1 : 30) solution. From Fig. 8, the ratio of intensity of the clusters (4, 0), (3, 1), (2, 2), (1, 3) and (0, 4) is very close to 1 : 4 : 6 : 4 : 1. This result is in good agreement with the theoretical distribution of clusters as shown in Fig. 7.

From Fig. 4, the ratio of the mass spectrum intensity of four molecular indole–isoquinoline clusters (4, 0), (3, 1), (2, 2), (1, 3) and (0, 4) is 1 : 8 : 42 : 10 : 3. This means that the formation probability of the (2, 2) cluster is very much higher than that estimated from the theoretical value for the ideal mixture, which is supporting evidence for the preferential association of a (1, 1) complex.

Schematic illustration for the nucleation of an intermolecular compound crystal

Fig. 9 shows a schematic illustration of the aggregation of a hydrogen-bonded complex of indole with isoquinoline.

The nucleation process of the indole–isoquinoline 1 : 1 intermolecular compound is considered to be as follows. (a) Indole and isoquinoline exist initially as separate molecules in the mixed solution. (b) 1 : 1 molar complexes are formed through an intermolecular hydrogen-bonding interaction. (c) The hydrogen-bonding complexes so formed behave like a
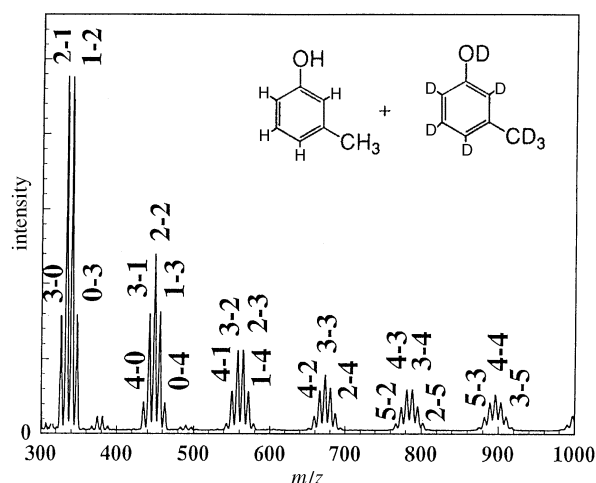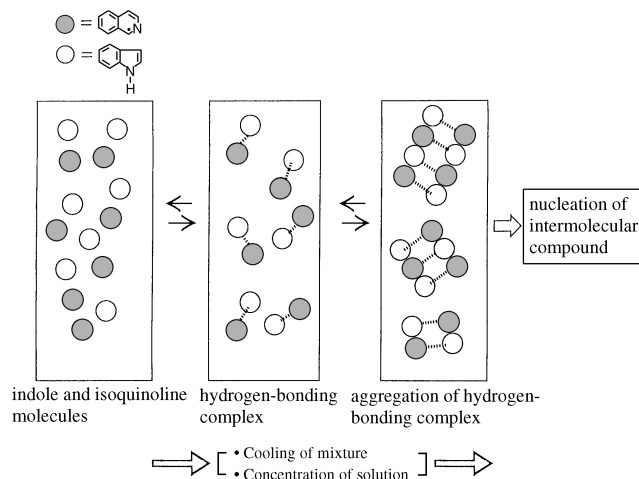

Fig. 9 Schematic illustration of the aggregation of the hydrogen-bonding complex of indole with isoquinoline

single molecule and aggregate to form stable clusters with a 1 : 1 molar ratio. (Such a process should be accelerated by cooling the mixture, concentration of the solution etc.)

Considering clusters in the liquid phase before nucleation, it seems that there exist many kinds of clusters, not only stable structures but also unstable ones. However, only stable embryonic clusters with a long lifetime can have the chance to grow into crystal nuclei.

Conclusion

(Indole)$_n$(isoquinoline)$_n$ ($n = 1, 2, 3, \ldots$) binary clusters were found to be produced through the preferential association of the hydrogen-bonded complex: (indole)$_1$(isoquinoline)$_1$. In correlation with the intermolecular compound between indole and isoquinoline with the molecular ratio 1 : 1, it should be noted that the nucleation for this intermolecular compound starts from these stable embryonic clusters.

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Fig. 8 Mass spectrum of clusters generated from m-cresol–$[^2H_8]$m-cresol mixture in acetonitrile. Molar ratio of m-cresol–$[^2H_8]$m-cresol/acetonitrile is 1 : 1 : 30, at nozzle temperature 180 °C. Paired numbers represent m, n for (m-cresol)$_m$($[^2H_8]$m-cresol)$_n$.