Polymorphism of (*S*)-triphenylglycol: kinetic dependent transformation of a new multipolymorphic system†

Rafael Barbas,[a] Marco Polito,[b] Rafel Prohens*[a] and Cristina Puigjaner*[a]

Received (in Cambridge, UK) 24th April 2007, Accepted 19th July 2007
First published as an Advance Article on the web 6th August 2007
DOI: 10.1039/b706209e

The appearance of six new polymorphic forms of (*S*)-triphenylglycol and the kinetically dependent transformation observed by DSC by means of quenching from the melt are reported.

Polymorphism is the ability of a substance to crystallize in different crystal modifications, each of them having the same chemical structure but different arrangements or conformations of the molecules in the crystal lattice. Different polymorphs exhibit different physicochemical properties such as solubility, dissolution rate, bioavailability and chemical and physical stabilities. So, crystal engineering has become a topic of great interest for both academic research and pharmaceutical industries as polymorphism has the potential to significantly affect the physical properties of a compound.[1]

Many compounds may appear in more than one crystalline form, either because of a different arrangement of molecules in the lattice or because of a different conformation of the molecules in the lattice. Frequently the most stable polymorph is not easy to obtain. Sometimes metastable forms show better properties than the stable one and therefore a considerable effort is expended in order to isolate them. Regardless of which form is chosen for development, it is of greatest importance for the chemical and pharmaceutical industry to ensure reliable and robust processes. The ability of a particular polymorph to crystallize is usually determined by both thermodynamic and kinetic features. These should be well understood in order to explore and to control the polymorphic behaviour of a compound. Hence, it is of great relevance, and even a regulatory requirement, to identify the possible polymorphic forms of a product and to know whether polymorphic modifications can transform reversibly (enantiotropy) or irreversibly (monotropy) at atmospheric pressure. When an organic compound exhibits polymorphism of an enantiotropic type, the knowledge of the different domains of thermodynamic stability for each form is crucial in order to obtain the desired form through a robust crystallization process and to define the appropriate storage conditions.[2]

(*S*)-Triphenylglycol ((*S*)-1,1,2-triphenyl-1,2-ethanediol) is a chiral auxiliary reagent which has found wide application in asymmetric aldol additions and ester enolate imine condensations. It has been used also in synthesis of natural products and biologically active compounds. Furthermore it has applications as a chiral solvating agent in NMR spectroscopy.[3]

The presence of hydroxyl and aromatic groups in this molecule, suggests the possibility of a wide number of intermolecular interactions which could lead to a polymorphic behaviour. To the best of our knowledge only an anhydrous form and a methanolate have been described in the literature.[4] It is not possible to tell *a priori* in how many polymorphic forms a given compound can exist, however, only a small number of molecules show more than three anhydrous forms.[5] To date, only one substance has been reported to exist in nine crystal forms, and is the highest multipolymorphic system known.[6] We here report the multiple polymorphic system of triphenylglycol which exists in at least six anhydrous forms, and an amorphous one.

In order to explore the possible polymorphic behaviour of triphenylglycol, we decided to study by thermal analysis the amorphous form obtained from quenching the melt, instead of by performing classical crystallization methods.

Interestingly, the heating of the amorphous form in a DSC experiment shows a collection of crystallization and melting phenomena demonstrating the complex polymorphic system (Fig. 1). From the glassy state (glass transition at 32 °C) form D crystallizes first and melts (mp 72 °C) with crystallization of other phases. With continuous heating, forms E (mp 110 °C), F (mp 116 °C), B (mp 119 °C) and A (mp 127 °C) melt successively.[7] It has been found that a heating rate of 10 °C min^{-1} must be applied in order to observe the maximum number of polymorphs in a DSC experiment. Lower heating rates lead to the

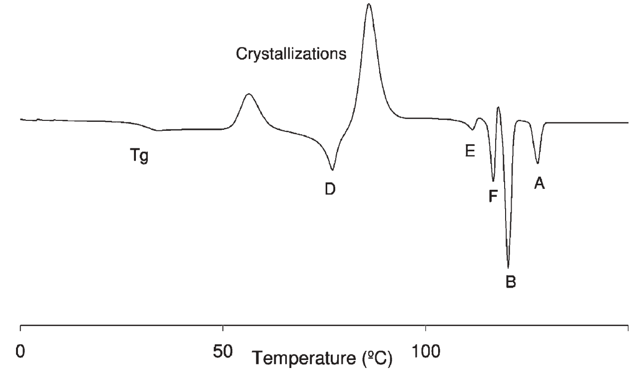

Fig. 1 DSC of a sample quenched from the melt.

---

[a] *Unitat de Química Fina, Serveis Científico-tècnics, Universitat de Barcelona, Josep Samitier 1-5, 08028 Barcelona, Spain. E-mail: cris@sct.ub.es; rafel@sct.ub.es; Fax: 34 934037206; Tel: 34 934034656*
[b] *Dipartimento di Chimica G. Ciamician, Università di Bologna, Via F. Selmi 2, 40126 Bologna, Italy*

† Electronic supplementary information (ESI) available: details of the three isolated forms characterization: IR and Raman spectroscopy, DSC and XRPD. Temperature variable XRD experiments. See DOI: 10.1039/b706209e

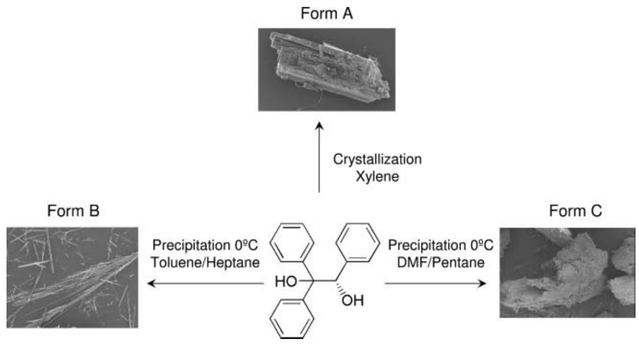

Fig. 2 Morphologies (SEM) of the crystal forms obtained by crystallization.

crystallization of fewer forms whereas higher heating rates are not suitable due to a loss in the resolution. The cooling rate during quenching seems to have no influence on the result.

In view of such complexity we decided to isolate as many forms as possible in order to characterize them. Attempts were made to crystallize triphenylglycol in different ways (Fig. 2). Three crystalline forms were obtained, one of them (form C, mp 86 °C) had not been previously detected by DSC. All three anhydrous forms were fully characterized by means of X-ray powder diffraction, DSC, IR and Raman spectroscopy.

It is of practical interest to know the relative thermodynamic stability of all forms. The main questions to solve are whether two polymorphs are monotropically (one form is more stable than the other at any temperature) or enantiotropically (a transition temperature exists, below and above which the stability order is reversed) related, and for an enantiotropic system, where transition temperature lies. According to the heat of fusion rule[8] form A (higher melting point and higher enthalpy of fusion than B) is monotropically related to form B. Moreover, form C (lower melting point and higher enthalpy of fusion) is enantiotropically related to forms A and B with a transition temperature at *ca.* 0 °C of form C to A and at *ca.* 20 °C of form C to B (Fig. 3).[9]

Since we were not able to isolate forms D, E and F by conventional crystallization methods, we explored alternative approaches in view of the observed thermal behaviour by DSC.

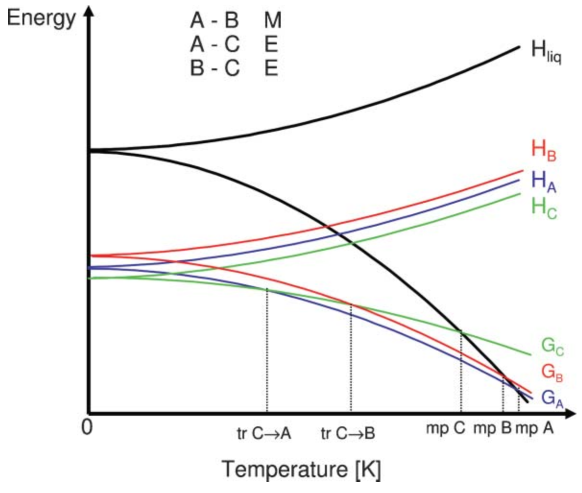

Fig. 3 Energy–temperature diagram of the three isolated forms.

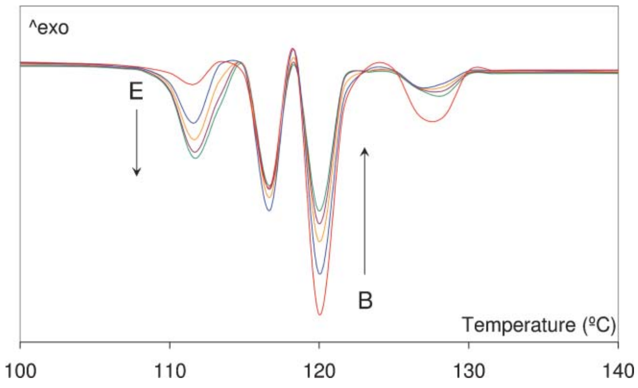

Fig. 4 DSC of five successive heating–cooling cycles.

After some heating–cooling cycles (Fig. 4) starting from form A in a DSC (heating rate 10 °C min^{-1}), form E grows at the expense of form B. Crystallization of the various polymorphic forms are time and temperature dependent, and a thermodynamic–kinetic competition in the crystallization of the different forms from the melt is observed.[10] This can be explained by some kind of kinetic amplification process leading to the metastable form E. After four cycles, the relative intensities of all forms remain invariable.

This suggests that form E is the first crystallizing form which transforms into the other three forms by crystallization from the melt during heating. Therefore, a suitable method for obtaining form E is being studied on this basis in our lab. Variable temperature X-ray diffraction experiments of quenching cycles have been conducted and reveal four different crystalline forms between 110 and 130 °C (Fig. 5). However, the assignation to each form is still ambiguous.

Further attempts at crystallization of metastable forms are also being conducted and studies on stability and solubility of the isolated forms are in development.

A crystal structure of triphenylglycol, was first reported by Weber's group[4] showing a monoclinic symmetry ($P2_1$) with a packing characterized by dimers and chains. It was not assigned to any form, as polymorphism of this molecule was not under study (Fig. 6). Since the diffractogram of our higher melting form matches with the one calculated from the published single crystal structure, we can conclude that the reported structure corresponds to form A.

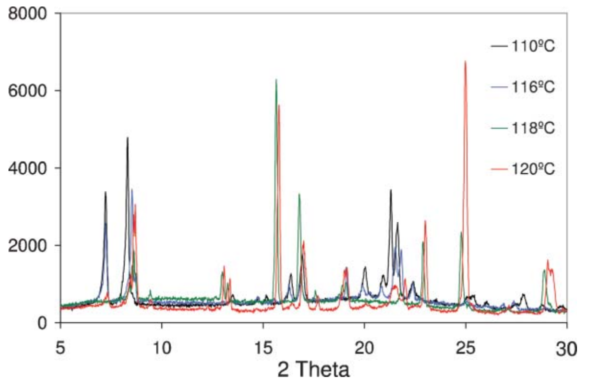

Fig. 5 Variable temperature X-ray powder diffraction of several quenched samples at different temperatures.

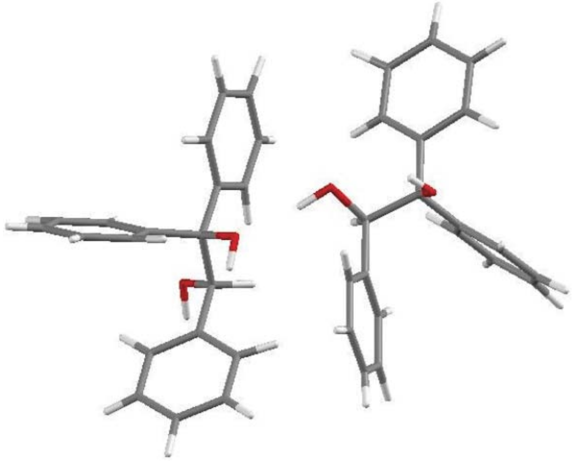

Fig. 6 Crystal structure of form A obtained by Weber's group.

Unfortunately, it has not been possible to grow single crystals of B and C forms suitable for X-ray structure determination, however an indexing from the powder pattern of B was attempted using DICVOL[11] that returned a monoclinic unit cell with lattice parameters: a = 25.59(1) b = 6.032(4) c = 11.655(7) Å, β = 121.82(7)°, V = 1528 Å^3. The volume suggests the presence of four molecules within the unit cell. The Pawley fit[12] in space group $P2_1$ gave a reasonable fit to the data, with a reduced χ^2 of 10.1. Moreover, the volume found for B, is consistent with the one previously reported[4] for polymorph A: a = 7.2840(3) b = 18.3188(18) c = 12.1577(9) Å, β = 106.025(4)°, V = 1559 Å^3, space group $P2_1$.

The authors thank the XRD Unit of the Scientific-Technical Services (University of Barcelona) for their contribution to this work.

Notes and references

1 J. Bernstein, *Polymorphism in Molecular Crystals*, Clarendon Press, Oxford, 2002; R. Hilfiker, *Polymorphism in the Pharmaceutical Industry*, Wiley-VCH, Weinheim, 2006; D. Braga and F. Grepioni, *Chem. Commun.*, 2005, 3635; J. Bernstein, *Chem. Commun.*, 2005, 5007.

2 D. Giron, M. Mutz and S. Garnier, *J. Therm. Anal. Calorim.*, 2004, **77**, 709.

3 D. Ridder, H. Wunderlich and M. Braun, *Eur. J. Org. Chem.*, 1998, 1071; M. Braun, H. Sacha, D. Galle and S. Baskaran, *Pure Appl. Chem.*, 1996, **68**, 561.

4 E. Weber, O. Hager, C. Foces-Foces and A. L. Llamas-Saiz, *J. Phys. Org. Chem.*, 1996, **9**, 50.

5 S. Ahn, F. Guo, B. M. Kariuki and K. D. M. Harris, *J. Am. Chem. Soc.*, 2006, **128**, 8441.

6 S. Chen, I. A. Guzei and L. Yu, *J. Am. Chem. Soc.*, 2005, **127**, 9881.

7 To the best of our knowledge only two melting points have been described without any mention of polymorphic behaviour: G. R. Pettit, S. B. Singh, D. L. Herald, P. Lloyd-Williams, D. Kantoci, D. D. Burkett, J. Barkoczy, F. Hogan and T. R. Wardlaw, *J. Org. Chem.*, 1994, **59**, 6287.

8 A. Burger and R. Ramberger, *Mikrochim. Acta I*, 1979, 259.

9 We have estimated the transition temperatures by using the following equation according to L. Yu, *J. Pharm. Sci.*, 1995, **84**, 966

$$T_{\mathrm{trs}} = \frac{\Delta H_{\mathrm{fus},2} - \Delta H_{\mathrm{fus},1} + k\Delta H_{\mathrm{fus},1}(T_{\mathrm{fus},1} - T_{\mathrm{fus},2})}{\dfrac{\Delta H_{\mathrm{fus},2}}{T_{\mathrm{fus},2}} - \dfrac{\Delta H_{\mathrm{fus},1}}{T_{\mathrm{fus},1}} + k\Delta H_{\mathrm{fus},1}\ln\left(\dfrac{T_{\mathrm{fus},1}}{T_{\mathrm{fus},2}}\right)}$$

10 S. Wishkerman, J. Bernstein and P. W. Stephens, *Cryst. Growth Des.*, 2006, **6**, 1366.

11 A. Boultif and D. Louër, *J. Appl. Crystallogr.*, 1991, **24**, 987.

12 G. S. Pawley, *J. Appl. Crystallogr.*, 1981, **14**, 357.