Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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To cite this Article Anthony, Addlagatta and Desiraju, Gautam R.(2001) 'Crystallization of Pseudopolymorphs of Some Gamboge Pigments. Pyridine, Dimethylformamide and Dimethylsulfoxide Solvates of Morellic Acid, Gambogic Acid and Guttiferic Acid', Supramolecular Chemistry, 13: 1, 11 — 23
To link to this Article: DOI: 10.1080/10610270108034878
URL: http://dx.doi.org/10.1080/10610270108034878

SUPRAMOLECULAR CHEMISTRY, Vol. 13, pp. 11–23
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Crystallization of Pseudopolymorphs of Some Gamboge Pigments. Pyridine, Dimethylformamide and Dimethylsulfoxide Solvates of Morellic Acid, Gambogic Acid and Guttiferic Acid*

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Morellic acid, gambogic acid and guttiferic acid are related naturally-occurring xanthone pigments that yield X-ray quality crystals only from solvents like pyridine, dimethylformamide (dmf) and dimethyl sulfoxide (dmso). The structures of four of these crystals have been determined and are found to contain solvents of crystallization. The solvents hydrogen bond to the carboxyl groups with O–H···O/N motifs previously seen in other carboxylic acids. Distinctive, however, is the presence of an extended though somewhat diffuse array of C–H···O hydrogen bonds that aggregates the entire solute-solvent assemblage in a multi-point manner. Pyridine and dmf are able to mimic each other with respect to their hydrogen bond donating and accepting characteristics and in this respect play equivalent roles in their solvates with morellic acid and gambogic acid. Dmso is seen to self-associate in its guttiferic acid solvate. It is possible that these solvents with multiple hydrogen bonding donor and acceptor capability can act as hydrogen bond nucleators, providing just enough rigidity to the solutes to ensure crystallization.

Keywords: Crystallization; Hydrogen bond; Solvation; Entropy

INTRODUCTION

Crystallization is a phenomenon of fundamental and applied importance but our knowledge of the events that take place during this process is often incomplete [1]. It is a matter of common experience that not all organic compounds crystallize from solution equally easily or well [2]. An examination of a family of naturally-occurring pigments that had been reported to display variable crystallization behavior with different solvents led to the present study. In a more general sense, a better understanding of crystallization would help, say, in finding ways of improving crystal quality or in controlling polymorphism.

The gamboge pigments are obtained from nearly all parts of the trees of the genus *Garcinia* in the Guttiferae family [3]. The fused ring xanthone structure of these compounds [4] is

*Dedicated to Professor Fumio Toda on the occasion of his 67th birthday.

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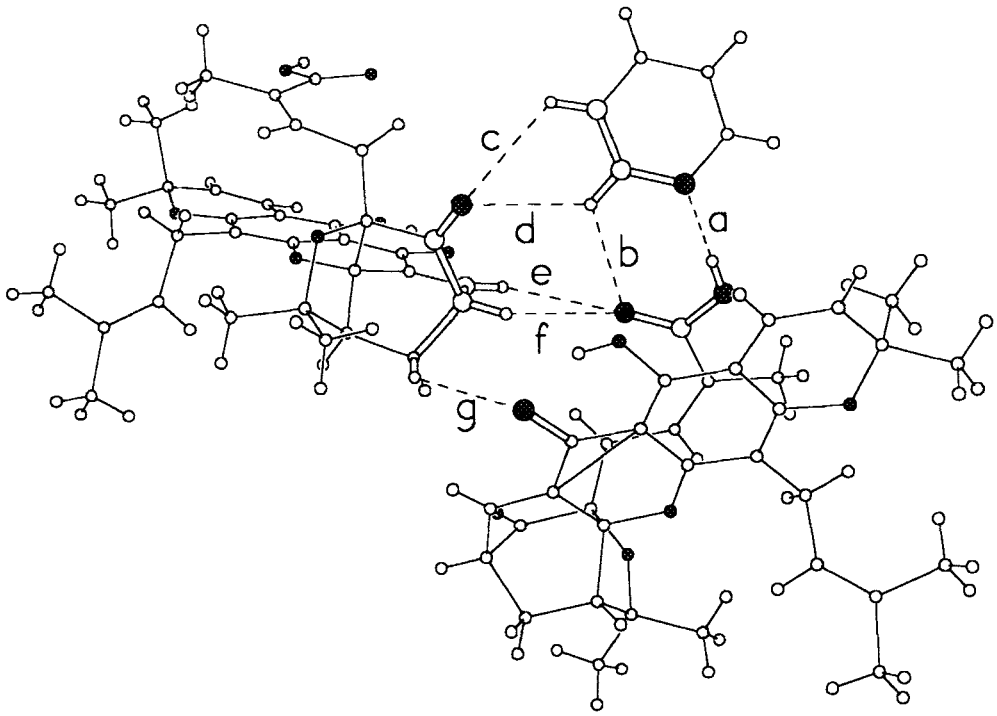
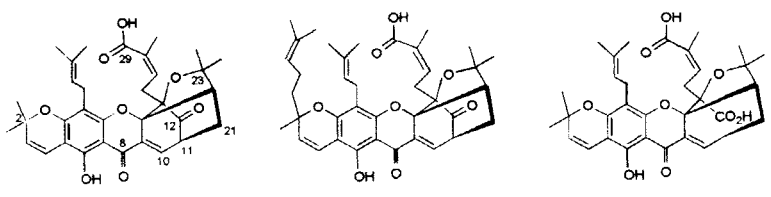


FIGURE 1 Structure of the (pyridine) · (morellic acid) solvate to show the attachment of the pyridine molecule. Hydrogen bonds are marked *a* through *g*. Notice that hydrogen bonds are both donated and accepted by the solvent. Notice also the hairpin shape of the acid molecule.

peculiar to natural products obtained from this group, especially *G. morella* and *G. hanburyi* found extensively in India and South-East Asia. The acidic constituents of these pigments are difficult to crystallize. Depending on the solvent used (formic acid, acetic acid), material is obtained that has been variously described as being fluffy, pasty, gummy or resinous [5–8]. Yet, with solvents like pyridine, dimethylformamide (dmf), dimethylsulfoxide (dmso) and tetrahydrofuran, diffraction quality crystals are obtained regularly. We report here the crystal structures of the pyridine solvate of morellic acid, **1**, the pyridine and dmf solvates of gambogic acid, **2**, and the dmso solvate of guttiferic acid, **3**. These acids are closely related, and as such the solvates may be termed *pseudopolymorphs* [9]. Structural analysis shows why these particular solvents are included in the crystal and also gives some hints about the crystallization event itself.



1 2 3

RESULTS

(Pyridine)·(morellic acid) 1:1 *solvate, (pyr)* (**1**). Figure 1 shows the association of two molecules of acid **1** with a molecule of pyridine. The pyridine molecule is not protonated by the carboxylic acid molecule on the right side of the figure but rather hydrogen bonded to it with

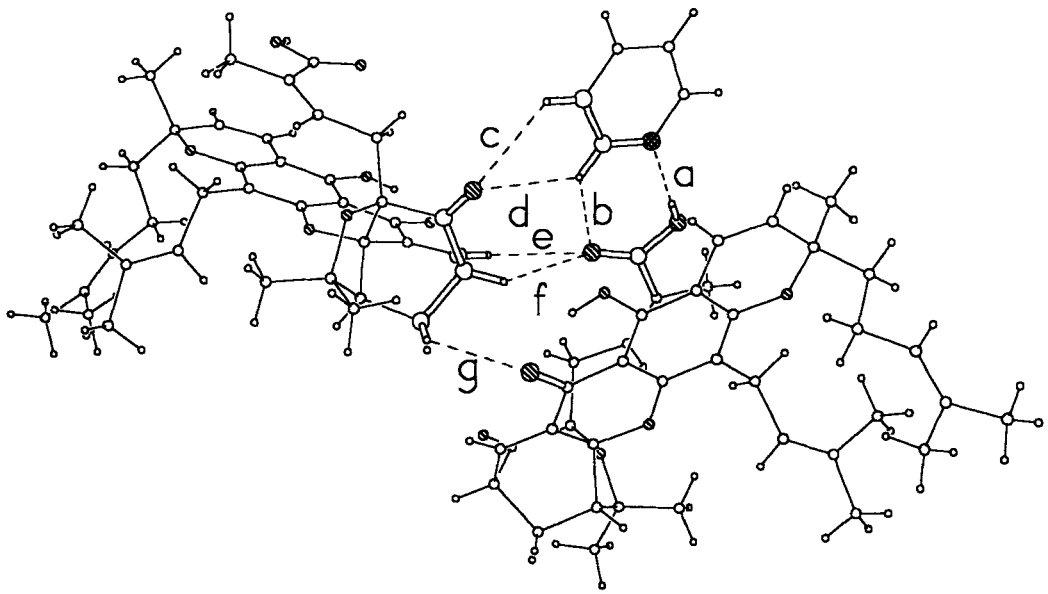


FIGURE 2 Structure of the (pyridine) · (gambogic acid) solvate. Notice the similarity to Figure 1. Hydrogen bond metrics (d, θ) are as follows: ***a***, 1.63 Å, 155°; ***b***, 2.70 Å, 122°; ***c***, 2.67 Å, 117°; ***d***, 2.52 Å, 123°; ***e***, 2.57 Å, 120°; ***f***, 2.69 Å, 122°; ***g***, 2.63 Å, 123°.

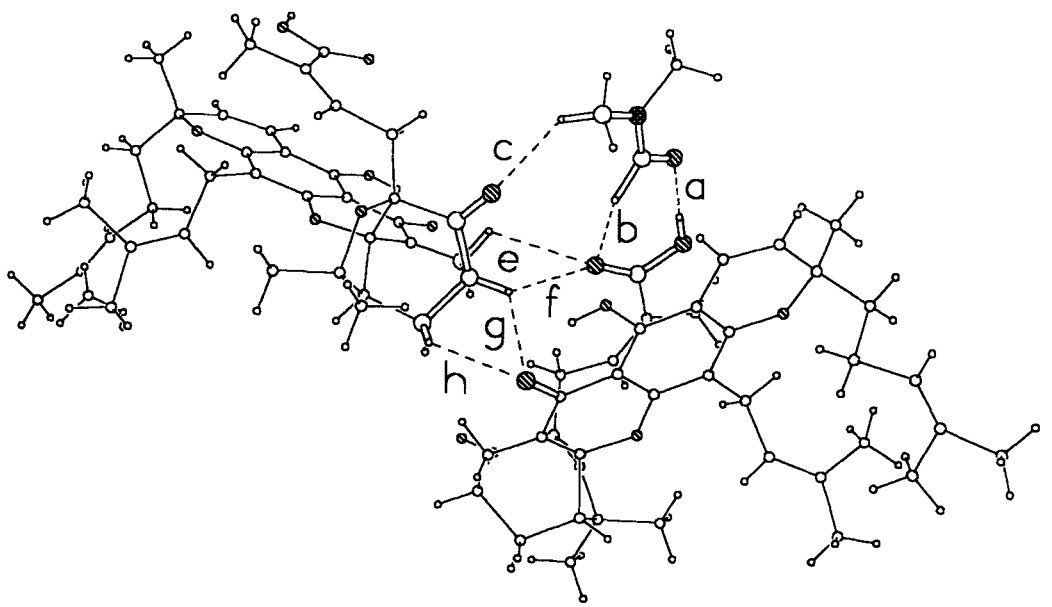
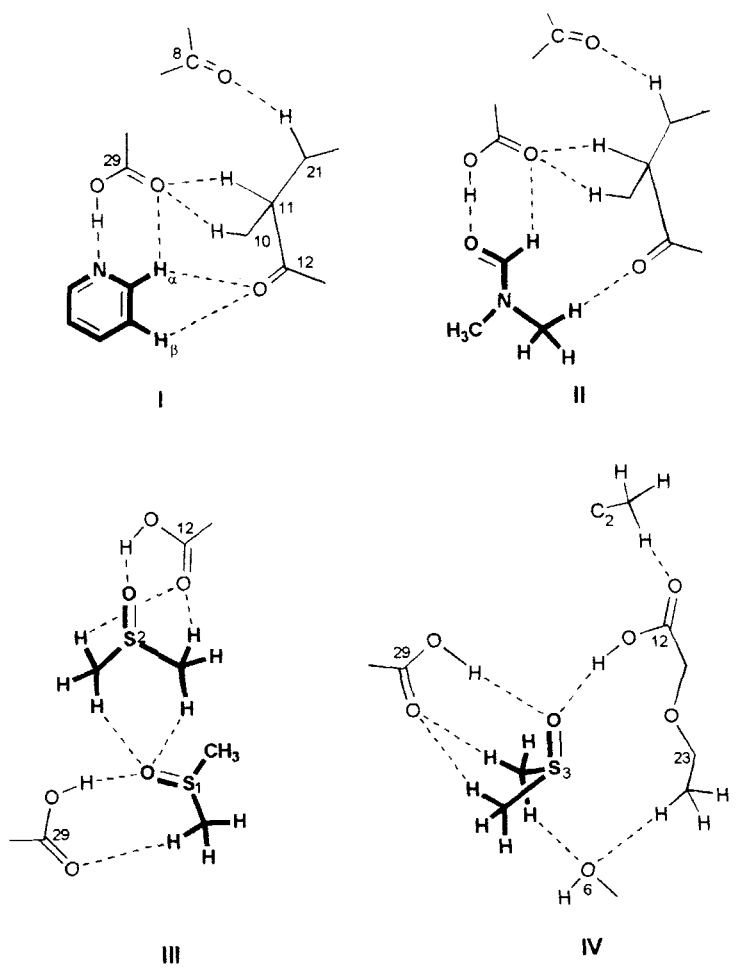


FIGURE 3 Structure of the (dmf) · (gambogic acid) solvate. Notice the mimicry between the dmf molecule here and the pyridine molecule in Figure 2.

strong O–H···N (1.67 Å, 172°) and weak C–H···O (2.82 Å, 120°) hydrogen bonds [11]. These are indicated *a* and *b* in the figure. There is precedent for this kind of association [12]. The pyridine is held to the other acid molecule *via* C–H···O bonds *c* (2.65 Å, 120°) and *d* (2.58 Å, 123°) via its activated donor groups. The loop is completed with the C–H···O interactions *e* (2.80 Å, 120°), *f* (2.68 Å, 131°) and *g* (2.71 Å, 129°). The role of the pyridine molecule in bringing the two acid molecules together is noteworthy. Interactions *e*, *f* and *g* are in themselves unremarkable. But through the aegis of the pyridine molecule, they serve to guide the morellic acid molecule into a hairpin-shape, with the carboxyl group (C29) and pyranone carbonyl (C8) situated rather close to one another.

(Pyridine)·(gambogic acid) 1:1 solvate, (pyr)·(2) and structure similarity. The structure of the (pyr)·(2) solvate is shown in Figure 2 and is very similar to that of (pyr)·(**1**). The pyridine is hydrogen bonded to the acid molecules in the same way. The O–H···N hydrogen bond is again labelled *a* and the six C–H···O interactions similarly labelled *b* through *g*. The interaction metrics are given in the figure caption. Despite the additional isoprenyl group in acid **2**, there is little difference in the packing of the two



SCHEME 1

pyridine solvates. This is true not only of the carboxyl-pyridine synthon with its O–H···N and C–H···O bonds but also the more diffuse C–H···O pattern (roughly 2.5–2.9 Å, 115–130°) between the pyridine and the neighboring acid molecules. The small and rigid pyridine molecule is of key importance in these two structures. Because of its multiple hydrogen bonding capability as an N-acceptor and a C–H donor, it is able to act as a template in organizing the conformationally flexible morellic and gambogic acid molecules in the crystal.

(Dimethylformamide)·(gambogic acid) 1:1 solvate, (dmf)·(2) and interaction mimicry between solvents. Figure 3 shows the structure of the (dmf)·(2) solvate. Remarkably, the packing is very similar to that of the (pyr)·(2) solvate. It has been noted previously that the formyl group of the dmf molecule hydrogen bonds to carboxylic acids *via* O–H···O and C–H···O bonds [13].

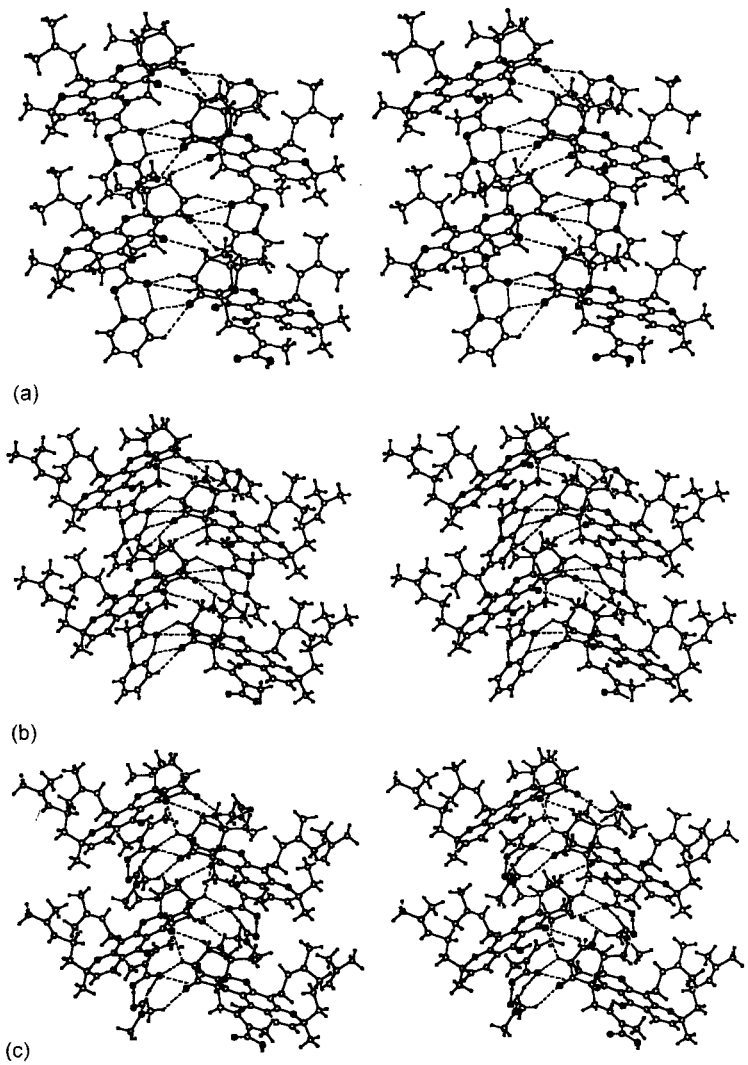


FIGURE 4 Stereoviews (top, middle, bottom) of the (pyr) · (1), (pyr) · (2) and (dmf) · (2) solvates. The [100] direction is vertical. N- and O-atoms are shaded. All hydrogen bonds are marked. Notice the close similarities between these three structures.

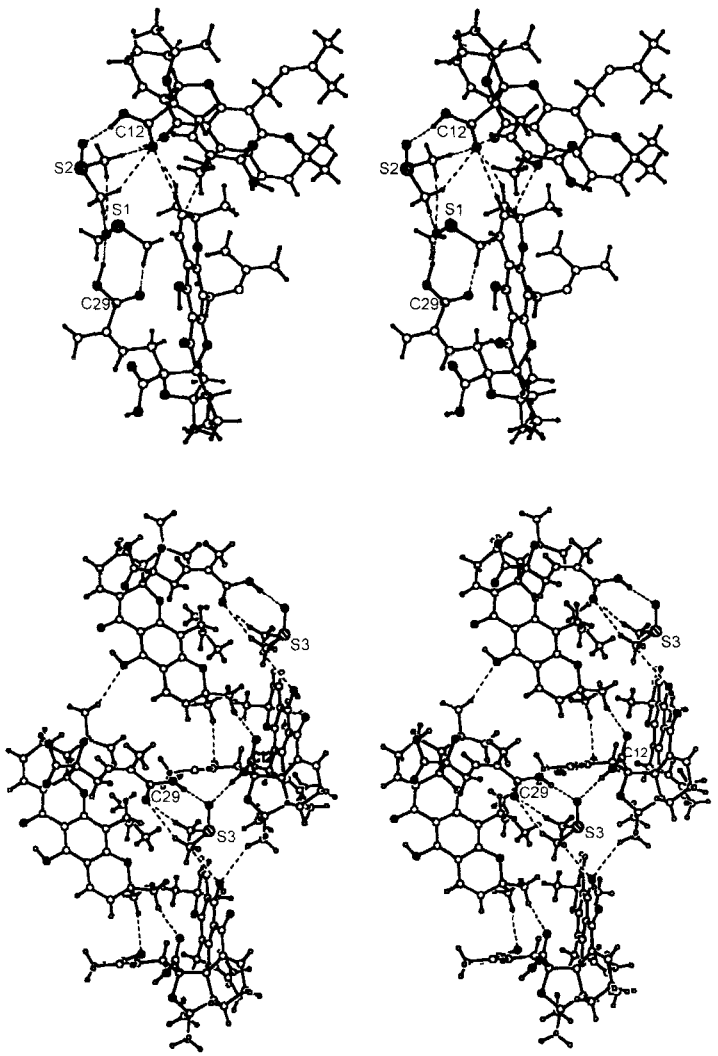


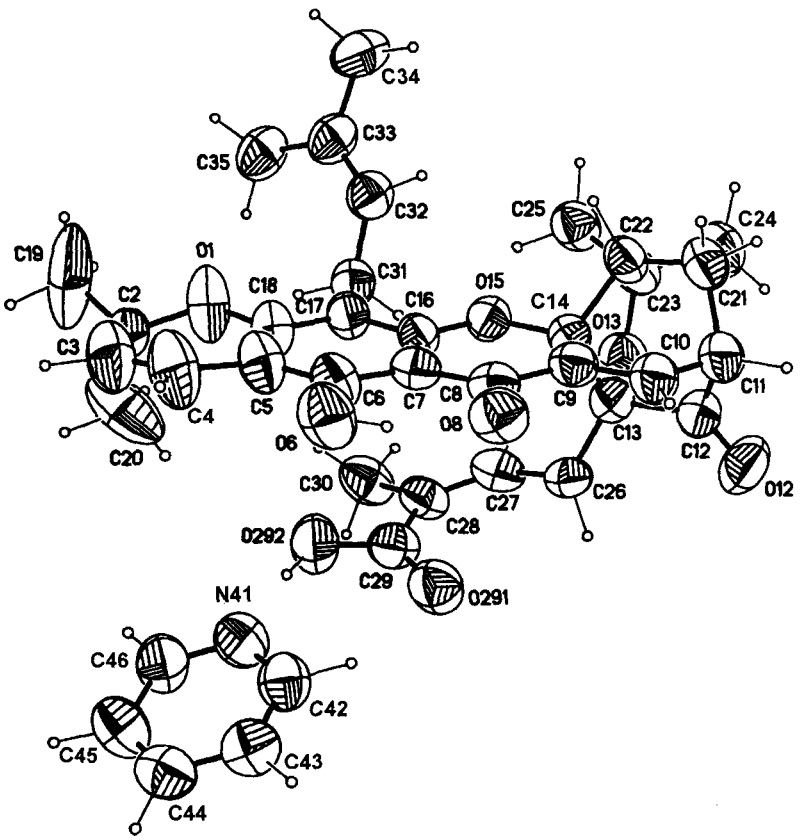
FIGURE 5 (a) Top. Stereoview of the dmso solvate of guttiferic acid, $(dmso)_3 \cdot (3)_2$ to show the solvent–solvent interactions between the symmetry independent molecules S1 and S2. Each dmso is further hydrogen bonded to carboxyl groups of adjacent screw-related acid molecules which are themselves linked *via* weak C–H···O bonds to complete the hydrogen bonding cycle. (b) Bottom. The same structure showing the interactions between the third dmso molecule S3 and surrounding solute. Notice the complexity of the packing arrangements and the many O–H···O and C–H···O hydrogen bonds. See Table II.

These are labelled ***a*** (1.60 Å, 176°) and ***b*** (2.83 Å, 117°) in Figure 3. However, what is extremely interesting and even unprecedented is that one of the methyl groups of the dmf also acts as a C–H donor to O12 of the neighboring screw-related acid molecule just like the H_β atom in pyridine. These equivalent interactions are marked *c* in Figures 2 and 3 and the metrics are (2.67 Å, 117°) and (2.41 Å, 141°) for the pyridine and dmf solvates respectively. The mimicry between the dmf and pyridine continues with some subtle variations which, however, are along chemically expected lines. While interactions ***e***, ***f*** and ***g*** are equivalent in the two structures, there is no equivalent for interaction ***d*** which is formed by the $C-H_\alpha$ group in (pyr)·(**2**). We rationalize this on the basis of the very poor donor ability of the formyl C–H

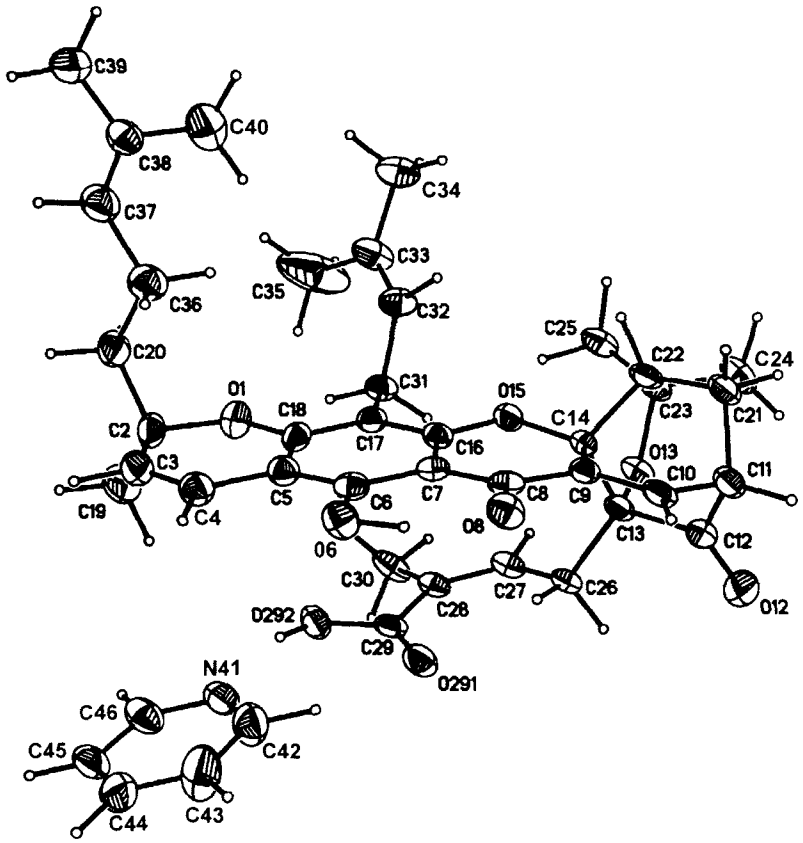
group in dmf [14]. The slight realignment of molecules that thus results in (dmf)·(**2**) might perhaps lead to the additional interaction *h* (2.84 Å, 118°). To summarize, this solvent mimicry between pyridine and dmf is shown in Scheme 1 and a comparison of synthons **I** and **II** is instructive.

Figures 4(a), 4(b) and 4(c) are stereoviews of the overall packing of the three crystal structures, (pyr)·(**1**), (pyr)·(**2**) and (dmf)·(**2**). The interactions discussed above have been extended along [100] in these figures, from which one notes that the structures are virtually identical. The unit cell dimensions and space group details are the same, and either pyridine or dmf is equally effective in binding the morellic or gambogic acid molecules together *via* a complex system of O–H···N/O and C–H···O hydrogen bonds. None of the C–H···O hydrogen bonds in these structures is particularly strong [15, 16]. Yet, they are numerous and occur in widely separated parts of these flexible molecules giving a convincing impression that they are able to pin down these conformationally flexible molecules into intricate networks.

(Dimethylsulfoxide)·(guttiferic acid) 3:2 solvate, $(dmso)_3\cdot(\mathbf{3})_2$ and solvent–solvent interactions. The role of the solvent in promoting crystallization is even more evident here. The packing is shown in Figures 5(a) and 5(b) and the recognition features are depicted schematically in synthons **III** and **IV** (Scheme 1). There are two symmetry-independent molecules of acid **3** and the isoprenyl side chain of one of them is disordered. There are three

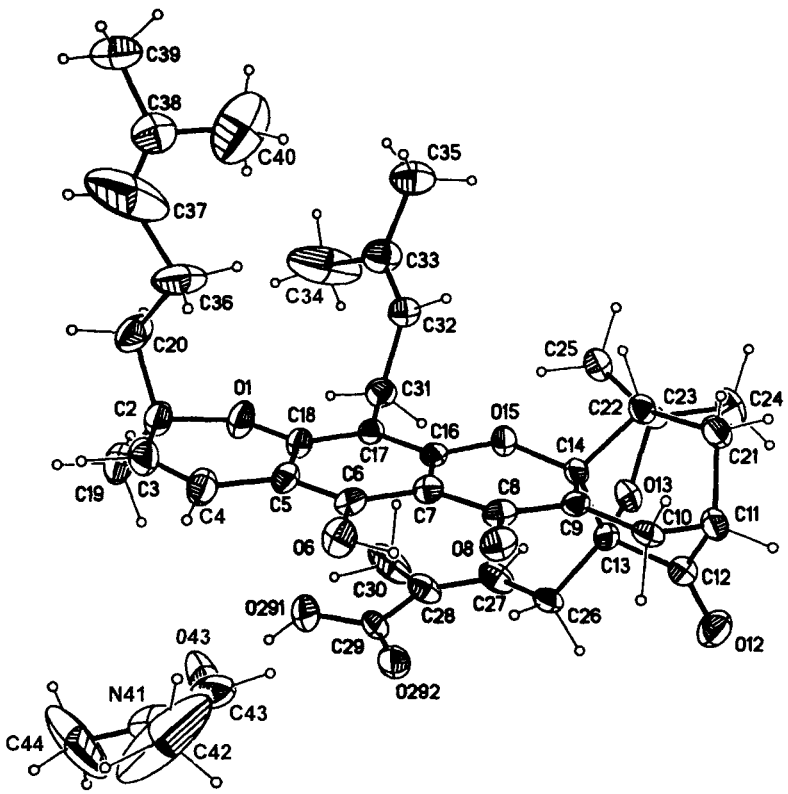


ORTEP diagram of (pyr) · (**1**) at 35% probability level.

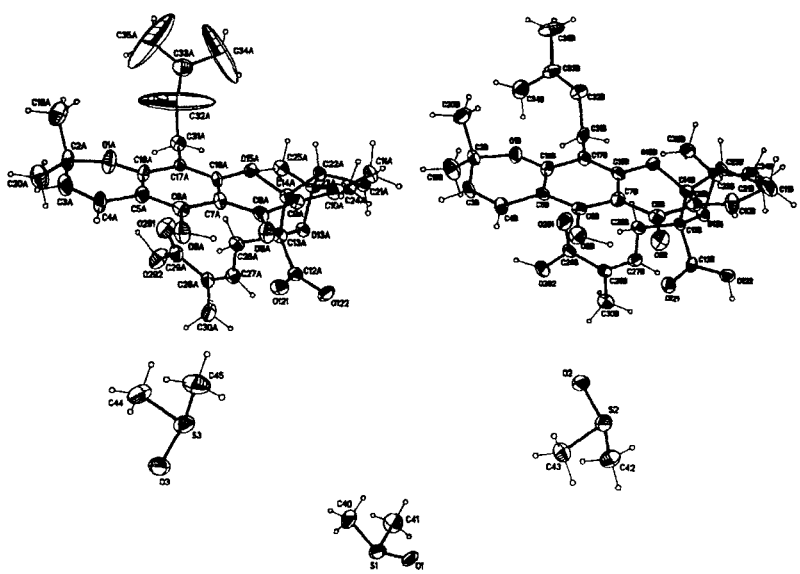


ORTEP diagram of (pyr)·(**2**) at 35% probability level.

symmetry-independent dmso molecules. Two of them (identified by atoms S1 and S2) are shown in Figure 5(a) and in synthon **III**. The S1 dmso is hydrogen bonded to the C29 carboxylic acid group *via* O–H···O (1.70 Å, 158°) and C–H···O (2.68 Å, 130°) hydrogen bonds. The S2 dmso is similarly hydrogen bonded to the C12 carboxylic acid group (O–H···O, 1.59 Å, 168°; C–H···O, 2.57, 2.31 Å, 141, 149°). This mode of dmso-carboxyl recognition is with precedent [17]. Additionally, however, the dmso molecules S1 and S2 are associated with each other *via* C–H···O bonds (2.43 Å, 160°). The third dmso molecule (identified by atom S3) is shown in Figure 5(b) and in synthon **IV**. It is linked to *syn* and *anti* carboxyl groups of distinct guttiferic acid molecules *via* O–H···O bonds (1.71, 1.84 Å; 167, 144°). The methyl groups of the S3 dmso and also of the acid molecules form several additional C–H···O bonds shown in Figure 5(b). The numerous C–H···O hydrogen bonds in this structure are detailed in Table II. We have noted the C–H···O bond-donating propensity of dmso recently [18]. When dmso is included in organic crystals, the main interaction is generally a strong hydrogen bond of the O–H···O or N–H···O type wherein dmso acts as an acceptor. However, the C–H groups in dmso are sufficiently activated by the sulfoxide group so that they also invariably donate a hydrogen bond as a supporting interaction. The implications of this are that dmso is usually C–H···O hydrogen bonded not only to the solute but also to itself in its solvates. The role of the solvent in $(dmso)_3\cdot(\mathbf{3})_2$ seems then to be that of an agent that can bind together acid molecules that



ORTEP diagram of (dmf)·(**2**) at 35% probability level.



ORTEP diagram of $(dmso)_3 \cdot (\mathbf{3})_2$ at 35% probability level.

presumably are unable to self-assemble into a crystal.

DISCUSSION

Two issues need to be considered: (1) why do pigments **1**–**3** include solvents like pyridine, dmf and dmso in their crystals? (2) why do they not form good crystals from other solvents? These questions are related.

Crystallization is a complex phenomenon. Generally, and independent of kinetic considerations [1], one may say that it begins with solute–solvent aggregates that contain solute–solute, solute–solvent and solvent–solvent interactions. The entropic gain in eliminating solvent molecules from these aggregates into the bulk solution, and the simultaneous enthalpic gain in forming stable solute species that contain robust supramolecular synthons provides an adequate driving force for nucleation and crystallization with the result that most organic crystals (85%) are unsolvated. However, if solute–solvent interactions are unusually important, say because of multi-point recognition between solute and solvent, the entropic advantage associated with solvent expulsion into the bulk could be overridden by these additional enthalpic factors resulting in retention of some solvent in the crystal. According to such a model, the formation of a solvated crystal may be likened to an interruption of the sequence of events that accompany 'normal' crystallization.

Multi-point recognition between solvent and solute indeed appears to be a critical factor that determines ease of solvation, especially for organic solvents capable of strong and/or weak hydrogen bonding. A recent CSD study has shown that the likelihood of inclusion of such solvents varies widely, being the maximum for dmf, dmso and dioxane, all of which can act as good and/or multiple hydrogen bond acceptors,

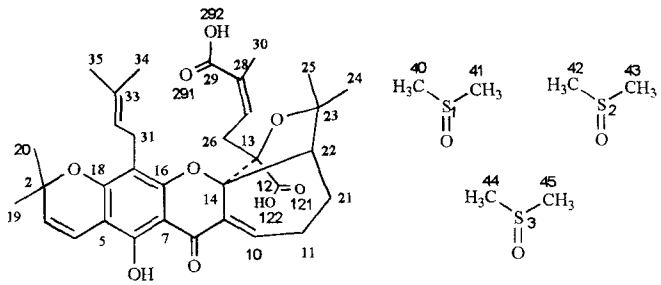
TABLE I Crystal data for the compounds in this study

	(pyr)·(**1**)	(pyr)·(**2**)	(dmf)·(**2**)	$(dmso)_3$·$(\mathbf{3})_2$
Emp. Formula	$C_5H_5N \cdot C_{33}H_{35}O_8$	$C_5H_5N \cdot C_{38}H_{44}O_8$	$C_3H_7NO \cdot C_{38}H_{44}O_8$	$(C_2H_6OS)_3 \cdot (C_{33}H_{37}O_9)_2$
Formula Wt.	638.73	707.83	701.85	695.32
Crystal system	orthorhombic	orthorhombic	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
a/Å	9.9048 (7)	9.515(1)	9.576 (2)	11.9627 (19)
b/Å	17.2116 (12)	18.158(7)	18.567 (5)	12.787 (2)
c/Å	20.1845 (15)	22.179(1)	21.800 (6)	23.492 (4)
α(°)	90	90	90	90
β(°)	90	90	90	90.214(2)
γ(°)	90	90	90	90
Z	4	4	4	2
V(Å^3)	3441.0 (4)	3832.1 (9)	3875.9 (17)	3593.6 (10)
D_{calc}(Mg/m^3)	1.237	1.227	1.204	1.285
F(000)	1356	1512	1508	1482
Index ranges	$-9 \le h \le 12$	$-11 \le h \le 4$	$-4 \le h \le 11$	$-12 \le h \le 14$
	$-21 \le k \le 21$	$-22 \le k \le 22$	$-23 \le k \le 22$	$-15 \le k \le 13$
	$-25 \le l \le 25$	$-26 \le l \le 27$	$-26 \le l \le 23$	$-29 \le l \le 29$
M.Pt.(°C)	119–120	147–148	99–101	104–106
R_1	0.0828	0.0407	0.057	0.0479
wR_2	0.2035	0.0838	0.1439	0.1090
Gof	1.215	0.753	0.761	0.497
N-total	6710	7500	7208	12839
N-observed	2887	3859	3211	4511
Variables	424	473	468	884

and also as activated C–H donors [18]. In contrast, solvents which do not have an effective enough donor–acceptor combination (acetone, ethyl acetate, diethyl ether) are not included so often. So, the presence of pyridine, dmf and dmso in the gamboge pigment crystals may be rationalized. In every case described in this paper, the solvent acts both as a hydrogen bond donor and as an acceptor. This leads to an extended hydrogen bonded array that contains solvent–solute, solute–solute and (in the case of the $(dmso)_3 \cdot (\mathbf{3})_2$ solvate), solvent–solvent interactions.

As for the failure of these pigments to form good crystals from other solvents, it may be mentioned that most carboxylic acids crystallize as dimers or catemers [19–21], following carboxyl–carboxyl recognition. In the present

TABLE II Hydrogen bonds in the crystal structure of $(dmso)_3 \cdot (\mathbf{3})_2$



		D	D	θ
Solute–solute	C(3B)–H···O(121B)	2.76	3.65	140
	C(11A)–H···O(292B)	2.46	3.21	125
	C(11A)–H···O(6B)	2.58	3.58	153
	C(19B)–H···O(121B)	2.50	3.42	142
	C(19A)–H···O(291A)	2.78	3.70	142
	C(20A)–H···O(121A)	2.37	3.29	141
	C(24A)–H···O(6A)	2.56	3.53	149
	C(24A)–H···O(15B)	2.82	3.85	158
	C(34A)–H···O(292A)	2.76	3.72	147
Solute–solvent	O(122)–H···O(3)	1.84	2.70	144
	O(124)–H···O(2)	1.60	2.56	165
	O(292A)–H···O(3)	1.73	2.67	160
	O(292B)–H···O(1)	1.70	2.61	152
	C(35B)–H···O(2)	2.69	3.63	145
	C(40)–H···O(13B)	2.30	3.37	170
	C(40)–H···O(291B)	2.68	3.48	130
	C(40)–H···O(292B)	3.01	3.73	124
	C(41)–H···O(121A)	2.55	3.62	169
	C(41)–H···O(122B)	2.66	3.60	145
	C(42)–H···O(121B)	2.56	3.48	141
	C(43)–H···O(8B)	2.63	3.35	123
	C(43)–H···O(121B)	2.32	3.30	149
	C(44)–H···O(291A)	2.71	3.67	146
	C(45)–H···O(6A)	2.74	3.49	126
	C(45)–H···O(291A)	2.55	3.54	152
Solvent–solvent	C(42)–H···O(1)	2.43	3.47	160
	C(43)–H···O(1)	2.76	3.71	147
	C(43)–H···O(3)	2.64	3.38	125
	C(44)–H···O(2)	2.56	3.30	125

cases, however, the formation of dimers or catemers may just not be enough to ensure crystallization because of the flexible nature of the molecules. The entropic penalty that has to be paid upon the loss of conformational freedom that would necessarily accompany crystallization is not perhaps compensated adequately by enthalpic factors. This is a general problem with medium to large-sized flexible molecules [22]. Solvents like pyridine, dmf and dmso which can act as multi-point hydrogen bond nucleators may immobilize distant portions of the solute molecules to an extent that is critically sufficient to induce crystallization. The isoprenyl side chains are especially flexible in these acids. This is evidenced by the disordered nature of this group in one of the acid molecules in the crystal of $(dmso)_3(\mathbf{3})_2$. Specific C–H···O bonds to these isoprenyl groups are not observed in the compounds studied here, but the overall rigidity conferred by the hydrogen bonded system is probably sufficient to ensure crystallization. In any event, the formation of solvent-free crystals appears unlikely while solvents like formic and acetic acids that have been traditionally used for these pigments [3–8] are unable to link the large acid molecules through extended multi-point recognition patterns.

EXPERIMENTAL SECTION

Acids **1**, **2** and **3** were isolated from the resinous exudation of *G. morella* by previously described procedures [7,8]. The acids were converted to their pyridine complexes (bright orange needles from aqueous pyridine). To obtain crystals of the respective solvates, the corresponding pyridine complexes were dissolved in the appropriate solvent and a few drops of water added till a slight turbidity persisted. The solutions yielded excellent crystals upon standing for a few days. Similar operations with other organic solvents resulted in powders or gums.

Crystal data for compounds in this study were collected on a Siemens P4 diffractometer at 150(2) K or a Bruker SMART diffractometer at 158(2) K, using Mo-Kα X-rays in the ω-2θ scan mode. Structure solution and refinement was carried out with SHELX-97 [10]. All carboxylic H-atoms were found in difference maps. Table I contains the pertinent crystallographic details.

CONCLUSIONS

As mentioned earlier, our knowledge of crystallization mechanisms is still quite rudimentary. However, structures such as the ones described in this paper provide a snapshot view of some of the events that may occur during crystallization. By selecting solutes that are unable to crystallize easily and solvents that seem to be essential to induce their crystallization, one can observe solute–solvent assemblages which might yet approximate the situation in the general organic crystal prior to expulsion of solvent into the bulk. Mimicry effects such as those observed here between pyridine and dmf surely suggest the importance of hydrogen bonding during crystallization, though other interactions such as hydrophobic, $\pi-\pi$ staking and van der Waals are also numerous. The observation of solvent–solvent interactions could serve as an additional handle in monitoring the structure of solutions. This could be especially appropriate for a solvent like dmso that self-associates easily. The dynamic events that take place during crystallization do not lend themselves easily to direct observation. Here, we have attempted to visualize some of these events by examining crystal structures which, though static, are still suggestive.

Acknowledgments

We thank Dr. D. Rajagopal Rao and Dr. K. N. Gurudutt, Central Food Technological Research Institute (Mysore) for supplying us with the title

compounds after isolating them from natural sources. Prof. W. T. Robinson and Dr. R. Kadirvelraj, Canterbury University (Christchurch) are thanked for X-ray data collection. Financial assistance from the Department of Science and Technology, Government of India (SP/S1/G19/94) is acknowledged. A. A. thanks the Council of Scientific and Industrial Research, New Delhi for fellowship support. Crystal data available from the authors.

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[2] Papers that deal with the relationship between organic crystal quality and chemical (structural) factors are not common. A selected list of papers that mention methods of improving crystal quality are given here with the method proposed in each case. Some of these methods are specific to the systems studied: (a) Addadi, L., Berkovitch-Yellin, Z., Weissbuch, I., van Mil, J., Shimon, L. J. W., Lahav, M. and Leiserowitz, L. (1985). *Angew. Chem. Int. Ed. Engl.*, **24**, 466. Tailor-made impurities; (b) Etter, M. C. and Baures, P. W. (1988). *J. Am. Chem. Soc.*, **110**, 639. Triphenylphosphine oxide as a complexing agent; (c) Dance, I. G., In: *The Crystal as a Supramolecular Entity* (Ed. Desiraju, G. R.) Perspectives in Supramolecular Chemistry, **2**, Wiley, Chichester, 1996, 137–233. The 'phenyl factor' that derives from the presence of triphenyl residues in the molecule; (d) Pedireddi, V. R., Jones, W., Chorlton, A. P. and Docherty, R. (1996). *Chem. Commun.*, p. 997. Molecular complexation; (e) Madhavi, N. N. L., Katz, A. K., Carrell, H. L., Nangia, A. and Desiraju, G. R. (1997). *Chem. Commun.*, p. 1953. Use of specific solvents; (f) Görbitz, C. H. and Torgersen, E. (1999). *Acta Crystallogr.*, **B55**, 104. Relationship between type of hydrogen bond network and crystal quality.

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