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Solid-phase racemic compound–conglomerate transformation of 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione

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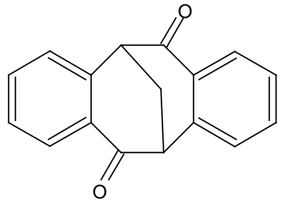
Abstract—For 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione (diketone), forming either a racemic compound (**R**) or a conglomerate (**C**) depending on the crystallization conditions, a solid-phase transformation (SPT) of **R** into **C** has been found. In addition, a solvent-mediated transformation of **C** into **R** has been realized. The SPT has been investigated by DSC and X-ray powder diffraction analyses and its peritectoid nature is proposed. On the basis of the obtained data a diagram of Gibbs free energy versus temperature (*G* vs *T*) for the two modifications of the diketone has been constructed.

1. Introduction

Classical crystallization techniques continue to be one of the most commonly used methods in industrial resolutions of racemic mixtures.[1–4] Crystallization with an enantiomerically pure seed (entrainment procedure) is still the easiest and the most inexpensive method for obtaining enantiomerically pure compounds.[1–7] Racemates exist as racemic compounds (heterochiral crystals), solid solutions (pseudo-racemates) or conglomerates (1:1 mixtures of homochiral crystals).[1–7] However, only conglomerates[1–7] and as has been shown recently, solid solutions[8] undergo resolution into enantiomers by direct crystallization. Yet, structural, thermodynamic and kinetic factors, which influence the formation of homo versus heterochiral crystals, are still not fully understood.

Many organic compounds including medicines exhibit polymorphism.[9–12] Among them there are examples of the formation of either a conglomerate or a racemic compound by the same compound.[2,13] Moreover, analysis of 163 pairs of polymorphic crystal structures showed that the part of the pairs with one centrosymmetric member and the other noncentrosymmetric one amounted to 24%,[14] which is evidence of reasonable prevalence of conglomerate–racemic compound pairs. Generally, polymorphs of the same compound have very close energies[14] that is, notably seen in the case of concomitant polymorphs.[10] Hence, detailed investigations of such examples provide us with the rare opportunities for studying factors that govern preferable conglomerate versus racemic compound formation.[2,5–8,15–19] These studies are also important for overcoming the problem of the detrimental influence of unstable racemic compound formation on performance of preferential crystallization.


2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione

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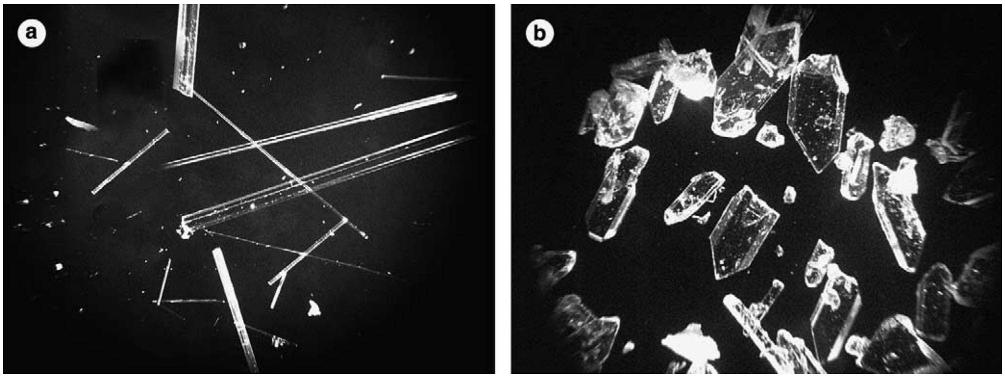

Figure 1. Single crystals of the racemic compound **1a** (a); single crystals of the conglomerate **1b** (b).

2,3:6,7-Dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione (diketone) is an example of one of the compounds that exists either as a racemic compound or as a conglomerate. The melting point of its enantiomers (193 °C) is higher than that of the racemate (147 °C) by 46 °C ($\Delta T_{\mathrm{e-r}}$).[20] Such a large difference is a sign of conglomerate formation.[1–3] Moreover, according to the data of Collet,[2] out of 123 compounds that form conglomerates with a known $\Delta T_{\mathrm{e-r}}$ only one (2,2′-diamino-1,1′-binaphthyl $\Delta T_{\mathrm{e-r}} = 51°$)[21] has a $\Delta T_{\mathrm{e-r}}$ larger than that of the diketone. In spite of that, crystallization of the diketone below 100 °C results in the racemic compound **R** (Fig. 1a) while the crystallization of the diketone above 100 °C leads to the conglomerate[13] **C** (Fig. 1b).

Herein we have investigated the two forms of the diketone **R** and **C** by means of the differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) analysis. On the basis of the obtained data, the relative thermodynamic stability and the possibility of the transformation between **R** and **C** have been ascertained.

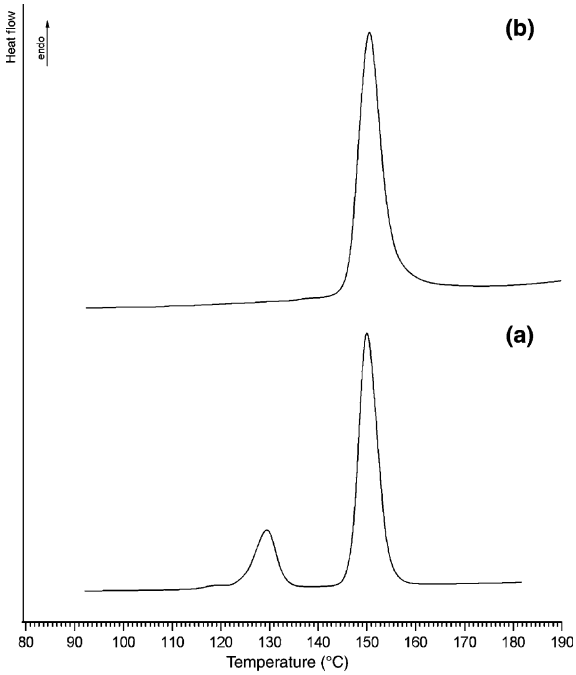

Figure 2. DSC curves of **R** (bottom) and **C** (top). The heating rate 2 °C/min.

2. Results and discussion

In the case of **R**, solid-phase transformation within the temperature range 124–135 °C prior to melting of the sample at 147 °C was detected by means of DSC analysis (Fig. 2 bottom). In contrast, we did not detect any transformations for **C** except for the melting of the sample at 147–153 °C (Fig. 2 top). From the DSC data, we concluded that the SPT of **R** into **C** occurs in the temperature range of 124–135 °C.

Our hypothesis was supported by the investigation of **R** and **C** using X-ray powder diffraction analysis (XRPD). As can be seen from Figure 3, the diffractograms of **R** (Fig. 3b) and **C** (Fig. 3d) obtained by crystallization are markedly different at 20 °C. At the same time they are in good agreement with the calculated diffractograms for hetero (Fig. 3a) and homochiral (Fig. 3e) crystals, respectively. However, we have found that upon heating of a sample of **R**, its diffractogram is fully transformed into the diffractogram corresponding to **C** (Figs. 3 and 4). The SPT of **R** into **C** is evident from Figure 4 which shows the result of the variable temperature XRPD analysis of the **R** form.

It should be noted that the phase transformation of **R** into **C** can be observed visually: single crystals of **R** become opaque upon heating at 140 °C for several minutes, whereas single crystals of the **C** form remain transparent.

Nevertheless, the DSC and XRPD data do not give us a complete understanding of the correlation between the two modifications of the diketone: whether the transformation of **R** into **C** is peritectoid[22] (reversible) or whether it is an irreversible transformation of metastable **R** into more stable **C**. The latter explanation may seem reasonable because a less stable form is normally expected to be generated first according to the Ostwald step rule[23] with a subsequent conversion into the more stable form. On the one hand the transformation of **R**

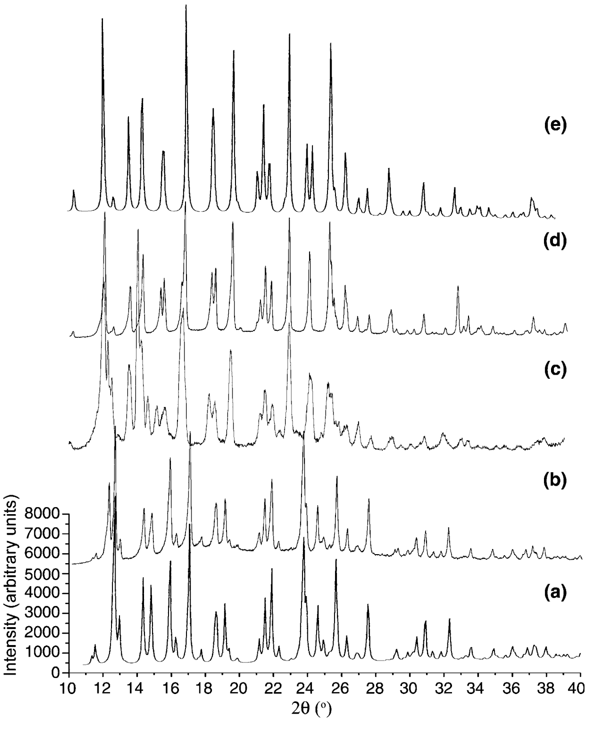

Figure 3. Powder X-ray diffractograms: (a) **R** (calculated); (b) **R** (experimental at 20 °C); (c) **R** (experimental) performed at 140 °C (after phase transformation **R** → **C**); (d) **C** (experimental); (e) **C** (calculated). The practically identical shapes of the diffractograms (c) and (d) suggest that the racemic compound **R** transforms into the conglomerate **C** upon heating.

into **C** is accompanied by an endothermic phenomenon, which indicates a peritectoid transformation. On the other hand the reverse SPT (i.e. **C** → **R**) was not detected either upon cooling of **C**, or after ageing it for a long time at the room temperature (three weeks; triturated crystals of **C**), even though peritectoid transformation implies reversibility.[22] A low rate of the SPT may be responsible for the lack of the reversibility of the transformation and for the fact that SPT **R** → **C** is observed starting from ≈120 °C, whereas **C** is formed by crystallization at the temperatures as low as 100 °C. Nevertheless, by grinding the sample and/or by seeding it with the stable phase, one can substantially increase the rate of the transformation of a metastable modification into a more stable one.[24] Furthermore, solvent-mediated transformation (SMT) is a very effective technique for achieving more stable polymorphs.[25]

In agreement with the aforementioned, we have found that when a suspension of **C** in *n*-octane, seeded with a small amount of **R**, is stirred at 22 °C, complete conversion of **C** into **R** occurs within two weeks as observed by DSC analysis. This observation suggests that the two forms are related by a peritectoid transformation. Alternatively, conversion of **C** into **R** is realized by recrystallization of **C** (racemic mixture of single crystals) below 90 °C. Despite the existence of the transformation of **C** → **R** through the intermediate solution (SMT) we could not detect *solid-phase* transformation of **C** → **R**; however this can be explained easily. Even though there are known cases of the formation of a racemic compound from a mixture of two opposite enantiomers by diffusion in the solid state,[26] this process is much slower than dissolution and crystallization.

We were able to detect SPT of **R** into **C** at 97 °C by DSC with a mixture of grinded crystalline **R** (99% w/w) and **C** (1% w/w) (Fig. 5). A small amount of crystalline **C** was added to sample **R** so as to increase the rate of the SPT of **R** into **C**.

Along with the fact that 100 °C was the starting temperature of conglomerate formation by crystallization, the observed SPT **R** → **C** at 97 °C confirmed that this was a true temperature of thermodynamic transformation at which free energies of the two forms are equal.

When measuring the melting points of single crystals of **R** we repeatedly observed that some crystals (mainly the smaller ones, which had the fewest defects) melted at 130 °C whereas the others melted at 147–149 °C. This observation, together with the data on the investigation of the phase transformations testifies that 130 °C, at which an endothermic phenomenon is observed by DSC, is the melting point of the racemic compound **R** and 147 °C is a melting point of the eutectic mixture of the two enantiomers.

On the basis of the obtained data we constructed a diagram of Gibbs free energy versus temperature (G vs T) (Fig. 6) for the two modifications of the diketone. Such a diagram is a simple and very informative means for describing both the possible phase transmutations in a polymorphic system and their relative thermodynamic stability.[2,10]

According to the diagram (Fig. 6), **R** is more stable below and **C** is more stable above T_{tr}. These two modifications are related by a peritectoid transformation with T_{tr} as the thermodynamic transition temperature. The melting point of the racemic compound **R** is 130 °C (T_{R}); 147 °C is the melting point of the eutectic mixture of the enantiomers (T_{E}); the melting point of the enantiomerically pure diketone is 193 °C (T_{A}). However, pure **R** could not be transformed into **C** at 97 °C (T_{tr}) though it could be heated up to its melting point (130 °C; T_{R}) followed by melting of first crystals of **R**. Conglomerate **C** is thermodynamically more stable at this temperature and, as a consequence, the melt immediately crystallizes to the **C** form. The first crystals of **C** then behave as a seed promoting rapid SPT of the rest of **R** into **C**. This SPT was observed by DSC and XRPD at approximately 130 °C (Figs. 2 and 4). Upon additional heating, the melting point of the generated **C** form occur at 147–149 °C. This temperature corresponds to the melting of the eutectic mixture of the enantiomers. The melting point of the pure enantiomers (T_{A}) is 193 °C, however not all of the single crystals of the **C** form obtained by high-temperature crystallization melts at T_{A} because of the low enantioselectivity during the crystal growth.[13] The onset of the melting of such crystals can often be observed at the eutectic temperature T_{E} (147 °C).

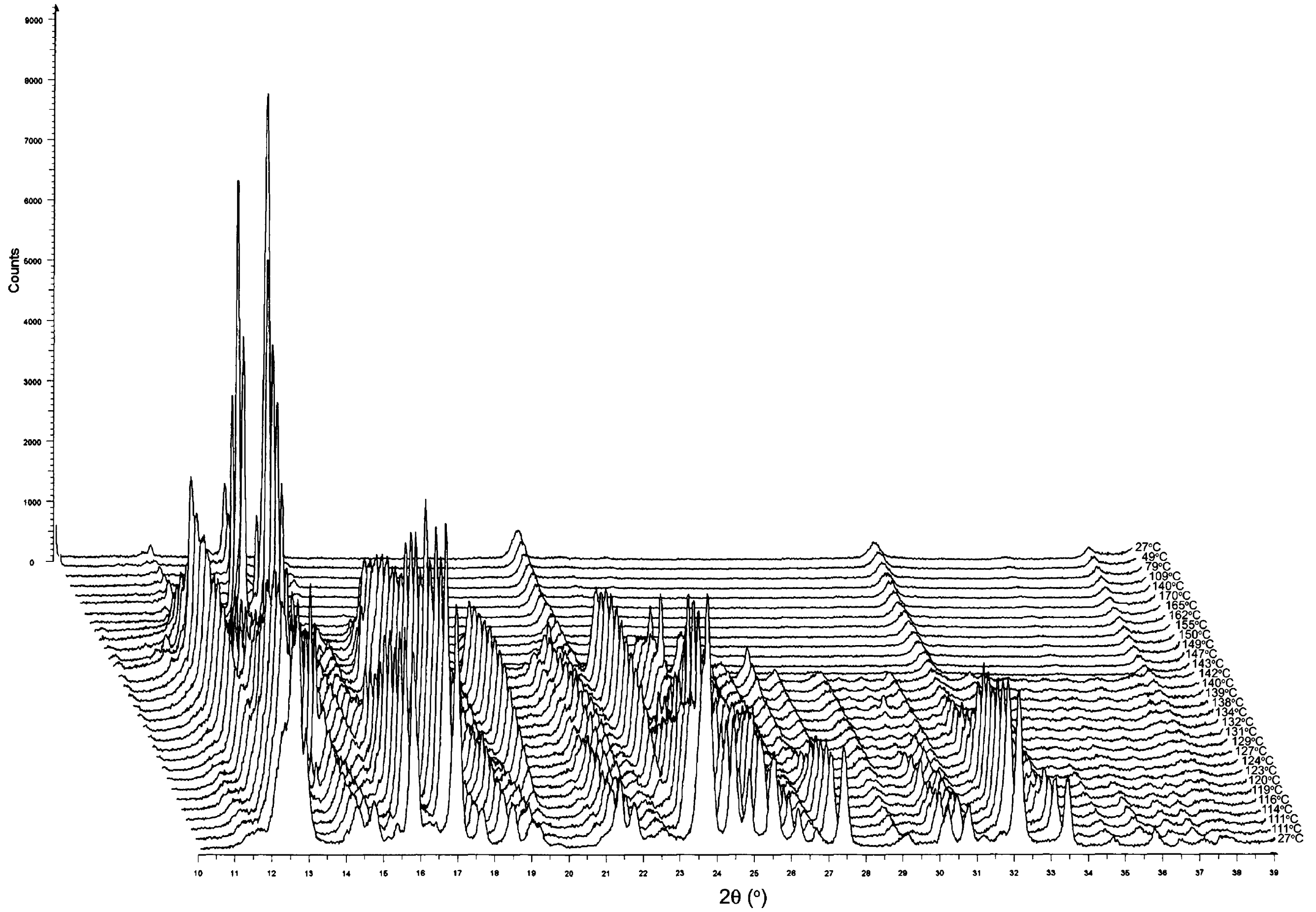

Figure 4. Variable temperature powder X-ray diffraction analysis of **R**. There is a solid-phase transformation of **R** into **C** upon heating within the temperature range of 116–129 °C.

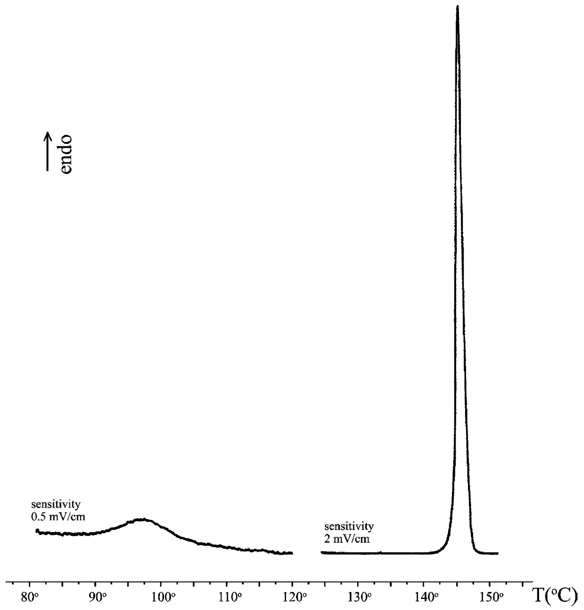

Figure 5. DSC investigation of the racemic compound **R** seeded with crystalline **C**. The first peak (97–98 °C) corresponds to the phase transformation **R** → **C**. This temperature (97–98 °C) corresponds to the system state at $\Delta G = 0$ (T_{tr} in Fig. 6). The peak at 147 °C corresponds to the melting of eutectic mixture of the enantiomers. The heating rate is 2°/min. Sample 3.25 mg.

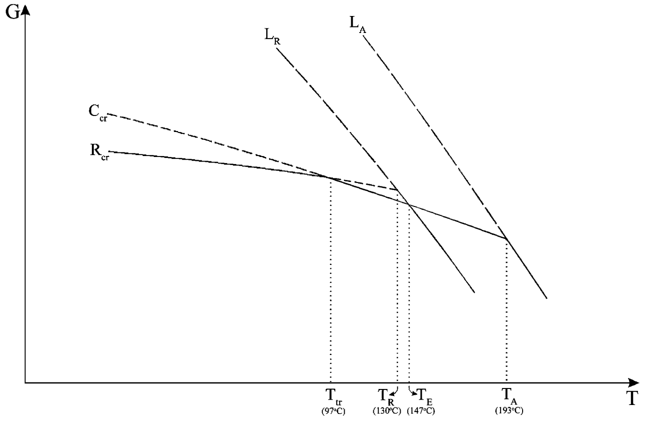

Figure 6. Schematic representation of the dependence of *G* (Gibbs free energy) on *T* (temperature); R_{cr} and C_{cr} characterize the free energies of the crystalline racemic compound **R** and the conglomerate **C**, respectively; L_R and L_A describe the free energy of the melts of hetero and homochiral compositions. The dashed lines show a metastable phase capable of spontaneous conversion to the corresponding more stable state.

In 1897, Kipping and Pope[27] gave a series of examples of possible racemic compound to conglomerate transformations upon heating. Their conclusion was based upon the identity of the melting temperatures of a racemic compound and the corresponding pure enantiomer. Nevertheless, this may not be correct, because when transforming a racemic compound into a conglomerate, a eutectic mixture is formed. Melting temperature of such a mixture is usually different from that of the corresponding pure enantiomers.

For the subject of our investigation Δ_{e-r} is 46 °C[20] and consequently ΔG (change of Gibbs free energy when forming a racemic compound from the two enantiomers) is positive,[2,19] that is, conglomerate **C** is thermodynamically more stable by Collet's rule of stability of racemic compounds.[2] However, as exemplified in the diketone's behaviour, this rule is only reliable at the melting point of a racemic compound[19] (T_R; Fig. 6). At this temperature, the Gibbs free energy of **R** is larger then that of **C**. However, when moving off the T_R, the possibility of an intersection of the curves G versus T for the racemic compound and the corresponding conglomerate is increased. According to the equation $G = H - TS$, which is shown graphically in Figure 6, the larger the difference in entropy between **R** and **C,** the higher the possibility of occurrence of a thermodynamic transition temperature at which $\Delta G = 0$. Such is the case for the diketone whose thermodynamic transition temperature is 97 °C, the **R** form being more stable below this temperature (Fig. 6).

3. Conclusion

Organic compounds are well known for their ability to form polymorphs depending on crystallization conditions. In particular, chiral ones can give a racemic compound and a conglomerate as the polymorphs. Provided that the conditions of the formation of the latter are known, it can be resolved into enantiomers by direct crystallization with an enantiomerically pure seed.

The diketone is one of such compounds. Its crystallization below 97 °C leads to the formation of the racemic compound **R**, while above that temperature to the conglomerate **C**.[13] Herein, we have investigated the thermodynamic aspects of its behaviour, namely the relative stabilities of the two forms and the possibility of the transformation between them.

A solid phase transformation of **R** into **C** upon heating above 97 °C has been detected by DSC and powder X-ray diffraction analyses. At the same time, the homochiral form **C** was converted into **R** by solvent mediated transformation at room temperature. It has been demonstrated that **R** and **C** are related by peritectoid transition at 97 °C. The ease of the mutual transmutations between **R** and **C** can be explained by virtually the same densities of the two forms[13] which shows the closeness of their thermodynamic stabilities despite the large difference in the melting points. On the basis of the obtained data a diagram of Gibbs free energy versus temperature has been constructed which clearly shows the range of the stability of **C** and consequently opens the way for the resolution of the diketone into enantiomers by direct crystallization.

4. Experimental

The diketone was prepared according to the Refs. 13 and 20. The racemic compound **R** and the conglomerate **C** were obtained according to the Ref. 13. Melting points were measured on a Boetius table (VEB Wagetechnik Rapido PHMK). The temperature resolved X-ray diffraction patterns were taken from a Siemens D 5000 Θ/Θ-diffractometer (radiation Cu Kα) and recorded with a position sensitive detector (Braun OED 50M) with an aperture of 6°. The experiments were carried out in a Bühler HDK S1 high temperature chamber. The DSC analyses were carried out using NETZSCH STA 409C.

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