Letter to the Editor

J. Appl. Cryst. (1975). **8**, 342

Unusual crystallization behaviour

Sir,

There are many instances, some reported in the literature, and many others not, of crystalline compounds behaving respectably for many months or years until nucleation of a more stable form. After this occurs, the previously obtained crystal form cannot be made to crystallize often even in laboratories many miles away. We have recently encountered such an event and became interested in the prevalence of such behaviour. The results were so interesting to us we felt your readers might be equally interested.

The compound that started us on this search is ampicillin, 6-[D(−)-α-aminophenylacetamido]penicillanic acid. It is readily crystallized as a trihydrate or anhydrous (two polymorphs). Early workers (Doyle, Fosker, Naylor & Smith, 1962; Grant & Alburn, 1965) obtained a monohydrate. Later the trihydrate was obtained and the later workers then disputed the earlier existence of a monohydrate (Austin, Marshall & Smith, 1965). Certainly no one has reported crystallization of the monohydrate despite persistent efforts since the trihydrate appeared. This seems to us to be a case of nucleation of a more stable form (trihydrate), ubiquitous nuclei of which preclude subsequent formation of the monohydrate. We have been able to find a large number of parallel cases. It seems to us important that crystallographers recognize this phenomenon as an important and relatively common behaviour. We would like to cite a few examples.

Ethylenediamine tartrate was recrystallized routinely on a large scale as a commercial piezolectric (anhydrous) crystal (Holden & Singer, 1960). After four years of research and production a monohydrate nucleated and grew preferentially. Soon the affliction spread to a second plant many miles away.

D-galactono-α-lactone apparently crystallized only in an anhydrous form until a monohydrate nucleated (Richtmeyer, Hann & Hudson, 1939) and since that time the anhydrous form has not been reported. Xylitol, first prepared in 1891, was considered a liquid until 1941 or 1942, when a form melting at 61 °C crystallized (Wolfrom & Kohn, 1942). These experiments were successfully repeated by Carson, Waisbrot & Jones (1943) and in the course of further recrystallizations a new form, melting at 94 °C, crystallized. Subsequent attempts to prepare the lower melting form were unsuccessful (Kim & Jeffrey, 1969).

A number of additional examples are known among the sugars. β-D-Mannose was prepared without difficulty (Hudson & Yanovsky, 1917), but in 1934 the α-form was prepared (Levene, 1935) and subsequent crystallization by the normal route for the β-form gave instead the α-form. Melibiose was first isolated in the β-form as a dihydrate (Bethelot, 1902), melting at 83 °C. This preparative method was repeated and an α-form monohydrate crystallized (*Ind. Eng., Chem.* 1953), melting at 179–181 °C. Similar results were reported later (Witonsky & Smith, 1959).

Turanose was officially described as a liquid but eventually it crystallized and has done so ever since (Powers, 1971). Benzophenone behaved similarly to turanose. Levulose existed for years as a viscous liquid until Jackson crystallized it and it has readily crystallized everywhere in the world since the first nucleation; α-D-lyxopyranose tetrabenzoate was crystallized as a form melting at 111–117 °C. Later, a form melting at 138–139 °C was isolated and spontaneously separated in subsequent crystallizations (Fletcher, Ness & Hudson, 1951).

Bavin (1959) reported a 115–116 °C m.p. for 10-methylbenzochrysene but after seeding with a 150 °C melting form obtained elsewhere (Bradsher & Rapoport, 1944) he was never able to obtain the lower melting form.

Many other examples could be cited – glycerin, gossypol, pentaerythritol *etc.* The phenomenon is apparently widespread. Most interesting to us is the fact that once one laboratory has recrystallized a compound, either for the first time or in a more stable form, other laboratories were able to do so. As Saylor picturesquely commented, 'as though the seeds of crystallization, as dust, had been carried upon the winds from end to end of the earth'.

We wish to acknowledge the help of M. Bavin, W. M. D. Bryant, H. G. Fletcher, N. H. Hartshorne, F. T. Jones, C. W. Mason, H. Powers, N. Richtmeyer and C. P. Saylor in compiling these examples.

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(*Received* 21 *January* 1974; *accepted* 27 *December* 1974)

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