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Incorporation mechanism of guest molecules in crystals: solid solution or inclusion?

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Abstract

Guest molecules (impurities or additives), together with some crystallization solvent, are often incorporated into the host crystals during crystallization from solution. The guest molecules may be incorporated either in solid solution or in liquid inclusions, or by both mechanisms. The mechanism of guest incorporation has been examined by a simple calculation method which is based on the equality of the guest/solvent mole ratio in the initial crystallization medium and in the putative inclusions. Application of this calculation method to eight guest + host systems described in the literature has shown that a negligible amount (at most 0.2%) of the guest molecules is incorporated into the crystal lattice in liquid inclusions. Therefore, it is concluded that the vast majority of the guest molecules are incorporated into the crystals in solid solution, as previously suggested, but hitherto unproven, for these guest–host systems.

Keywords: Solid solution; Inclusion; Guest; Incorporation mechanism; Guest/solvent mole distribution ratio; Segregation coefficient

1. Introduction

Upon crystallization of crystals (the host) from solution, impurities or additives (the guest molecules) in the crystallization medium are often found in the host crystals at various levels depending on the nature of the system, the treatment of the crystals upon harvesting, and the crystallization conditions, including the concentrations of both the host and the guest in the crystallization medium, supersaturation of the host, desupersaturation rate, and degree of agitation (Chow et al., 1984; Chow and Grant, 1988a,b, 1989a). This phenomenon may be termed 'doping' of the 'host' crystals by the 'guest' molecules. Structurally, the guest may be

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closely related to the host, e.g. synthetic impurities (Chow et al., 1984, 1985) or chiral isomers (Duddu et al., 1993, 1996; Li and Grant, 1996), or may differ significantly from the host, e.g. a macromolecular surfactant (Al-Meshal et al., 1985) or the solvent itself (Law et al., 1994; El-Said, 1995). As a consequence of incorporation of the guest molecules, the properties of the host crystals may be modified, often profoundly. Such properties may include the morphology or habit, particle size distribution, specific surface area, true density, energetics (both bulk and surface), entropy, crystallinity, dissolution rate, and mechanical properties (Chow et al., 1984, 1985; Chow and Grant, 1989b; Chow and Hsia, 1991; Law and Grant, 1994).

A fundamental question that arises from this phenomenon is: How do the guest molecules become incorporated into the host crystal? A related question is: What are the state(s) and location(s) of the guest molecules in the host crystal? Only when we have obtained answers to these questions can we understand the doping phenomenon and utilize it for crystal engineering and chiral separation.

The guest molecules may occupy two main locations: (a) on or near the surface of the host crystals or particles; (b) in the lattice of the host crystals. In the lattice of the host crystals, the impurities can further exist in (i) zero-dimensional or point defects (substitutional or interstitial solid solutions), (ii) one-dimensional or line defects (dislocations), (iii) two-dimensional or surface defects (grain boundaries), or (iv) three-dimensional or phase defects (solid, liquid, or gaseous inclusions). Several studies, using the technique of adsorption measurements (Michaels and Tausch, 1961), surface washing (Chow and Hsia, 1991; Gordon and Chow, 1992; Chow et al., 1995) or progressive dissolution (Go and Grant, 1987) of the resulting crystals, have demonstrated that an appreciable amount of guest molecules are located on or near the surface of the crystals, although they may be adsorbed to different extents on to different crystallographic faces (Michaels and Tausch, 1961). The differentiation between the guest molecules on the surface and the guest molecules in the crystal lattice is well understood and has been quantified. The nature and location of the guest molecules in the lattice of the host crystals, on the other hand, are not well understood. The objective of this paper is to derive a method for calculating the concentration of the guest molecules in the host crystals, when the guest is present either in solid solution or in the liquid inclusions, and to use this method to deduce the most reasonable of these alternatives.

With this objective in mind, we discuss here a method for differentiating between two types of defect, namely liquid inclusions, a three-dimensional defect, and solid solutions, mainly a zero-dimensional defect, but sometimes present in one-dimensional and two-dimensional defects.

Liquid inclusions arise from the entrapment of pockets of saturated solution within the host crystals during crystallization from solution (Buckley, 1951; Mullin, 1993). The mechanism of their formation is still unclear and is currently under investigation in several laboratories, including ours. Several possible mechanisms have been proposed over the years (Denbigh and White, 1966; Rosmalen and Bennema, 1977) and reviewed by Mullin (1993). Because liquid inclusions consist of pockets of saturated solution trapped inside the crystals, the mole ratio of the guest molecules with respect to the crystallization solvent should be identical or similar in the resulting crystals and in the solution of crystallization. Therefore, if the guest molecules are brought into the crystals exclusively by liquid inclusions, a straight line with a slope, K, close to unity should be obtained when the mole ratio of the guest molecules with respect to the entrapped crystallization solvent in the resulting crystal is plotted against the mole ratio of the guest molecules with respect to the solvent in the crystallization medium. For convenience, K is here termed the guest/solvent mole distribution ratio. In other words, if liquid inclusion is the major pathway, the amount of guest molecules in the crystals, calculated from the solvent content in the crystals, and the mole ratio of the guest/solvent in the crystallization medium, should account for most of the guest molecules in the crystals. We apply this approach to eight systems for which appropriate published data exist.

Table 1
Host concentration, solvent content of the crystals, segregation coefficient, k, and guest/solvent mole distribution ratio, K, of four crystalline host + guest + solvent systems

Crystallization system			Host concentration in solution (M)	Solvent content (mole fraction)	k	K ($\times 10^3$)	Reference
Host	Guest	Solvent					
(−)-EN[a]	(+)-EN[a]	Water	0.134	0.017	0.153[g]	3.82	Duddu et al., 1993
(+)-PS[b]	(−)-PS[b]	Water	0.33	0.006	0.24[g]	6.7	Duddu et al., 1996
AA[c]	Oleic acid	Water	0.308	0.059[d]	0.624[e]	1.90	Chow et al., 1985
AA[c]	1-Octanoic acid	Water	1.232	0.06[f]	0.995	5.25	Law and Grant, 1994

[a] EN, ephedrinium 2-naphthalenesulfonate.
[b] PS, pseudoephedrinium salicylate.
[c] AA, adipic acid.
[d] Water content ranges from 0.044 to 0.059 mole fraction, so the highest water content was taken for simplicity.
[e] Calculated from the data in Table 1 from Chow et al., 1985.
[f] Water content ranges from 0.035 to 0.060 mole fraction, so the highest water content was taken for simplicity.
[g] Mole fraction, instead of mole ratio, was used in the calculation of k. This approximation leads to a small increase ($<5\%$) in the k value defined in this report.

Table 2
Incorporation of 3-acetoxymethyl-5,5-diphenylhydantoin (AMDPH) into phenytoin crystals by liquid inclusions[a]

Concentration of AMDPH in solution (g/l)	Amount of AMDPH in crystals ($x^c \times 10^4$)	Amount of AMDPH in crystal lattice[b] ($x^c \times 10^4$)	g/h ($\times 10^4$)	g/h (by inclusions) ($\times 10^8$)	Percentage of AMDPH in crystal lattice by inclusions ($\% \times 10^3$)
0.50	3.34	1.67	1.67	0.43	2.60
1.00	4.77	2.39	2.39	0.88	3.68
2.00	7.97	3.98	3.99	1.75	4.39
3.00	10.40	5.20	5.20	2.63	5.05
5.02	15.84	7.92	7.93	4.39	5.54
9.00	54.87	38.41	38.56	7.87	2.04
12.00	46.71	32.70	32.81	10.49	3.20

[a] Data taken from Fig. 5 in Chow and Hsia, 1991. Each data point was measured from an enlarged figure, therefore is approximate. Solvent (methanol) contents of 20 ppm (upper limit) were used in the calculation.

[b] Calculated by subtracting the amount adsorbed on the surface from the total amount: 50% surface adsorbed for crystals prepared at 0.5–5 g/l AMDPH, 30% surface adsorbed for crystals prepared at 9–12 g/l AMDPH.

[c] x is the symbol for mole fraction.

Table 3
Incorporation of 3-propanoyloxymethyl-5,5-diphenylhydantoin (PMDPH) into phenytoin crystals by liquid inclusions[a]

Concentration of PMDPH in solution (g/l)	Amount of PMDPH in crystals ($x^c \times 10^4$)	Amount of PMDPH in crystal lattice[b] ($x^c \times 10^4$)	g/h ($\times 10^4$)	g/h (by inclusions) ($\times 10^8$)	Percentage of PMDPH in crystal lattice by inclusions ($\% \times 10^3$)
0.51	3.26	0.98	0.98	0.34	3.50
0.98	5.63	1.69	1.69	0.66	3.89
2.00	10.01	3.00	3.00	1.34	4.46
3.01	16.12	4.83	4.84	2.02	4.18
4.01	18.89	5.67	5.67	2.69	4.75
5.04	23.83	7.15	7.15	3.38	4.72
7.01	36.65	18.33	18.36	4.70	2.56
8.98	39.42	19.71	19.75	6.02	3.05
10.93	56.83	28.41	28.49	7.33	2.57

[a] Data taken from Fig. 4 in Gordon and Chow, 1992. Each data point was measured from an enlarged figure, therefore is approximate. Solvent (methanol) contents of 16 ppm (upper limit) were used in the calculation.

[b] Calculated by subtracting the amount adsorbed on the surface from the total amount: 70% surface adsorbed for crystals prepared at 0.5–5 g/l PMDPH, 50% surface adsorbed for crystals prepared at 7–11 g/l AMDPH.

[c] x is the symbol for mole fraction.

Table 4
Incorporation of 3-butanoyloxymethyl-5,5-diphenylhydantoin (BMDPH) into phenytoin crystals by liquid inclusions[a]

Concentration of BMDPH in solution (g/l)	Amount of BMDPH in crystals ($x^c \times 10^4$)	Amount of BMDPH in crystal lattice[b] ($x^c \times 10^4$)	g/h ($\times 10^4$)	g/h (by inclusions) ($\times 10^9$)	Percentage of BMDPH in crystal lattice by inclusions (% $\times 10^5$)
0.51	5.29	3.96	3.97	0.21	5.23
1.02	8.59	6.44	6.45	0.41	6.39
2.02	11.99	9.00	9.00	0.81	9.03
3.00	20.06	15.04	15.06	1.21	8.01
5.02	26.99	20.25	20.29	2.02	9.96
7.01	38.33	28.74	28.83	2.82	9.79
8.99	45.23	33.92	34.04	3.62	10.64
11.98	49.86	37.39	37.53	4.82	12.85

[a] Data taken from Fig. 4 in Chow et al., 1995. Each data point was measured from an enlarged figure, therefore is approximate. Solvent (methanol) contents of 1 ppm (upper limit) were used in the calculation.

[b] Calculated by subtracting the amount adsorbed on the surface from the total amount: 25% surface adsorbed for crystals prepared at all concentrations of BMDPH.

[c] x is the symbol for mole fraction.

Table 5
Incorporation of *p*-acetoxyacetanilide (PAA) in paracetamol crystals by liquid inclusions[a]

Concentration of PAA in solution (g/l)	Amount of PAA in crystal lattice ($x^b \times 10^4$)	g/h ($\times 10^4$)	g/h (by inclusions) ($\times 10^7$)	Percentage of PAA in crystal lattice by inclusions (%)
0.051	1.53	1.53	2.01	0.131
0.10	2.91	2.91	3.93	0.135
0.20	4.98	4.99	7.94	0.159
0.30	8.91	8.91	11.6	0.130
0.40	11.3	11.3	15.7	0.139
0.50	18.2	18.2	19.6	0.108
0.71	21.7	21.8	27.6	0.127
0.91	31.1	31.2	35.5	0.114
1.00	34.7	34.8	39.3	0.113
1.26	43.2	43.4	49.2	0.113
1.50	43.9	44.1	58.8	0.133
1.75	45.9	46.1	68.6	0.149
2.00	45.3	45.5	78.3	0.172

[a] Data taken from Fig. 1 in Chow et al., 1985. Each data point was measured from an enlarged figure, therefore is approximate. Solvent (water) content ranges from 0.013 to 0.042 mole fraction, the highest solvent content was taken for simplicity.
[b] x is the symbol for mole fraction.

2. Method of calculation

All data available show that the amount of guest molecules incorporated into the crystals increases as their concentration increases in the crystallization media, although to different extents depending on the nature of the guest molecules and the host crystals. The calculations were carried out in one of two ways, depending on whether or not the segregation coefficient is known. For systems whose segregation coefficient, k, is known or can be easily calculated from the data presented, the slope, K, of the above-mentioned plot is calculated from k, from the initial mole ratio of the host molecules and the solvent in the crystallization solution, and from the solvent content of the host crystals, assuming that all the solvent is present in the crystals as liquid inclusions. The following equation is employed and the results are summarized in Table 1:

$$K = (g/s)/(G/S) = [(g/h)\cdot(h/s)]/[(G/H)\cdot(H/S)]$$
$$= [(g/h)/(G/H)]\cdot[(h/s)/(H/S)] = k(h/s)/(H/S)$$

where K is the guest/solvent mole distribution ratio, the slope of the plot of interest; H, G, and S are the numbers of moles of the host, guest, and solvent, respectively in the crystallization solution; h, g, and s are the numbers of moles of the host, guest, and solvent, respectively within the crystals; k is the segregation coefficient, which is here defined as $(g/h)/(G/H)$.

In those cases for which the segregation coefficient is not known, the amount of guest molecules, g, brought into the crystal by liquid inclusions is calculated, instead, by the following equation:

$$g/h = (g/s)/(h/s) = (G/S)/(h/s)$$
$$= (G/H)\cdot(H/S)/(h/s)$$

The results of the above calculation are then compared to the experimental values as shown in Tables 2–5.

3. Results and discussion

The K values, which range from 1.9×10^3 to 6.7×10^3 in Table 1, are much larger than unity, the theoretical value when inclusion of saturated solution is the exclusive mechanism of guest incorporation. This large discrepancy strongly indicates that liquid inclusion is not the sole mechanism. In fact, the reciprocal of K, which ranges from 0.015 to 0.053%, should give the

proportion of guest incorporated as liquid inclusions. Tables 2–5 show that the amount of guest incorporated as liquid inclusions accounts for, at most, 0.2% of the guest molecules in the crystals. Hence, most ($\geq 99.8\%$) of the guest molecules are present within the lower dimensional defects, rather than in the three-dimensional defects.

In the above calculations, we have assumed that all the solvent molecules are present in the crystals as liquid inclusions and that no solvent molecules are adsorbed on to the surface of the crystals or are present in the lower dimensional defects. This assumption actually favors liquid inclusions. However, in most crystals, solvent molecules are probably present on the surface and in the lower dimensional defects, to some extent. We have also assumed that the concentration of the guest in the crystallization solution remained unchanged over the course of crystallization, another assumption that favors liquid inclusions. As we know, when guest molecules are incorporated into the host crystals, their concentration in the solution decreases. In cases in which the solvent content varies depending on the level of doping, we have taken the highest level of solvent content in the crystals, which again favors liquid inclusions. Despite the various biases taken to favor liquid inclusion as a mechanism of guest incorporation, the actual impact of liquid inclusion on the extent of guest incorporation is so small as to be virtually negligible.

Of course, crystallization is a highly dynamic process. The liquid inclusions that are present in crystals may change over time as a result of changes of the environment, such as temperature and pressure. In their early work on liquid inclusions in hexamethylene crystals, Denbigh and White (1966) observed changes of the shapes of liquid inclusions with time, presumably due to processes of dissolution and crystallization. However, the amount of guest molecules within the liquid inclusions will remain the same as the inclusions relocate, unless they escape from the crystals. When pathways do exist that lead the inclusions to the surface of the crystals, e.g. along cracks or fractures, the trapped solvent may gain access to the environment and evaporate upon drying, leaving the guest molecules in the original cavities. As a result, the guest molecules that are brought into the crystals by liquid inclusions will remain with the crystals after the solvent has disappeared. This process is unlikely to occur during harvesting of the crystals, because the liquid inclusions that are sealed within the crystals at some point during the crystallization process remain sealed up during the usual drying process of the finished crystalline products (Denbigh and White, 1966). Normal drying processes have proven to be inefficient for removing the liquid inclusions (Denbigh and White, 1966; Wilcox, 1968). A small fraction of solvent that is removed by drying will then tend to expose the washing medium to the inner cavities of the inclusions that remain. Therefore, the guest molecules left behind in these cavities will tend to be removed during the early stages of washing (Chow and Hsia, 1991; Gordon and Chow, 1992; Chow et al., 1995) or of dissolution (Go and Grant, 1987) and will not contribute to the analyzed guest molecules in the crystal lattice. Diffusion or redistribution of the guest molecules to the other regions of the host crystals from the liquid inclusions seem unlikely when only traces of guest molecules are present in the reservoir.

As mentioned earlier in this paper, adsorption of guest molecules on the crystal surfaces is quite significant. The usual sub-unity values of segregation coefficient indicate that crystals usually reject foreign molecules, impurities or additives, during growth. For this reason, the local concentration of the guest molecules may be higher in the vicinity of the growing crystal surfaces than the concentration of the guest molecules in the bulk of the crystallization solution. This difference in the guest concentration is mainly dictated by the extent of adsorption of the guest molecules on the host crystal surfaces, by the segregation coefficient, by the rate of crystal growth, by the degree of agitation, and by the diffusion of the guest molecules in the crystallization medium. Because of such a concentration difference and the process of their formation, liquid inclusions may be richer in guest molecules than the mother liquor from which the crystal grew (Mullin, 1993). The extent of this enrichment of guest molecules in the liquid inclusions is not known. However, considering the

experimental conditions employed, including low crystallization rate, efficient agitation, and low viscosity of the crystallization solutions, the enrichment of guest molecules in liquid inclusions is expected to be very minor.

Having excluded the major contribution of liquid inclusions as the mechanisms of incorporation of guest molecules into the crystal lattice, it is very likely that the formation of solid solutions, as previously suggested, is the dominant mechanism of guest incorporation. In fact, several guest + host systems (Chow et al., 1995; Duddu et al., 1996) exhibit negative deviations from linear relationships of guest uptake upon increasing the concentration of the dissolved guest, indicating that the solubility limit of the solid solution is being approached. In some systems (Chow et al., 1985; Chow and Hsia, 1991; Li and Grant, 1996), achievement of the solid solubility limit is evident from the plateaus of the guest uptake curves.

The exact location(s) of the guest molecules in the various lattice defects (namely zero-, one- or two-dimensional lattice defects) is still not clear at this stage and requires further detailed investigation.

4. Conclusion

The incorporation of guest molecules (additives or impurities) in crystals via the formation of liquid inclusions has been examined by a simple calculation method for differentiating between liquid inclusions and lower dimensional defects. This calculation is based on the equality of the guest/solvent mole ratio in the initial crystallization medium and in the resulting host crystals. Application of this calculation to eight guest + host systems whose data are available in the literature leads to the conclusion that liquid inclusions account for a tiny fraction of the guest molecules incorporated in the crystals and that these guest molecules are mainly associated with lower dimensional defects within the crystal lattice of the host. This study confirms and reinforces previous findings in this area.

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