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Relaxation behaviour of D(−)-salicin as studied by Thermally Stimulated Depolarisation Currents (TSDC) and Differential Scanning Calorimetry (DSC)

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ABSTRACT

Thermally Stimulated Depolarisation Currents (TSDC) measurements on D(−)-salicin have been carried out in the temperature region from −165 °C up to 150 °C. The slow molecular mobility was characterised in the crystal and in the glassy state. The value of the steepness index or fragility (T_g—normalized temperature dependence of the relaxation time) was obtained by Differential Scanning Calorimetry (DSC) from the analysis of the scanning rate dependency of T_g. The existence of an unknown polymorph of salicin is also reported.

1. Introduction

D(−)-Salicin is a glucoside consisting of a carbohydrate moiety linked to an aromatic ring with a bulky substituent, a $-CH_2OH$ group, in *ortho* position (see Fig. 1).

Discovered in 1830 in the bark of willow tree, the history of salicin as a pharmacologically active compound is related to that of aspirin, and it is reviewed in several works (Jack, 1997; Lévesque and Lafont, 2000; Marson and Pasero, 2006). The importance of D(−)-salicin in the pharmaceutical area is emphasized by several publications. It acts as a precursor compound for the synthesis of acetyl salicylic acid, and it is helpful for mild feverish colds and infections (influenza), acute and chronic rheumatic disorders, mild headaches, and pain caused by inflammation. It does not have the dangerous side effects associated with aspirin.

The present work is a study of the molecular mobility in solid salicin (crystalline and amorphous). It is often underlined that the knowledge of the time scales of molecular motions in amorphous systems, i.e. the knowledge of the relaxation map that characterises the molecular dynamics in a given material, is needed for profiting from the advantages of the amorphous state, and is an important requirement for a safe storage and use of amorphous pharmaceutical solids (Shambling et al., 1999). In a recent paper (Masuda et al., 2005), the results of a dynamic ^{13}C NMR study of amorphous salicin and indomethacin emphasized a particularly rich local or intramolecular mobility in salicin, strikingly different from that found in indomethacin. The technique of Thermally Stimulated Depolarisation Currents (TSDC) is a dielectric-related technique which has been frequently used to study slow molecular mobility in the glassy state (Lavergne and Lacabanne, 1993; Sauer, 2002; Moura Ramos et al., 2006). One advantage of the TSDC technique is its low equivalent frequency (van Turnhout, 1975) that leads to an enhanced resolution of the different relaxation processes. Some years ago we published a very careful study by TSDC of the molecular mobility in amorphous indomethacin (Correia et al., 2001a). In the present work we report TSDC results obtained on amorphous salicin, which will allow us to compare the information provided by the two techniques of NMR and TSDC.

2. Experimental

2.1. Materials

D(−)-Salicin (2-(hydroximethyl)phenyl-β-D-glucopyranoside, molecular formula $C_{13}H_{18}O_7$ and molecular weight $M = 286.28\ g\ mol^{-1}$), CAS number 138-52-3, was purchased from Acros, mass fraction > 0.99. It was dried under vacuum at $p \approx 1.3 \times 10^{-3}$ Pa and at $T = 420$ K in a schlenck tube covered with aluminium foil (salicin is light sensitive (Hilden and Morris, 2003)).

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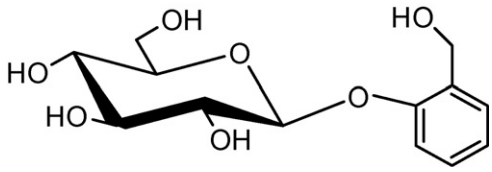

Fig. 1. Chemical structure of D(−)-salicin.

Several techniques were used to fully characterise our samples. The ^{1}H NMR spectra was in agreement with that reported by Dommisse et al. (1986) in acetone-d_6. The FT-IR spectrum was similar to those reported in the literature (Shimomura et al., 1989; Pearl and Darling, 1959), and did not evidence any band that could be attributed to adsorbed water (namely at 1680 cm^{-1}). The X-ray powder diffraction pattern found for D(−)-salicin indicates that we are in the presence of a pure orthorhombic phase whose crystal structure is in excellent agreement with that obtained by single crystal X-ray (Ueno, 1984).

2.2. Thermally Stimulated Depolarisation Currents

Thermally Stimulated Depolarisation Current (TSDC) experiments were carried out with a TSC/RMA spectrometer (TherMold, Stamford, CT, USA) covering the range from −170 to +400 °C. For TSDC measurements the sample was placed between the electrodes of a parallel plane capacitor with effective area of ∼38 mm^2 and immersed in an atmosphere of high purity helium (1.1 bar). The TSDC technique is adequate to probe slow molecular motions (20–3000 s). The fact that the relaxation time of the motional processes is temperature dependent and becomes longer as temperature decreases, enables to immobilize them by cooling. This is the basis of the technique. In order to analyse specific regions of the TSDC spectrum the partial polarisation (PP) procedure, also called thermal windowing or cleaning or sampling, is often used. This PP method, where the polarising field is applied in a narrow temperature interval, enables to resolve a distributed relaxation into its individual motional modes. The partial polarisation procedure allows to retain (or to freeze) a polarisation that arises from a narrow variety of dipolar motions. The physical background of the TSDC technique is presented elsewhere (van Turnhout, 1975; Chen and Kirsch, 1981). The basic description of the TSDC experiment, and the discussion of the nature of the information it provides, is presented in detail in recent publications (Correia et al., 2001a,b).

2.3. Differential Scanning Calorimetry

The calorimetric measurements were performed with a 2920 MDSC system from TA Instruments Inc. Dry high purity He gas with a flow rate of 30 cm^3/min was purged through the sample. Cooling was accomplished with the liquid nitrogen cooling accessory (LNCA) which provides automatic and continuous programmed sample cooling down to −150 °C. The samples of ∼8–15 mg were introduced in aluminium pans, hermetically sealed using a sample encapsulating press. The measuring cell was continually purged with high purity helium gas at 30 mL/min. An empty aluminium pan, identical to that used for the sample, was used as the reference. The calibration procedures are described in detail elsewhere (Moura Ramos et al., 2003).

3. Results and discussion

3.1. D(−)-Salicin in the crystalline phase

The melting peak of D-(−)-salicin obtained by DSC (see Fig. 2) showed an onset at T_{on} = 200.2 °C and a maximum at T_{max} = 201.6 °C

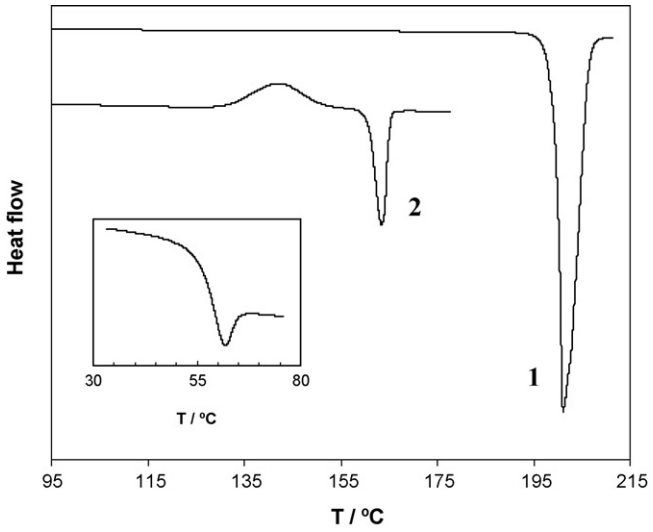

Fig. 2. Differential Scanning Calorimetry results obtained for D(−)-salicin with a heating rate of 10 °C min^{-1}. Curve 1 shows the melting peak of the most stable polymorph (T_{max} = 201.6 °C), while curve 2 shows cold crystallisation followed by the melting peak of another polymorph (T_{max} = 163.4 °C). The inset shows the glass transition signal. The heat flow is expressed in arbitrary units.

(heating rate 10 °C min^{-1}). The values T_{fus} = 197.3 °C (Tsukushi et al., 1995) and T_{fus} = 192.8 °C (Fukuoka et al., 1989) were previously reported in the literature.

The melting enthalpy, also obtained by DSC, was $\Delta_{fus}H = (193.8 \pm 1.3)$ J g^{-1} = (55.5 ± 0.4) kJ mol^{-1} (mean over five determinations; the reported uncertainty corresponds to the standard deviation of the mean). The value previously reported in the literature is $\Delta_{fus}H$ = 53.2 kJ mol^{-1} (Tsukushi et al., 1995). The previous values refer to the most stable polymorph since we were able to detect another polymorph not yet reported in the literature, that melts after cold crystallisation at T_{max} = 163.4 °C (see Fig. 2). However, the occurrence of this polymorph is very infrequent, so that we were not able to clearly define the exact conditions of its formation.

In the crystalline phase a slow molecular mobility was detected by TSDC. It is a strong dielectric strength relaxation which is observed in the temperature range between 50 and 150 °C of the TSDC spectrum. Fig. 3 shows some partial polarisation peaks of this relaxation; the global peak in displayed in the inset.

It can be seen from Fig. 3 that the relaxation is clearly delimited in the temperature axis, given that the dielectric strength of the PP peaks decreases as the polarisation temperature increases in the higher temperature side of the relaxation. Note also that at some 50 degrees below the melting point a conductivity tail appears in the TSDC spectrum of the crystalline salicin (see inset of Fig. 3). The temperature dependent relaxation time of the PP peaks of this mobility was obtained by the usual Bucci method (Bucci et al., 1966), and the results indicate that we are dealing with approximately localised molecular motions, with a low degree of cooperativity. In fact, the activation enthalpy of the different motional modes, represented in Fig. 6 as a function of the temperature location of the corresponding peak, show that the values found in crystalline salicin (points in the higher temperature side of the Figure (open diamonds)) do not appreciably deviate from the Starkweather line (Sauer et al., 1990), also called zero entropy line, that depicts the behaviour of noncooperative relaxations. The deviation from the line is indeed small compared for example to that observed for the full symbol in Fig. 6 that corresponds to the glass transition relaxation (see later), so that strictly speaking we can say that the relaxation is narrowly distributed in enthalpy (from ∼100 to 140 kJ/mol) and in entropy (from 0 up to 26 J/(K mol)).

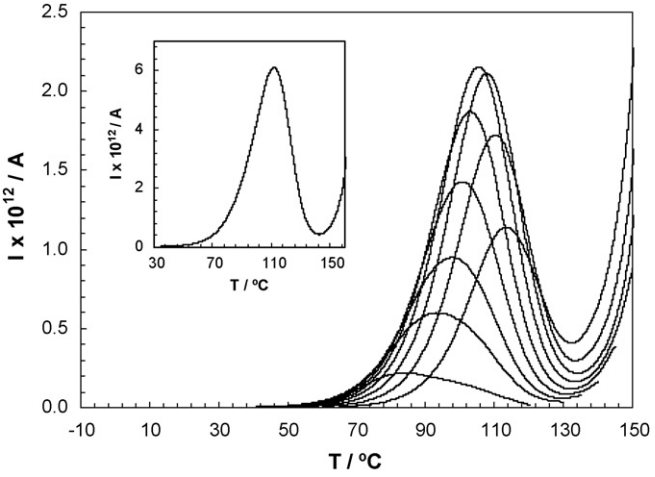

Fig. 3. Partial polarisation (PP) components of the relaxation in the crystalline phase of salicin. The polarisation temperatures, T_P, were 70 °C and from 80 to 115 °C, with intervals of 5 °C. The other experimental conditions were: strength of the polarising electric field, $E = 450\ V\ mm^{-1}$; polarisation time, $t_P = 5$ min; width of the polarisation window, $\Delta T = 2$ °C; heating rate, $r = 4$ °C min^{-1}. The inset represents the global peak obtained with polarisation temperature, $T_P = 110$ °C, polarisation time, $t_P = 5$ min, strength of the polarising electric field, $E = 450\ V\ mm^{-1}$, freezing temperature, $T_0 = -20$ °C, heating rate, $r = 8$ °C min^{-1}.

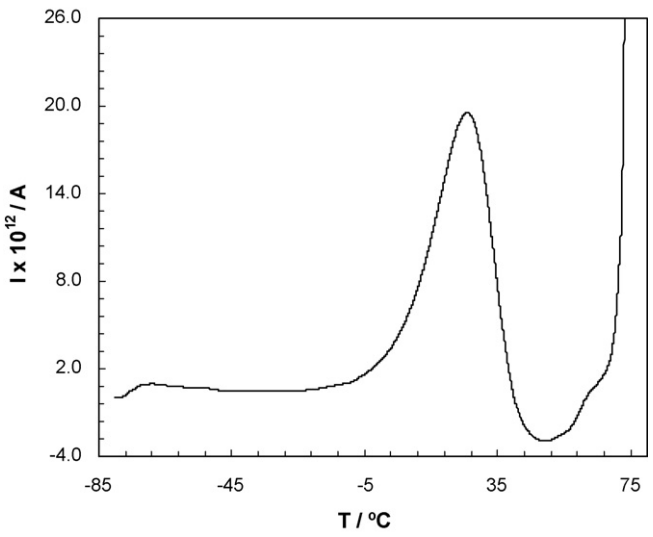

Fig. 4. TSDC thermogram obtained from a global experiment with polarisation temperature, $T_P = 55$ °C. The other relevant experimental parameters are: strength of the polarising electric field, $E = 450\ V\ mm^{-1}$, polarisation time, $t_P = 5$ min, freezing temperature, $T_0 = -80$ °C, heating rate, $r = 8$ °C min^{-1}. Note that no polarisation was created between 50 and 60 °C, in the glass transformation range.

3.2. D(−)-Salicin in the amorphous solid state

D(−)-Salicin in the solid amorphous phase was prepared by cooling the isotropic liquid from 205 °C. The substance displayed excellent glass forming ability, with a wide supercooled liquid temperature region and generally high thermal stability against crystallisation. The calorimetric glass transition temperature was $T_g = 55.5$ °C (at 10 °C min^{-1}), which can be compared with the values $T_g = 59.8$ °C (Fukuoka et al., 1989) and $T_g = 59.4$ °C (Tsukushi et al., 1995) previously reported. The heat capacity jump in the glass transformation range was found to be $\Delta C_P = (0.65 \pm 0.01)\ J\ °C^{-1}\ g^{-1} = (186.1 \pm 2.9)\ J\ °C^{-1}\ mol^{-1}$ (average over 20 experiments, where the uncertainty indicated corresponds to the standard deviation of the mean), which agrees with the value $\Delta C_P = 188\ J\ °C^{-1}\ mol^{-1}$ previously reported (Tsukushi et al., 1995).

3.2.1. Secondary relaxations

The mobility in the glassy state was studied by TSDC and the observations are as follows:

1. In the glass transformation range (50–60 °C) there is no TSDC evidence for the presence of the α-relaxation peak. Fig. 4 shows the result of an experiment that was specifically designed to activate the mobility associated with the glass transition. A relaxation peak with maximum intensity at ∼25 °C (that will be discussed below) is observed, but no signature of the α-peak is apparent. A conductivity tail also appears at ∼55 °C which grows as usual with increasing temperature, but it seems not sufficiently strong to hide the glass transition peak, i.e. to explain its absence. Let us also note that, after being studied by TSDC, the samples were analysed by DSC, and that the results confirmed unambiguously the fully amorphous state of those samples. The absence of a glass transition peak in the glass transformation region of the TSDC spectrum of salicin is thus rather mysterious, and cannot be ascribed to crystallisation.
2. A secondary relaxation not present in the crystalline phase was detected (Fig. 5), indicating that the sample is in the amorphous state, despite the absence of the TSDC glass transition peak. The components of this relaxation, obtained by the partial polarisation procedure, displayed in Fig. 5, show kinetic parameters that nearly obey to the so-called zero entropy line, i.e. that correspond to low amplitude, local, non-cooperative motions. In fact, from Fig. 6 we can see that the points in the low temperature side of the Figure (open triangles) are close to the zero entropy line.

Furthermore, this secondary relaxation is broad and presents some kind of structure, with two differentiated components, as shown in the inset of Fig. 5: a higher intensity (higher dielectric strength) one, with maximum intensity at ∼−135 °C, near

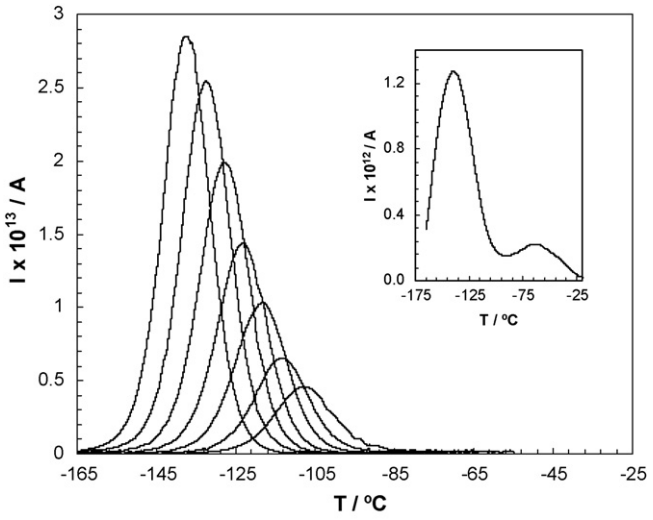

Fig. 5. Partial polarisation (PP) components of the β-relaxation of salicin. The polarisation temperatures, T_P, were from −140 to −110 °C, with intervals of 5 °C. The other experimental conditions were: strength of the polarising electric field, $E = 450\ V\ mm^{-1}$; polarisation time, $t_P = 5$ min; width of the polarisation window, $\Delta T = 2$ °C; heating rate, $r = 4$ °C min^{-1}. The inset represents the global peak obtained with polarisation temperature, $T_P = -50$ °C, polarisation time, $t_P = 5$ min, strength of the polarising electric field, $E = 450\ V\ mm^{-1}$, freezing temperature, $T_0 = -165$ °C, heating rate, $r = 8$ °C min^{-1}.

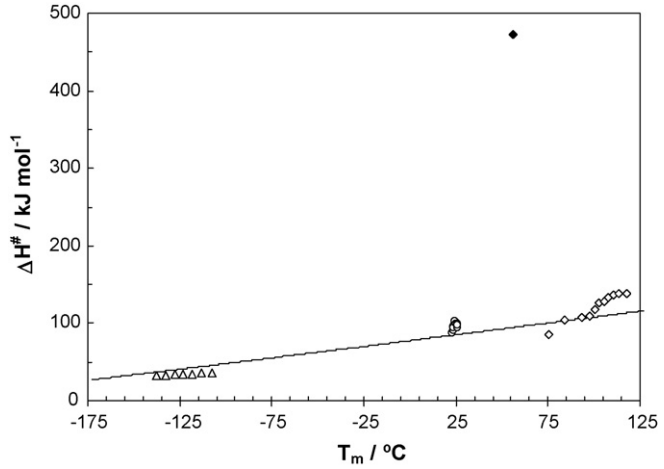

Fig. 6. Activation enthalpy, $\Delta H^{\neq}$, of the partial polarisation components of the β and α relaxations of salicin as a function of the peak's location, T_m. The line is the zero entropy line. The points on the left-hand side (open triangles) correspond to the β-relaxation of salicin (peaks in Fig. 5). The points in the centre of the figure correspond to the sub-T_g relaxation with $T_m \cong 24\,^{\circ}C$ (some of the corresponding peaks are shown in Fig. 7). The points on the right-hand side (open diamonds) correspond to the relaxation in the crystalline phase of salicin (peaks in Fig. 3). The filled symbol corresponds to the result obtained by DSC relative to the glass transition relaxation.

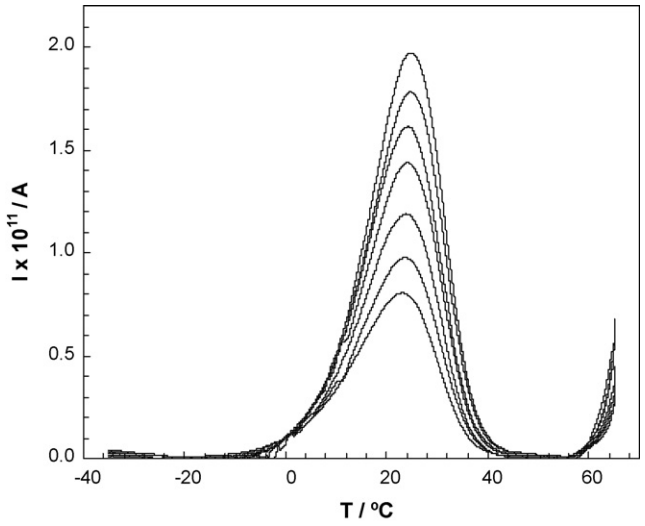

Fig. 7. Partial polarisation (PP) components of the sub-T_g molecular mobility at $T_{max} = 24\,^{\circ}C$ of salicin. The polarisation temperatures, T_P, were from 8 to 20 °C, with intervals of 2 K. The intensity of the peaks increases as the polarisation temperature increases, but for T_P higher than 20 °C (peaks not shown for clarity) the intensity decreases with increasing T_P. The other experimental conditions were: strength of the polarising electric field, $E = 450\,V\,mm^{-1}$; polarisation time, $t_P = 5$ min; width of the polarisation window, $\Delta T = 2\,^{\circ}C$; heating rate, $r = 4\,^{\circ}C\,min^{-1}$.

the lower temperature limit of our equipment (which is about −165 °C), and a lower intensity one at higher temperature (at −60 °C). No partial polarisation experiments could be carried out on this component as a consequence of its exceedingly low intensity (no PP peaks are shown in Fig. 5, and the corresponding points are not presented in Fig. 6). Our aging studies indicate that these two components are not influenced by aging. As argued in previous works (Moura Ramos et al., 2007a,b), the faster motional modes, at lower temperatures, that are not affected by aging, are believed to have an intramolecular origin. These are local motions that consist of internal rotations of one part of a molecule relative to the other part or conformational modifications of a cyclic unit, which occur without significant interference of the neighbouring molecules.

3. A strong relaxation peak with $T_{max} = 24\,^{\circ}C$ is also observed, already shown in Fig. 4. The motional components (partial polarisation) of this relaxation, some of them shown in Fig. 7, show a low degree of cooperativity, i.e. they nearly obey to the zero entropy line as indicated in Fig. 6 (open circles).

In a dynamic Nuclear Magnetic Resonance study referred before (Masuda et al., 2005), based on the measurement of spin-lattice relaxation times, it was shown that salicin displays a rich local mobility in the equilibrated glassy state, some 40 degrees below T_g. This mobility detected by NMR probably corresponds to that we observe at 24 °C by TSDC. This NMR study compares salicin with indomethacin, both in the solid amorphous state, and demonstrates that amorphous salicin has a molecular mobility much higher than amorphous indomethacin. The molecular mobility of amorphous indomethacin was studied before by TSDC (Correia et al., 2001a), and the main features of the mobility are as follows: 1, a glass transition peak with a maximum intensity near the calorimetric glass transition temperature; 2, a secondary relaxation process which is partially disguised in the lower temperature side of the main α-process, which probably corresponds to a Johari-Goldstein relaxation; 3, another secondary relaxation that appears in the TSDC spectrum in the temperature region between −100 and −165 °C. The most important differences between the TSDC results on salicin and indomethacin are the absence in salicin of the glass transition peak, and the presence in this substance of a strong relaxation peak at 24 °C, some thirty degrees below T_g. The features of this mobility appear as strikingly different from the general features of both the α and the β-relaxation. On the one hand, as stressed before, it displays a local, non-cooperative nature. Furthermore, the ageing studies we carried out on this relaxation did not reveal any influence of the ageing time on the intensity, shape or temperature location of the corresponding relaxation peaks. This finding reinforces the conviction that the molecular origin of this relaxation is strongly different from that of the alfa-relaxation. On the other hand, the temperature location (temperature of maximum intensity, T_m) of the different partial polarisation components of this relaxation is the same (no change of T_m when the polarisation temperature, T_P, varies) as shown in Figs. 7 and 8, denoting a motional process with

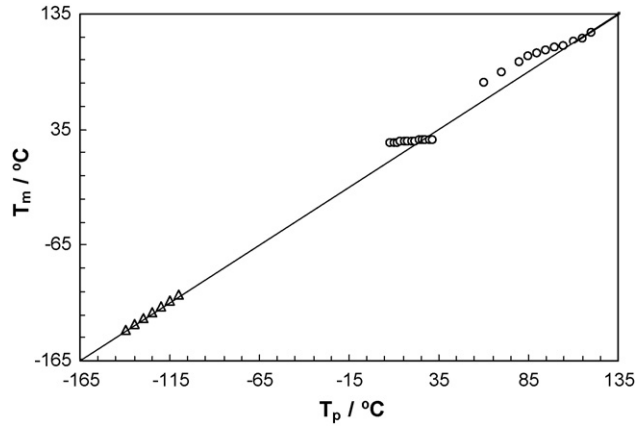

Fig. 8. Temperature of maximum intensity of the partial polarisation peaks, T_m, as a function of the corresponding polarisation temperature, T_P. The points on the left-hand side, with T_P between −140 and −110 °C, correspond to the β-relaxation of salicin (peaks in Fig. 5). The points with T_P between 8 and 30 °C correspond to the sub-T_g relaxation at ∼25 °C (some of the corresponding peaks are shown in Fig. 7). The points on the right-hand side, with T_P between 70 and 115 °C, correspond to the relaxation in the crystalline phase of salicin (peaks in Fig. 3). The straight line with unity slope and intercept at the origin is shown as a reference.

a single relaxation time, i.e. a non-distributed relaxation. It is to be noted that this behaviour is markedly different from that observed for the secondary relaxations (points in the left-hand side of Fig. 8).

3.2.2. Glass transformation and fragility

Unlike TSDC, DSC allowed a complete characterisation of the glass transformation in salicin. Among the methods of thermal analysis allowing the determination of the activation energy of structural relaxation at T_g, $E_a(T_g)$, one of them is based on the scanning rate dependency of T_g (Crowley and Zografi, 2001). On the other hand, the fragility index of a glass-forming system can be estimated from that activation energy at the glass transition temperature. In the present work we use the Differential Scanning Calorimetry (DSC) technique in order to estimate the activation energy of structural relaxation at T_g, $E_a(T_g)$, and the fragility index, m, of salicin. It is well known that the DSC results obtained on heating depend on the thermal treatments used to produce the glass (namely on the cooling rate), present the so-called overshoot peak in the heat capacity, and are influenced by ageing effects (Simatos et al., 1996). However, we carried out all the DSC experiments in the heating mode due to the difficulty of obtaining reliable thermograms under cooling conditions (Simatos et al., 1996). One of the reasons is probably that the accurate control of the temperature is most difficult on cooling than on heating. The calibration of the temperature-scale during cooling is also reported to be problematic. We will thus analyse the influence of the heating rate on the onset temperature, T_{on}, of the glass transition signal.

It was shown (Moynihan et al., 1974) that the dependence of the glass transition temperature, T_g, on the heating or cooling rate, $|q|$, of a conventional DSC experiment is given by

$$\frac{d \ln|q|}{d\, 1/T_g} = -\frac{E_a}{R} \quad (1)$$

where E_a is the activation energy for the relaxation times controlling the structural enthalpy relaxation. It is to be enhanced that a necessary constrain for applying Eq. (1) on heating is that, prior to reheating, the glass must be cooled from above to well below the glass transition region at a rate equal to the reheating rate.

The value of E_a obtained from Eq. (1) can thus be used to calculate the fragility index, m, of a glass forming system, which is defined as the slope of the $\log \tau(T)$ *versus* T_g/T line at the glass transition temperature, i.e. at $T = T_g$ (Bohmer et al., 1993; Bohmer and Angell, 1994),

$$m = \left[\frac{d \log_{10}\tau(T)}{d(T_g/T)}\right]_{T=T_g} \quad (2)$$

where τ is the structural relaxation time which slows down to ~100 s at T_g. Eq. (2) can be expressed in terms of the apparent activation energy, E_a, as

$$m = \frac{1}{2.303}\left[\frac{E_a(T_g)}{RT_g}\right] \quad (3)$$

The results of our experiments on the influence of the heating rate on the onset temperature, T_{on}, of the glass transition signal are shown in Table 1. Fig. 9 shows the representation of $\ln|q|$ as a function of $1/T$, for the data presented on Table 1, and it can be seen that despite some scattering the data points display a linear tendency.

From the linear regression analysis of the data in Table 1, we obtain an activation energy of $E_a = 473\ kJ\ mol^{-1}$ (standard deviation of $\pm 27\ kJ\ mol^{-1}$), which is indicated in Fig. 6 as a full circle. The calculated fragility index is $m = 75$. Note that in the calculation of the fragility index we considered that the glass transition temperature was $T_g = 55.5\ ^\circ C$ (measured at $10\ ^\circ C\ min^{-1}$ on heating). From these results we can conclude that salicin is a relatively fragile liquid with a fragility index higher than salol ($m = 61$, Bohmer et al., 1993; Moura Ramos et al., 2004) and sorbitol ($m = 71$, Correia et al., 2001b; Bohmer et al., 1993).

Table 1
Onset temperature, T_{on}, of the calorimetric glass transition signal for different heating rates, q

$T_{on,g}$ (°C)	q (°C s^{-1})
53.36	0.0333
53.56	0.0500
53.66	0.0500
54.05	0.0667
53.92	0.0833
54.80	0.1000
54.68	0.1167
55.03	0.1333
55.19	0.1500
55.72	0.1667
56.12	0.1667
55.55	0.1833
56.00	0.2000
55.87	0.2167
56.68	0.2333
56.27	0.2500
56.69	0.2667
56.53	0.2833
57.01	0.3000
56.75	0.3167
57.45	0.3333

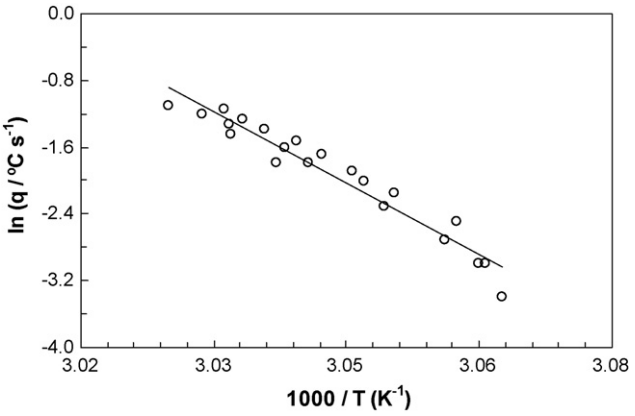

Fig. 9. "Arrhenius plot" (logarithm of the heating rate, q, as a function of $1/T_{g,on}$, where T is expected in Kelvin) for the glass transition of salicin studied by DSC.

4. Summary and conclusions

Thermally Stimulated Depolarisation Currents (TSDC) measurements on D(−)-salicin allow to clearly identify a mobility in the crystalline phase, characterised by a strong dielectric strength and low activation energies and entropies. On the other hand, the slow mobility in the amorphous solid state was studied by this experimental technique. The essential observations can be synthesised as follows: (a) a broad and low intensity secondary relaxation was observed, which appeared in the temperature axis far below the glass transformation range, and probably extends below the temperature of liquid nitrogen, i.e. below the available temperature range of our experimental apparatus; (b) the α-relaxation peak is not present in the TSDC thermogram in the temperature region of the calorimetric glass transition where it was expected to appear; (c) another sub-T_g relaxation was detected, located at thirty degrees below the glass transition, whose features are considerably dif-

ferent from the general features observed for both the α and the β-relaxations.

The steepness index or fragility, m, of D(−)-salicin was determined by DSC based on of the scanning rate dependency of T_g. The obtained value was $m \cong 75$.

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