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New menthol polymorphs identified by flash scanning calorimetry

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Menthol, which is used in the food, pharmaceutical and cosmetic industries, was studied by flash scanning calorimetry. New levorotatory and racemic menthol polymorphs were thus identified. This study is also forward-looking regarding the use of organic molecules by flash scanning calorimetry, which is frequently used for polymer studies.

The physical or chemical stability of organic compounds can strongly depend on their polymorphic form. In the early 20th century, Fred E. Wright qualitatively introduced four levorotatory menthol polymorphs.[1] Two years ago, our team highlighted polymorphism of enantiomeric and racemic menthol by conventional differential scanning calorimetry (DSC).[2] As a matter of fact, by optimizing the scan rate, we were able to isolate metastable forms of menthol. Consequently, for the first time, melting point and enthalpy have been proposed for both β L- and DL-menthol. Moreover, the phase diagram established between levorotatory and dextrorotatory menthol confirmed such new data, and X-ray powder diffractions allowed us to determine the unit cell parameter of each metastable form. The existence of two polymorphs − pseudo-racemates (PR) in that case − of racemic menthol, noted PR1 and PR2, was deduced from the phase diagram. Since the menthol metastable state is time-[3] and aging temperature-dependent, and therefore scan-rate-dependent, Flash Scanning Calorimetry (FDSC)[4-10] was chosen to characterize menthol behavior under higher scan rates than those which can be used with conventional DSC or even hyper DSC devices. Consequently, for the first time, we prove in the present study that a new menthol enantiomeric polymorph, called γ L-menthol, can be thermally identified and characterized by flash scanning calorimetry, namely the Mettler Toledo Flash DSC 1™. Furthermore, this technique also made it possible to isolate the DL-menthol PR1, which, before the present work, had only been theoretically suggested by modeling.[2]

Although hyper DSC − 25 times faster than conventional DSC − has already been proven to be helpful for polymorph characterization of carbamazepine[11] or a Merck development compound,[12] we demonstrate here that flash DSC, which is 120 times faster than hyper DSC or 3 000 times faster than conventional DSC, can be used to characterized a metastable form of both L- and DL-menthol.

(1R,2S,5R)-5-méthyl-2-(propan-2-yl)cyclohexanol, otherwise known as L-menthol and DL-menthol, was provided by Acros Organics and Alfa Aesar, respectively. The chemicals, crystallized in their most stable state − *i.e.* the α form − at ambient conditions of temperature and pressure, were used without purification. Flash Scanning Calorimetry experiments were performed by means of a Flash DSC 1™ (Mettler-Toledo, Switzerland). For each experiment, a micron-sized single-crystal was settled by electrostatic force on the center of the FDSC chip sensor (MultiSTAR UFS 1™) under a microscope. The Flash DSC furnace was purged by a nitrogen gas to avoid any chemical reaction or water vapor condensation. The experiments were performed at 1 000 $K.s^{-1}$ scan rate. Therefore, when a given sample undergoes an energetic transformation during the temperature scan, the corresponding FDSC thermogram - heat flow as a function of the temperature - presents a signal that is proportional to the measured physical phenomenon.

The study presented by Fred E. Wright introduced the morphological shape and melting point of four L-menthol polymorphs. Melting points of 42.5, 35.5, 33.5 and 31.5 °C were qualitatively pointed out by thermal microscopy for α to δ L-menthol polymorphs, respectively.[1] By using conventional differential scanning calorimetry devices, our recent work allowed us to determine the melting data for α and β L-menthol, *i.e.* $T_{fus} = 42.9 \pm 0.3$ °C and $\Delta_{fus}H = 14.1 \pm 0.2$ $kJ.mol^{-1}$ for the α form, and $T_{fus} = 35.3 \pm 0.3$ °C and $\Delta_{fus}H = 14.0 \pm 0.2$ $kJ.mol^{-1}$ for the β form.[2] In the same way, for DL-menthol we obtained $T_{fus} = 33.8 \pm 0.3$ °C and $\Delta_{fus}H = 14.2 \pm 0.2$ kJ.mol-1 for the α form, and $T_{fus} = 27.3 \pm 0.3$ °C and $\Delta_{fus}H = 9.3 \pm 0.2$ kJ.mol-1 for the β form (also called PR2).[2] Moreover, the latter study demonstrated that menthol polymorph stability hierarchy was scan-rate-dependent. In order to get more insight into menthol polymorph stability at very high cooling and heating rates, L- and DL-menthol were also examined by FDSC (Figures 1 and 2, respectively).

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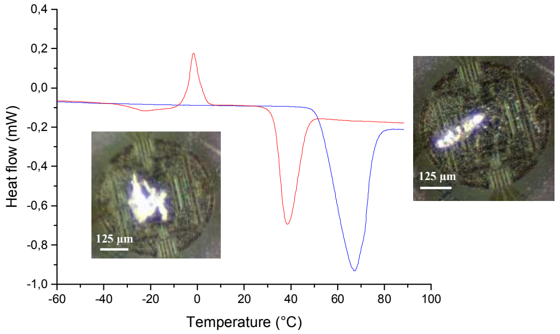

Fig. 1 FDSC curves obtained for L-menthol upon first (—) and second (—) heating scan. The photographs show the sample on the Flash DSC 1 MultiSTAR UFS 1™ sensor before the first heating (left) and after the second heating (right).

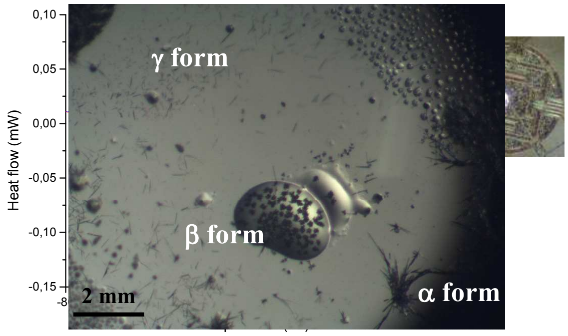

Fig. 2 FDSC curves obtained for DL-menthol upon first (—) and second (—) heating scan. The photographs show the sample on the Flash DSC 1 MultiSTAR UFS 1™ sensor before the first heating (left) and after the second heating (right).

Fig. 3 Photograph of a L-menthol sample observed with a thermal microscope. After quenching the molten state at 50 K.min^{-1} to -180 °C, then heating at 5 K.min^{-1}, the photograph was taken at 20 °C. During the heating, three distinguishable polymorphs of menthol grow, and then melt one after the other at 33, 36, and 43 °C for the γ, β, and α forms, respectively.

The stable L-menthol form, *i.e.* the commercial α-form, was first examined by FDSC. As shown in Figure 1, the onset of the corresponding melting signal is obtained at 50 °C. The shift of 7 °C compared to the real melting data, ~ 43 °C,[1, 2, 13, 14] can be explained by the fact that, for the first heating, the contact between the ca. 100 nanogram single-crystal and the chip surface is not optimized (*cf.* photographs in Figure 1). This had already been shown with FSC applied to polymers[15, 16] or metal alloys.[17, 18] Nevertheless, for such compounds, once the sample has been melted once, the onset temperature which is measured after cooling corresponds to the real melting point. In our case, the onset of the signal obtained after the second heating (T_{fus} = 32.8 ± 0.6 °C, Figure 1) is therefore a coherent value. Moreover, as previously demonstrated, once the stable menthol is molten, it firstly recrystallizes into a metastable form.[2] Consequently, the FDSC signal obtained after the second heating process can be attributed to the γ L-menthol metastable polymorph that it is known to melt at ~ 33.5 °C, according to experiments performed by Wright.[1] As far as melting enthalpy is concerned, Flash DSC does not straightforwardly allow a quantitative determination since it is not possible to determine the sample mass.[6] However, since the melting enthalpy of α L-menthol is known and since no sublimation of the sample occurs during the ultra-fast temperature program (only 170 ms are necessary. *Cf.* photographs in Figure 1), one can determine by comparison the melting enthalpy of γ L-menthol obtained after the second heating process. That way, $\Delta_{fus}H$ of levorotatory γ menthol has been estimated at 6.2 kJ.mol^{-1}. It has to be noted that the FDSC curve recorded upon the second heating presents a small endothermic signal around -30 °C, followed by an exothermic signal at around -10 °C. The endothem and exotherm correspond to the menthol glass transition and to the crystallization of the γ L-menthol ($\Delta_{cryst}H$ = -1.9 kJ.mol^{-1}), respectively. This may explain why the γ phase can only be obtained by FDSC. Indeed, due to the slow scan rate of conventional DSC, L-menthol crystallizes into its stable phase upon cooling, whereas the FDSC ultra-fast scan rate induces a cold crystallization (crystallization upon heating) into a metastable form.

Based on those results, similar experiments were conducted with racemic menthol. DL-menthol, contrary to the corresponding levorotatory enantiomer, has not been extensively studied regarding its polymorphism and its structure. Our group has already performed an exhaustive survey on such an issue. This work led to the α and PR2 forms characterization from X-ray and DSC experiments on the one hand, and permitted to highlight another polymorph, called PR1, that melts at 23.3 °C according to thermodynamic simulation, on the other hand.[2] Interestingly, flash scanning calorimetry allowed us to identify a DL-menthol polymorph that melts at 22.7 ± 0.6 °C (Figure 2). This result is in accordance with the melting point we reported for DL-menthol PR1 three years ago.

At this stage, it is noteworthy that the temperature difference between the experimental melting point obtained by flash scanning calorimetry and the reported melting point is the same for γ L-menthol and for γ DL-menthol, *i.e.* ~ 0.7 °C, which is within the error range. Moreover, the γ melting points have also been confirmed by thermal microscopy experiments, as presented in Figure 3.

Racemic menthol melting enthalpy was estimated the same way as for the enantiomer. The following value $\Delta_{fus}H$ = 1.9 ± 0.2 kJ.mol^{-1} was obtained. This value, although lower than the melting enthalpy measured for PR2 DL-menthol,[2] as expected for two polymorphs monotropically related, has to be carefully taken into consideration. Indeed, incomplete recrystallization may have occurred between the first and the second heating processes. However, at least one can have access to $\Delta_{fus}H$ order of magnitude for this third racemic menthol polymorph, discovered here for the first time.

The present study demonstrates the power of flash scanning calorimetry for qualitative and quantitative characterization of small molecule polymorph studies. We identify menthol polymorphs that had never been isolated or studied before, due to their extreme metastability. Indeed, depending on the time and temperature quenching conditions, various states of metastability can be obtained. However, ultra-fast quenching times cannot be reached with conventional scanning calorimetry. Interestingly, flash scanning calorimetry offers here new perspectives by stabilizing unexampled polymorphs. Polymorphism studies being an interesting research area for material sciences development such as crystal engineering, using the new flash scanning technique to study small organic compounds opens the way to the investigation of new phases and physical transitions between them.

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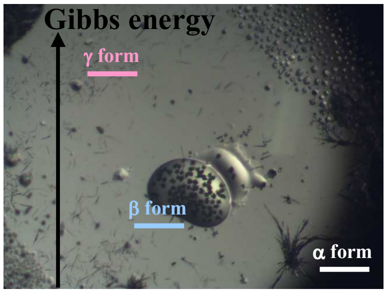
Graphical abstract



Menthol polymorphism screening by thermal microscopy in order to corroborate flash DSC results.