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Thermal analysis of novel biphenylamide derivatives: influence of positional and functional group isomerism on solid state properties

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Abstract:	The physicochemical properties of a small library of 4-methyl-biphenylamide derivatives have been investigated by means of differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and hot-stage microscopy (HSM). The obtained results show that positional isomerism has a significant influence on the thermal behaviour of the 4-methyl-biphenylamide derivatives. Two polymorphic forms were found for the ortho-substituted derivatives, whilst the para-substituted derivatives exhibit three polymorphic forms. The ortho-substituted biphenylamides were more likely to generate metastable forms when cooled from the melt. Furthermore, self-heating properties were revealed by the para-substituted 4-methyl-biphenylamide derivatives, in which the highly energetic crystallization processes raised the sample temperature by as much as 4°C during cooling. Such a high energy exothermic crystallization process suggests crystallization to be highly favourable, from a thermodynamic standpoint. Hence the p-substituted derivatives are unlikely to generate amorphous forms. Based on the melting points of the most stable polymorphic form (Form I) and the activation energy of the evaporation processes, the para-substituted compounds demonstrate greater thermal stability over their ortho-substituted counterparts. This further suggests that para-substituted compounds, due to their steric effects have greater interactions between individual molecules in the crystalline form.
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Thermal analysis of novel biphenylamide derivatives: influence of positional and functional group isomerism on solid state properties

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ABSTRACT

The physicochemical properties of a small library of 4-methyl-biphenylamide derivatives have been investigated by means of differential scanning calorimetry (DSC), thermogravimetric analysis (TG) and hot-stage microscopy (HSM). The obtained results show that positional isomerism has a significant influence on the thermal behaviour of the 4-methyl-biphenylamide derivatives. Two polymorphic forms were found for the ortho-substituted derivatives, whilst the para-substituted derivatives exhibit three polymorphic forms. The ortho-substituted biphenylamides were more likely to generate metastable forms when cooled from the melt. Furthermore, self-heating properties were revealed by the para-substituted 4-methyl-biphenylamide derivatives, in which the highly energetic crystallization processes raised the sample temperature by as much as 4°C during cooling. Such a high energy exothermic crystallization process suggests crystallization to be highly favourable, from a thermodynamic standpoint. Hence the p-substituted derivatives are unlikely to generate amorphous forms. Based on the melting points of the most stable polymorphic form (Form I) and the activation energy of the evaporation processes, the para-substituted compounds demonstrate greater thermal stability over their ortho-substituted counterparts. This further suggests that para-substituted compounds, due to their steric effects have greater interactions between individual molecules in the crystalline form.

INTRODUCTION

Biphenyls are important structural analogues that have applications across a wide range of industries, from textiles to pharmaceuticals [1-4]. From a pharmaceutical viewpoint, the biaryl scaffold is a “privileged structure”, owing to their ability to provide ligands for multiple receptors [5]. As such, the synthesis of biphenyl derivatives has received a great deal of attention and has resulted in the development of libraries of biphenyl

containing compounds that are both important intermediates in the production of pharmaceutically useful active substances, and as potential lead compounds/drug candidates with a wide variety of pharmacological activity.

A recent article [6] documents the synthesis and characterization of a biphenyl amide library with interesting solid-state properties, in which the asymmetric unit (Z') ranges from 1 to 6. This biphenyl library (consisting of amide functionality of different molecular size and at varying positions on the biaryl scaffold) is therefore an interesting set of compounds to investigate by means of thermal analysis from an academic and industrial perspective. The purpose of this study is to use this library of model compounds to investigate the influence of positional isomerism and the size of the amide substituents on the thermal behaviour of these biphenyl compounds.

MATERIALS AND METHODS

Materials

N-(4'-Methylbiphenyl-3-yl)acetamide (4-MBA (1)), N-(4'-Methylbiphenyl-3-yl)cyclopropanecarboxamide (4-MBA (2)), N-(4'-Methylbiphenyl-4-yl)acetamide (4-MBA (3)), N-(4'-Methylbiphenyl-4-yl)benzamide (4-MBA (4)) and N-(4'-Methylbiphenyl-4-yl)cyclopropanecarboxamide (4-MBA (5)) were synthesised and crystallised as reported previously (Baltus et al., 2012); the molecular structures are presented in Table 1. All compounds were >95% pure, as determined by ^{1}H NMR and CHN analysis.

Table 1 here

Instrumentation

Thermogravimetric analysis (TG)

Modulated thermogravimetric (MTG) and conventional TG studies were performed using Q5000 IR (TA Instruments, UK). All experiments were performed using sample masses of 1.85 ± 0.25 mg in a standard aluminium pan under a nitrogen atmosphere at a flow rate of 25 $cm^{-3}min^{-1}$. For the TG experiments, samples were heated from ambient temperature to 400°C at 10°$Cmin^{-1}$. In the MTG studies each sample was equilibrated at 100°C (with the exception of (4-MBA 5, which was equilibrated at 50°C) and heated to 350°C. The temperature modulation settings were +/-5°C amplitude for a period of 200 s with an underlying heating rate of 5°$Cmin^{-1}$.

Differential scanning calorimetry (DSC)

DSC studies were performed using a Q2000 (TA Instruments, UK) calorimeter under a nitrogen atmosphere at a flow rate of 50 $cm^{-3}min^{-1}$ in hermetically sealed Tzero aluminium pans. Sample masses of 1.65 ± 0.51 mg were analysed, typically in the temperature range 0 to 250°C using various heating and cooling rates (defined in the accompanying Figures and text).

Hot-Stage Microscopy (HSM)

HSM investigations were conducted using an FP8HT hot-stage with an FP90 digital temperature controller (Mettler Toledo, UK) on a DME Model 13595 microscope (Leica Microsystems, China) equipped with a PL-A622 firewire camera (PixiLINK, Canada). Samples were heated from ambient temperature to 250°C at 10°$Cmin^{-1}$.

RESULTS

The results obtained from TG experiments are presented in Fig.1. All samples, with the exception of 4-MBA (5), undergo a single process resulting in 100 % mass loss. Sample 4-MBA (5) undergoes a small change between 150 and 200°C with an associated mass loss of 2.5 ± 0.3% (Table 2) followed by complete loss of mass. With the aid of hot-stage microscopy (HSM) all processes observed were found to result from the evaporation of the melted samples.

Fig 1 here

Table 2 here

MTG experiments were performed to determine the activation energies associated with the evaporation processes, to better understand the relative stability differences imposed by the amide substituent positioning and the size on the biaryl scaffold. In MTG the linear heating rate is modulated resulting in an oscillating temperature programme. The result obtained in this experimental approach enables a model-free determination of the activation energy. A theoretical consideration of MTG and the method used to extract kinetic parameters are provided elsewhere [7, 8].

The resultant TG and DTG curves from the MTG experiments are presented in Fig. 2. The two o-substituted biphenylamide derivatives (4-MBA (1) and 4-MBA (2)) undergo similar transformations to those observed in the conventional TGA experiments, which shows that the evaporation behaviour of these two compounds are not influenced by the temperature modulation. However, compounds 4-MBA (3) and 4-MBA (5), which are the p-substituted counterparts of compounds 4-MBA (1) and 4-MBA (2) respectively, were significantly influenced by the oscillating temperature programme. 4-MBA (3) undergoes two mass loss processes as opposed to the single process observed in the conventional TGA. The first of the two mass loss processes observed for 4-MBA (5) in the conventional TGA now has a greater percentage loss of mass (6.0 ± 0.5%) and occurs at a lower temperature (100-150°C) in the MTG results.

The first mass loss processes for the p-substituted biphenylamides were confirmed (by HSM) to be melt-evaporations of a small cluster of particles that exist in an alternative crystalline form. After evaporation, the remaining samples of 4-MBA (4) undergo decomposition (this was confirmed by the presence of a small patch of dark residue after the completion of the experiment). It appears that the o- and p-substituted biphenylamide

derivatives respond differently to heating rate fluctuation. The p-substituted compounds undergo two evaporation processes, whilst the o-substituted compounds undergo a single process. While positional isomerism influences the TG profile, no differences are observed when the size of the amide substituent is considered.

Fig 2 here

An approach employed to investigate the nature of a given reaction in kinetic studies is to monitor how the activation energy value changes as a function of conversion [9-11]; conversion is the fraction of sample that has undergone some chemical or physical transformation. In the case of TG the conversion is related to the mass fraction remaining after a particular process, i.e. the amount of sample remaining. A plot of the activation energy as a function of mass fraction is presented in Fig. 3. In MTG experiments several modulation cycles are needed before a reliable activation energy value is acquired, hence at the beginning of any MTG activation energy plot, unrealistically high data points are observed. The kinetic parameters again become unrealistically high at the end of the experiment, which is due to the absence of any reacting material. Because the values at the two extremes of the data are unreliable, the apparent activation energies associated with the first evaporation process for 4-MBA (3) and 4-MBA (5) and the decomposition process for 4-MBA (4) are ignored. The average activation energies across the mass fraction of 20 to 95 % were calculated and are presented in Table 3.

All five samples demonstrated some degree of activation energy dependence on the progression of the evaporation process. As such they all exhibit complex behaviour and are therefore unlikely to follow first order kinetics [12].

Fig 3 here

Table 3 here

DSC was employed to investigate the thermotropic transitions of the 4-methyl biphenylamide derivatives. The initial scan shows that all samples, with the exception of 4-MBA (5), exhibit no transitions prior to melting (Fig. 4). 4-MBA (5) undergoes several processes before the main melting transition at 213 ± 1°C (melting of Form I), indicating a mixture of polymorphic forms. When heated from 20°C at a rate of 10°Cmin^{-1} some particles melt at 98 ± 1°C (Form III), which evaporates immediately (not observed in DSC plot due to hermetic sealing). At 193 ± 1°C other particles (Form II) melt and crystallize almost immediately at 194 ± 1°C into needle shaped

crystals (Form I). The newly crystallized (Form I) particles and other Form I particles already in the sample then melt at 213 ± 1°C. These inferences are supported by HSM investigations (Fig. 5).

When a comparison of the melting onset temperatures of the highest melting forms (Form I) detected so far is made between o- and p-substitutions, it becomes clear that positional isomerism has an influence on the physical stability of the biphenyl amides. The onset temperatures of the Form I observed for the p-substituted biphenyl amides are higher than there o-substituted counterparts. For example, Form I of the p-substituted 4-methyl biphenylacetamide (4-MBA (3)) melting onset is at 223 ± 1°C, whilst Form I of the o-substituted 4-methyl biphenylacetamide (4-MBA (1)) has a melting onset at 149 ± 1°C. At the same token, the onset of the highest melting form (Form I) of the p-substituted 4-methyl biphenylcyclopropanecarboxamide (4-MBA (5)) is 208 ± 1°C, which is 13°C higher than that observed for Form I of its o-substituted counterpart (4-MBA (2)), which melts at 195 ± 1°C.

The DSC results show that molecular size has no influence on the physical stability of these materials. With that said, the compound that exhibits the greatest physical stability is the 4-methyl biphenylbenzamide (4-MBA (4)), which has the largest molecular size of the series of compounds analysed. The onset temperature for the melting transition observed for this compound is 227 ± 1°C.

Fig 4 here

Fig 5 here

Several temperature programmes, namely different heating and cooling rates, were employed to further investigate the thermotropic behaviour of these 4-methylbiphenylamide derivatives. Compound 4-MBA (4) demonstrated no thermotropic polymorphic behaviour when different heating and cooling rates were employed and is thus ignored.

Ortho-substituted Biphenyl Acetamide (4-MBA (1))

Influence of heating rates

After initially heating past the melting point of Form I, 4-MBA (1) crystallizes into a lower melting form (Form II) upon cooling at 10°Cmin^{-1}. During the second heating cycle (Fig. 6(a)) at 10°Cmin^{-1}, Form II melts at 136 ± 1°C and crystallizes at 141 ± 2°C into Form I, which then melts at 149 ± 1°C (Fig. 6(b)). Increasing the heating

rate to 50°Cmin^{-1} supresses the crystallization into Form I after Form II melts, hence the reduction in the enthalpy change (ΔH) of Form I from 114 ± 5 Jg^{-1} observed at 10°Cmin^{-1} to 6 ± 1 Jg^{-1} when heated at 50°Cmin^{-1}. Crystallization of Form I is totally prevented at heating rates above 50°Cmin^{-1} (Fig. 6(a)).

Fig 6 here

The heating rate dependence of the melt-crystallization into Form I was investigated further by the application of various heating rates below 50°Cmin^{-1} (Fig. 7 (a)) using a constant cooling rate of 10°Cmin^{-1}. At a very low heating rate (1°Cmin^{-1}) it appears that only the melting process of Form I occurs. However with increasing temperature Form II becomes more prominent, as observed by the increase in the signal of the melting endotherm at 136 ± 1°C. On closer inspection of the DSC curve obtained at a heating rate of 1°Cmin^{-1} (Fig. 7 (b)), a broad exothermic solid-solid transition between 100 and 125°C and a small endothermic transition at 136°C (melting of Form II) is detected. This is not observed at higher heating rates. This result suggests that when a low heating rate is applied, Form II undergoes a solid-solid transition into Form I. The solid-solid conversion of Form II into Form I is kinetically hindered at higher heating rates; as such the solid-solid conversion occurs at a higher temperature, where it overlaps with the melting process of Form II . It is therefore likely that the crystallization into Form I after Form II melts results from seeding of small amounts of Form I, which is generated by partial conversion of Form II prior to melting. Since the transformation of Form II to Form I is an exothermic process, the thermodynamic relationship between Form II and Form I is monotropic, according to the heat-of-transition rule [13, 14]. This monotropic relationship was confirmed by heating the sample at a scan rate of 1°Cmin^{-1} to 130°C, cooling to 0°C and re-heating. On the second heating the solid-solid transition is not observed, only the melting of Form I.

The percentage contribution of the melting enthalpies observed for Form II and Form I to the total enthalpy change observed for both melting endotherms was calculated and plotted as a function of heating rate (Fig. 7 (c)). From the graph it is evident 100% of Form I can be generated by heating to 130°C at a heating rates of $\leq$1°Cmin^{-1}.

Fig 7 here

Influence of cooling rates

Application of different cooling rates appears to have the opposite effect on the ratio of Form II to Form I generated (when compared to that observed when different heating rates are used). At low cooling rates a

greater proportion of Form II is generated upon heating at 10°Cmin^{-1}, whilst at higher cooling rates a greater proportion of Form I is detected (Fig. 8 (a)).

At a cooling rate of 1°Cmin^{-1} Form II is generated, which on heating melts and undergoes crystallization into Form I. No other transitions are detected below the melting temperature of Form II. When the sample is cooled at 5°Cmin^{-1} an exothermic solid-solid transition that overlaps with the melting of Form II is detected (Fig. 8 (b)), as a result a greater ratio of Form I (when compared with that obtained for a cooling rate of 1°Cmin^{-1}) is observed. This solid state conversion is the transformation of Form II to Form I. As the cooling rate is increased to $\geq$20°Cmin^{-1}, another exothermic transition (between 40 and 60°C) is detected. These results demonstrate the complex nature of the thermotropic polymorphic behaviour of o-substituted 4-methyl biphenylacetamide (4-MBA (1)).

The observation of the exothermic transition between 40 and 60°C (Fig. 8 (b)) can be explained by the HSM results (Fig. 8 (c)). When the sample is allowed to cool (via Newtonian cooling) it exhibits different degrees of super-cooling. As such, the majority of the sample crystallizes into Form II and a certain proportion does not crystallize even when cooled to 0°C. Upon heating, the super-cooled liquid crystallizes into Form II_b (which has a needle like crystal habit) and Form I. The different degrees of super-cooling seem to influence the crystal form that the liquefaction crystalizes into. This rationale is based on the fact that at lower cooling rates a greater proportion of Form II is generated, whilst at higher cooling rates a greater proportion of Form I is generated upon heating. Hence, the increase in the ratio of Form I observed in DSC as the cooling rate is increased is due to the generation of greater amounts of super-cooled liquefactions that are more likely to crystallize into Form I.

A plot of percentage contribution of the melting enthalpies (heat of fusion) observed for Form II and Form I in this study is presented in Fig. 8 (d). From the graph it is clear that it is not possible to generate 100% Form I or Form II by the cooling rate method.

Fig 8 here

Ortho-substituted Biphenyl cyclopropanecarboxamide (4-MBA (2))

Varying the heating rate has no effect on the phase behaviour of 4-MBA (2) i.e. the sample undergoes a single melting process when cooled at 10°Cmin^{-1} and heated at various heating rates (Fig 9 (a)). When the sample is heated at 10°Cmin^{-1} after being subject to high cooling rates $\geq$100°Cmin^{-1}, it undergoes a solid-solid transition into Form I which melts at 195 ± 1°C. Hence when 4-MBA (2) is cooled very fast it crystallizes into a

metastable form (Form II), which is not observed at lower cooling rates. The transformation of Form II into Form I (at 52 ± 1°C) is irreversible and the fact that the heat of transition is exothermic confirms the thermodynamic relationship between the two crystal forms to be monotropic.

At 1°Cmin^{-1}cooling rate the exothermic crystallization of 4-MBA (2) is so energetic that it appears to self-heat i.e. the temperature of the sample is raised temporarily before it continues cooling (Fig. 9 (a)); a phenomenon that is not observed for any of the other cooling rates employed or for 4-MBA (1) at the same cooling rate. The exothermic crystallization, upon cooling, raises the temperature of the sample by ~1°C.

Fig 9 here

Para-substituted Biphenyl Acetamide (4-MBA (3))

Application of various heating and cooling rates revealed three polymorphic forms of 4-MBA (3). At very high heating rates (150°Cmin^{-1}) 4-MBA (3) exhibits two melting endotherms (Fig. 10 (a)). The lower melting endotherm (Form II) is only detected when the sample is heated $\geq$100°Cmin^{-1} or above and appears as a small shoulder on the melting of Form I, at 224 ± 1°C. This suggests that cooling compound 4-MBA (3) at 10°Cmin^{-1} generates a mixture of solid forms i.e. Form I and small amounts of Form II, which can only be detected at very high heating rates.

When the sample is subjected to different cooling rates and heated at 10°Cmin^{-1}, three processes are detected (Fig. 10 (b)). The first is a melting process with an onset temperature of 203 ± 1°C, which overlaps with a crystallization exotherm at 214 ± 1°C. The crystallization generates a new crystal form which melts 222 ± 1°C. The melting temperature of this new crystal form is 2°C lower than that observed for Form I (224 ± 1°C) but has a similar melting enthalpy (141 ± 5 Jg^{-1}) and is therefore denoted Form I_b. Varying the heating rates has no effect on the processes observed.

The crystallization of the melt upon cooling of 4-MBA (3) also exhibits a highly energetic exothermic process, that results in the self-heating of the sample (Fig. 10 (c)). At a low cooling rate (1°Cmin^{-1}) the sample temperature increases by 3.5°C ± 0.5 during the crystallization process before it continues cooling, whilst at a higher cooling rate $\geq$60°C the increase in temperature is $\leq$1°C.

Fig 10 here

Para-substituted Biphenyl cyclopropanecarboxamide (4-MBA (5))

As previously explained, the initial 4-MBA (5) sample consists of three crystalline forms. When the sample is heated past the melting point of Form I and cooled, Form III and Form II are not detected upon the second heating. However, at heating rates $\geq$50°Cmin^{-1}, the melting point of Form II is detected, which crystallizes into Form I before melting again (Fig. 11 (a)).

The behaviour of 4-MBA (5) was found to be influenced by varying the cooling rate (Fig. 11 (b)). At a lower cooling rate (1 to 5°Cmin^{-1}) only the melting endotherm of Form I is detected. However at a cooling rate of 10°Cmin^{-1} or more, the sample crystallizes into Form II and Form I. This is supported by HSM (Fig. 11 (c)) investigations which show the needle-dendritic morphology of Form I and the irregularly shaped cubic morphology of Form II. Form II melts at 193 ± 1°C and the melt is seeded by Form I crystals in close proximity, generating more Form I crystals which then melts at 213 ± 1°C.

Fig 11 here

DISCUSSION

The results obtained demonstrate that the molecular size of the amide substituents on the biphenyl scaffold cannot be correlated with any of the thermal properties investigated by means of TG and DSC. However, some interesting relationships were observed when positional isomerism is considered.

From the TG investigation it has been highlighted that the p-substituted biphenyl amides undergo two stage evaporation processes. These evaporation processes result from the melting of different crystalline forms of the compounds. However, only a single evaporation process is observed for the o-substituted biphenylamides. A comparison between the DTG peak temperature of the second evaporation process, observed for para-substituted biphenylamides, with that of the o-substituted biphenylamides show para-directing substitutions to improves the thermal stability of these compounds i.e. the o-substituted biphenylacetamide and biphenylcyclopropanecarboxamide have a DTG peak of evaporation at 322 and 341°C, respectively, whilst p-substituted biphenylacetamide and biphenylcyclopropanecarboxamide have DTG peak of evaporation at 331 and 347°C, respectively.

Whilst the calculated average activation energies for the samples may be considered similar, there are differences observed that are greater than their standard deviations (Table 2). When the two biphenylacetamides (4-MBA (1) and 4-MBA (3) are compared, it is found that the p-substitutions have higher activation energy of

evaporation (97 ± 12 $kJmol^{-1}$) than that observed for the o-substitution (75 ± 7 $kJmol^{-1}$). Similar behaviour is observed for the biphenylcyclopropanecarboxamides i.e. the para-substitutions exhibit higher activation energy (99 ± 24 $kJmol^{-1}$) when compared with the o-substitution (78 ± 5 $kJmol^{-1}$). This indicates that the p-substituted are more kinetically stable, as they exhibit higher activation energy barrier that must be overcome for the evaporation process to progress.

The reason for the differences observed in the thermal and kinetic stability between the o- and p-substitutions of these biphenyls is unclear. However it is inferred that such behaviour could be due to the difference in the ability of molecules to interact, which is influenced by attractive/repulsive forces and the spatial arrangements of the molecules in the liquid state.

When the melting peak temperature of the highest melting forms (Form I) are compared, p-substituted biphenylamides generally exhibit higher thermo-physical stability i.e. the temperature of their Form I crystals are higher than those of o-substituted biphenylamides. This is due to better molecular stacking ability of p-substitution compared to o- substituted compounds. Similar observations could not be made when the enthalpies (Jg^{-1}) of the melts are considered. Hence the energy required to convert Form I, of the biphenylamide derivatives studied, to liquid does not seem to be correlated with positional isomerism or molecular size.

It appears that it is possible to differentiate the polymorphic behaviour of o- from p-substitutions. The o-substituted biphenylamides seem to have the tendency to generate metastable forms upon cooling the neat liquid, that converts to the more stable forms i.e. they undergo solid-solid transitions into the more stable form on heating. The p-substituted biphenylamides, on the other-hand, crystallize into two forms that melt upon heating.

An aspect of this study was to probe the notion that the Z' value (the number of molecular formula unit within a unit cell) has some influence on the number of possible crystal forms/transformation that can be found. It was therefore of interest to examine the relationship between the number of polymorphic transformations detected and the Z' value. In the previous study, compounds 4-MBA (3) and 4-MBA (5) were found to generate crystals with the highest Z' values (> 1) of the biphenylamide compounds synthesised [6]. This suggest that these two compounds should exhibit greater degree of polymorphism i.e. they can undergo a greater number of crystalline

arrangements, when compared with 4-MBA (1), 4-MBA (2) and 4-MBA (4), all of which have Z' values of 1. The results obtained, however, demonstrate that this is not the case when thermotropic polymorphism is of concern. With the exception of 4-MBA (4), which did not exhibit any thermotropic transition/conversions, all compounds exhibit at least two thermotropic phases regardless of the Z' values. However, compound 4-MBA (3) which was found in previous study to exhibit the unusual Z' value of 6 was found to demonstrate highly unusual, highly energetic crystallization process, which causes the sample's temperature to be raised by >3°C during cooling. The relatively high energy associated with the crystallization of compound 4-MBA (3) is likely due to the higher number of molecular formula units (6 molecules) condensing and forming hydrogen bonding within a single asymmetric unit cell.

CONCLUSIONS

This investigation has demonstrated that the 4-methyl-biphenyl derivatives studied undergo thermotropic polymorphism, in which at least two crystal forms are detected with the exception of N-(4'-methylbiphenyl-4-yl)benzamide (4-MBA (4)), which melts at 227 ± 1°C. N-(4'-methylbiphenyl-3-yl)acetamide (4-MBA (1)) has two thermotropic polymorphic forms, Form II melts at 36 ± 1°C, crystallizes at 141 ± 2°C into Form I which melts at 149 ± 1°C. N-(4'-Methylbiphenyl-3-yl)cyclopropanecarboxamide (4-MBA (2)) crystallizes into Form II when the melt is cooled at $\geq$100°Cmin^{-1}. Form II converts at 52 ± 1°C into Form I which melts at 195 ± 1°C. Three polymorphic forms were found for N-(4'-Methylbiphenyl-4-yl)acetamide (4-MBA (3)). For this compounds Form II melts at 203 ± 1°C, Form I (melts at 224 ± 1°C) and Form I_b melts at 222 ± 1°C. N-(4'-Methylbiphenyl-4-yl)cyclopropanecarboxamide (4-MBA (5)) also exhibits three polymorphic forms in which Form III melts at 98 ± 1°C, Form II at 193 ± 1°C and Form I at 213 ± 1°C.

The results presented show that it is possible to correlate certain parameters of thermal properties of materials with positional isomerism. For the 4-methyl-biphenylamide derivatives studied, it was found that the thermo-physical stability is significantly enhanced when the amide substituent is directed in the para- position as opposed to the ortho position of the 4-biphenyl scaffold. For example, the kinetic stability of the evaporation process of these compounds is improved by steering the amide substituents in the para position. Furthermore the ortho-substituted 4-methyl-biphenylamides are more likely to generate metastable forms during crystallization from the melt. On the other hand, p-substitution of the amides on the 4-methyl-biphenyl scaffold generates materials with highly energetic crystallization process that raises the sample temperature during cooling, even at

a cooling rate of 10°Cmin^{-1}, a phenomenon that was not observed for the o-substituted amides at the same cooling rate. The material that demonstrates the most energetic crystallization process is N-(4'-methylbiphenyl-4-yl)acetamide (4-MBA (3)). Such high energy exothermic crystallization process suggests crystallization to be highly favourable, from a thermodynamic stand point. Hence the p-substituted 4-methyl-biphenylamide derivatives are unlikely to generate amorphous forms.

It was not possible to correlate molecular size with any of the parameters associated with the thermal properties of the biphenyl derivatives studied. Perhaps this is due to the fact that molecular size differences investigated are not great enough to generate any observable differences.

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14. Burger A, Ramberger R. On the polymorphism of pharmaceuticals and other molecular crystals. II. Microchimica Acta 1979; 72(3): 273-316.

Figure

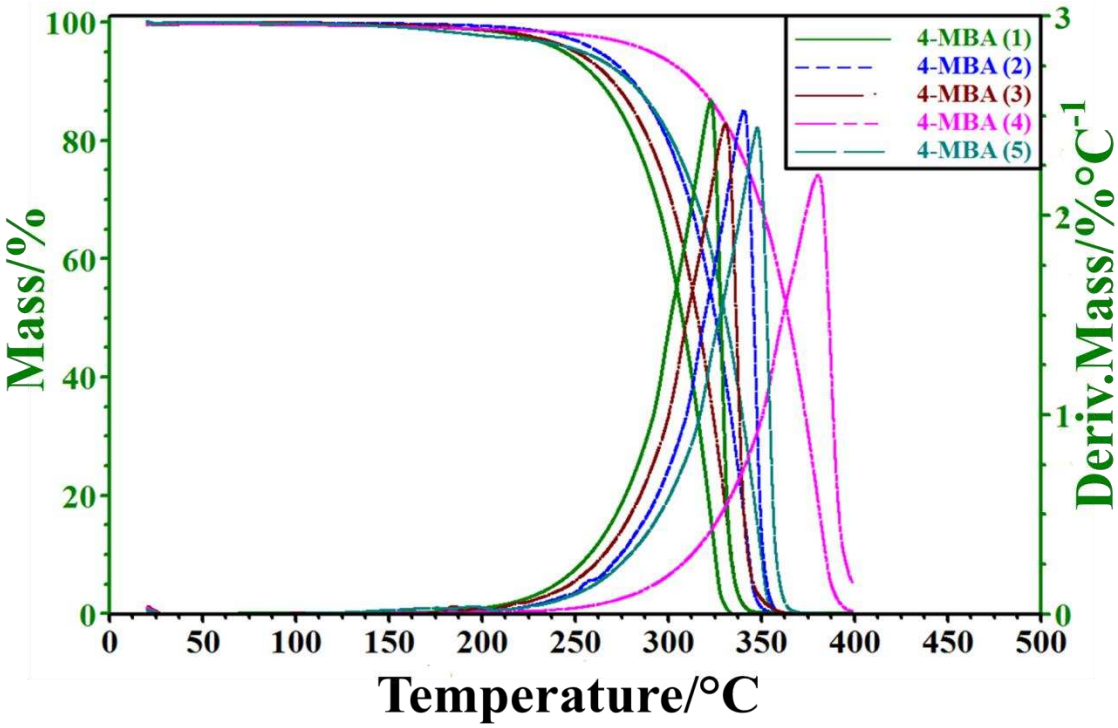


Fig. 1. TG and DTG curves obtained for the 4-methyl-biphenylamide derivatives in a standard TG experiments. Samples were heated from ambient temperature to 400°C at 10°Cmin^{-1}.

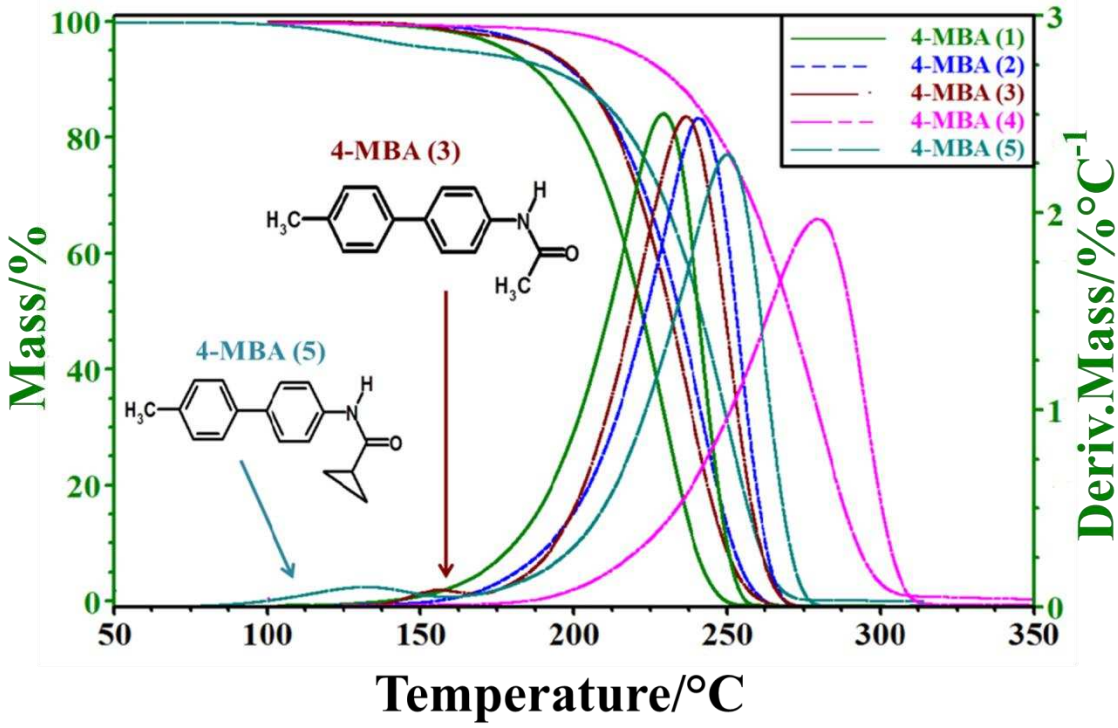


Fig. 2. TG and DTG curves obtained for the 4-methyl-biphenylamide derivatives in modulated TG experiment. Samples were heated from 100°C (with the exception of 4-MBA 5, which was equilibrated at 50°C) to 350°C at a modulation settings of +/-5°C amplitude for a period of 200 s with an underlying heating rate of 5°°Cmin^{-1}.

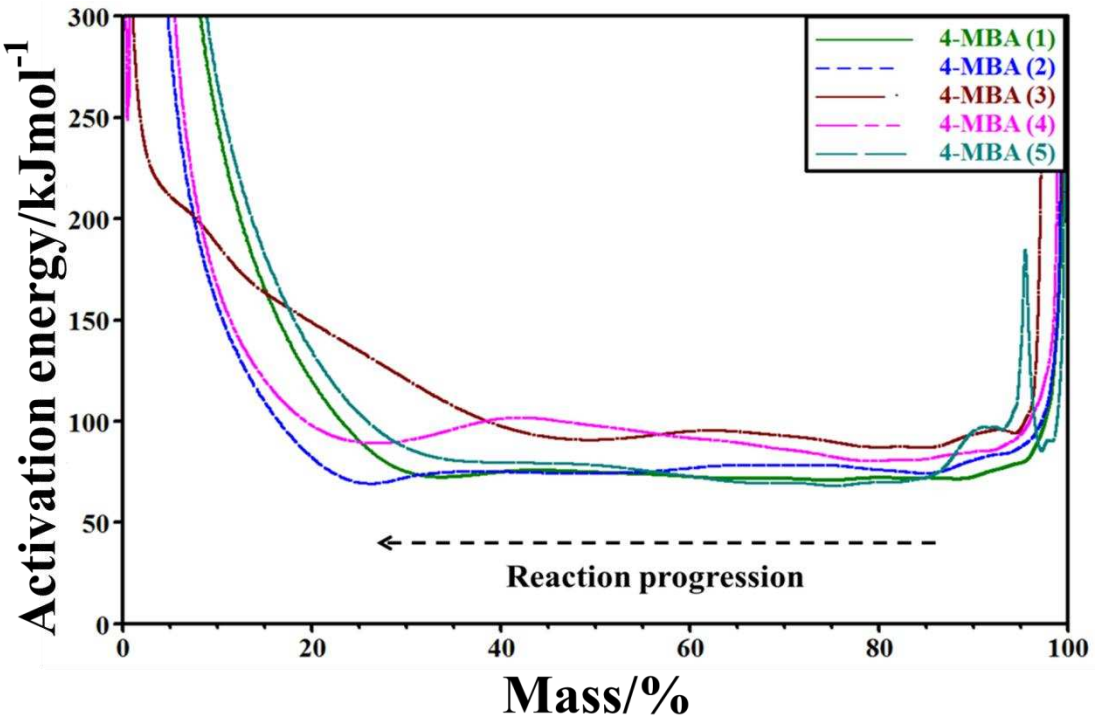


Fig. 3. Activation energies obtained from MTG experiments as a function of change in mass of the 4-methyl-biphenylamide derivatives.

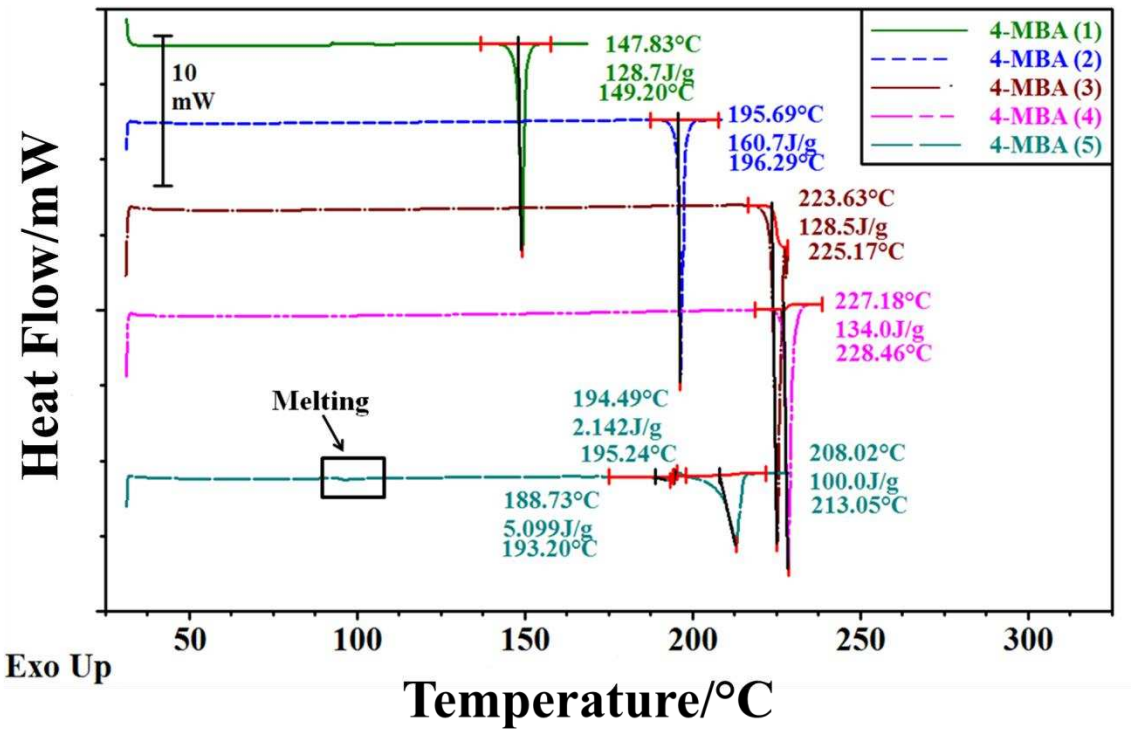


Fig. 4. DSC curve overlay of the initial heating of the 4-methyl-biphenylamide derivatives obtained at a heating rate of 10°Cmin^{-1}.

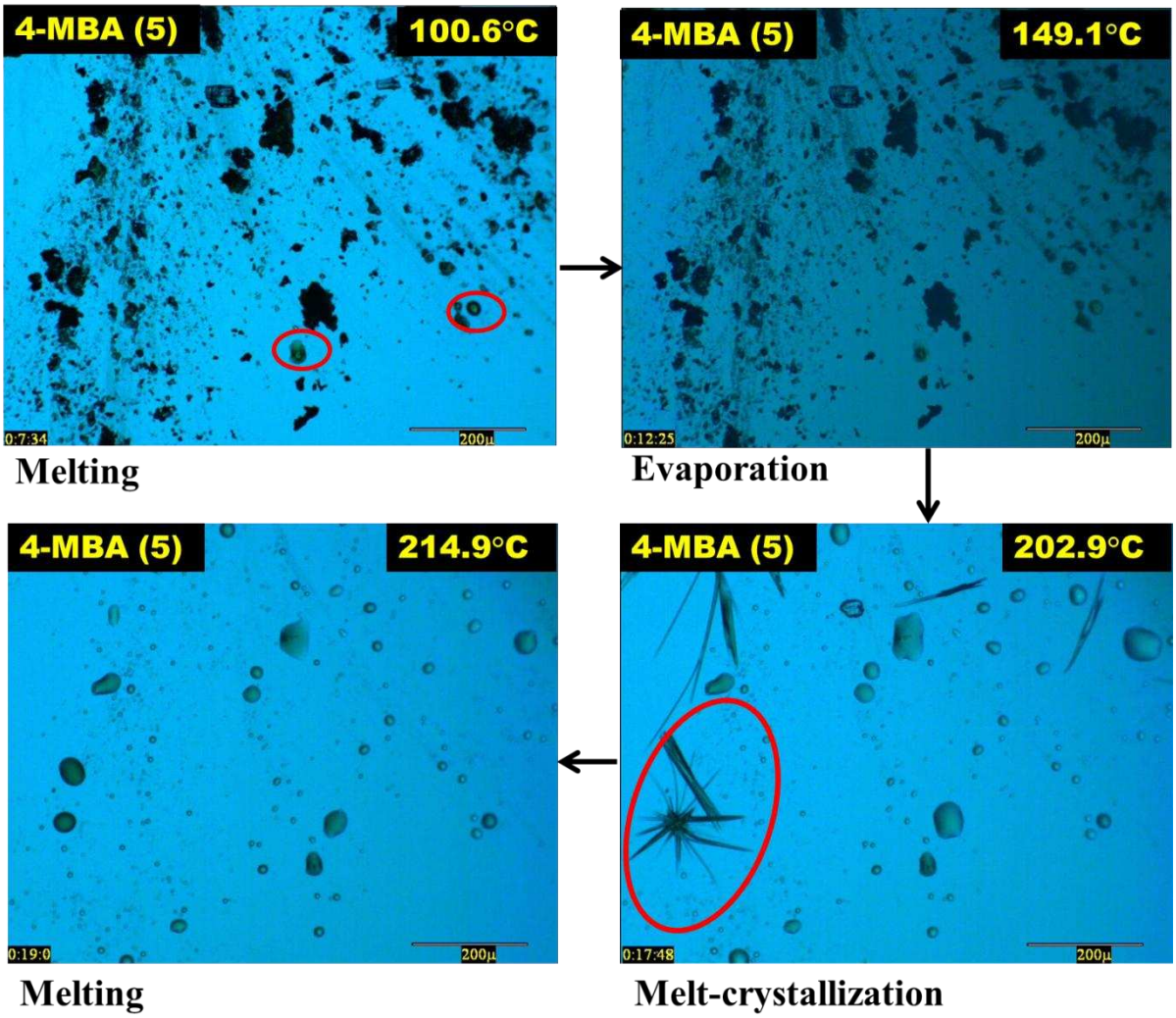


Fig. 5. HSM images of 4-MBA (5) heated from 25°C to 250°C at 10°Cmin^{-1}.

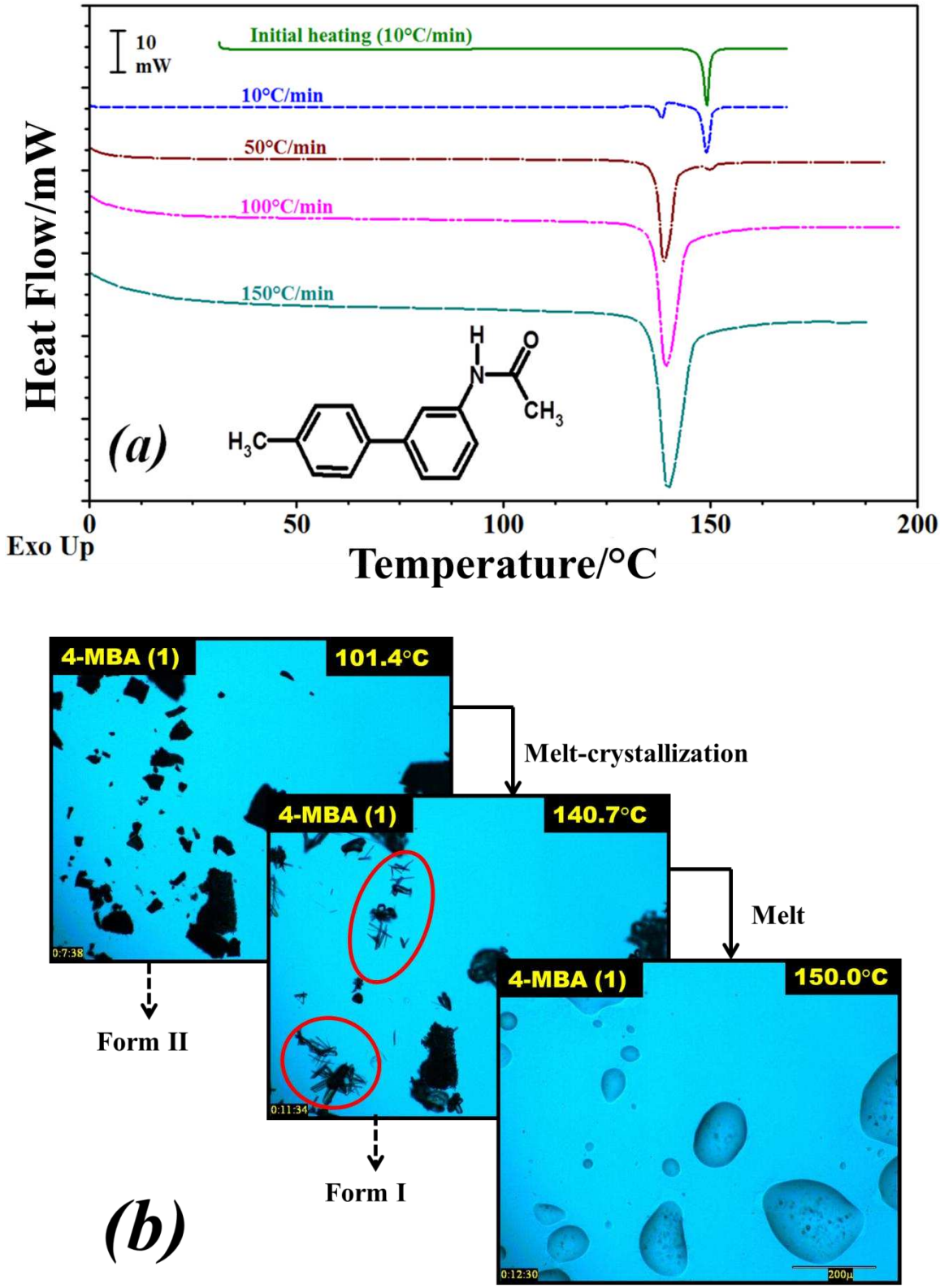
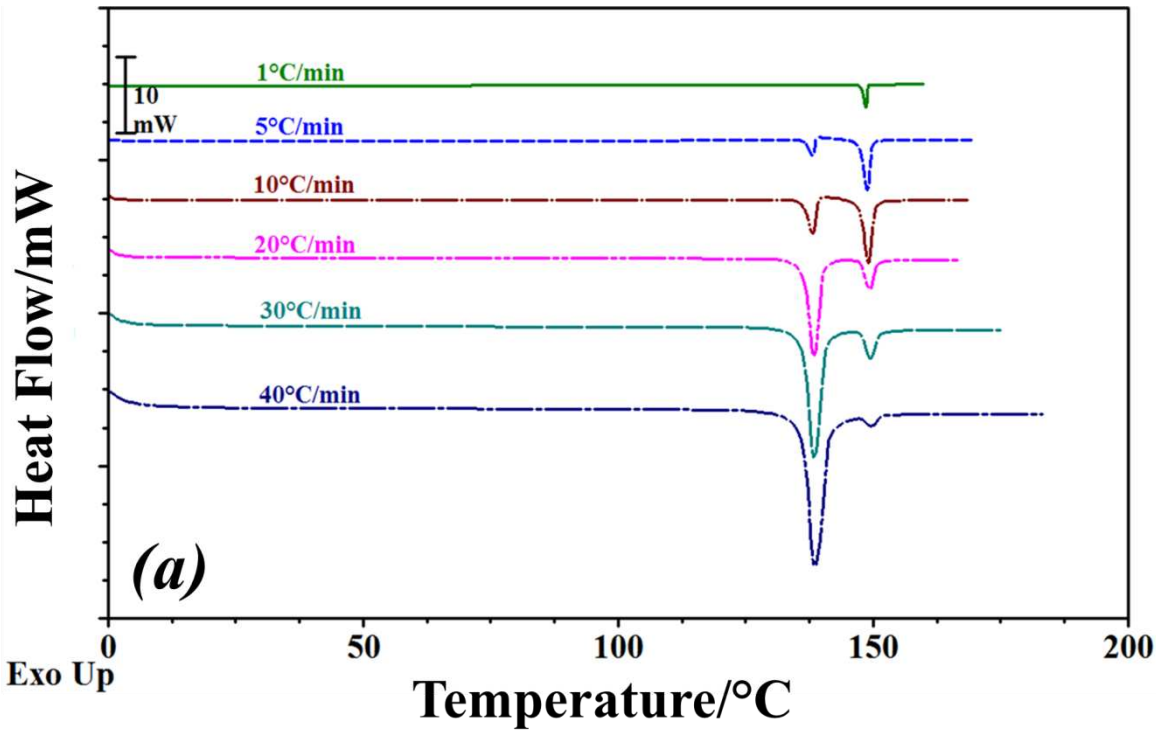
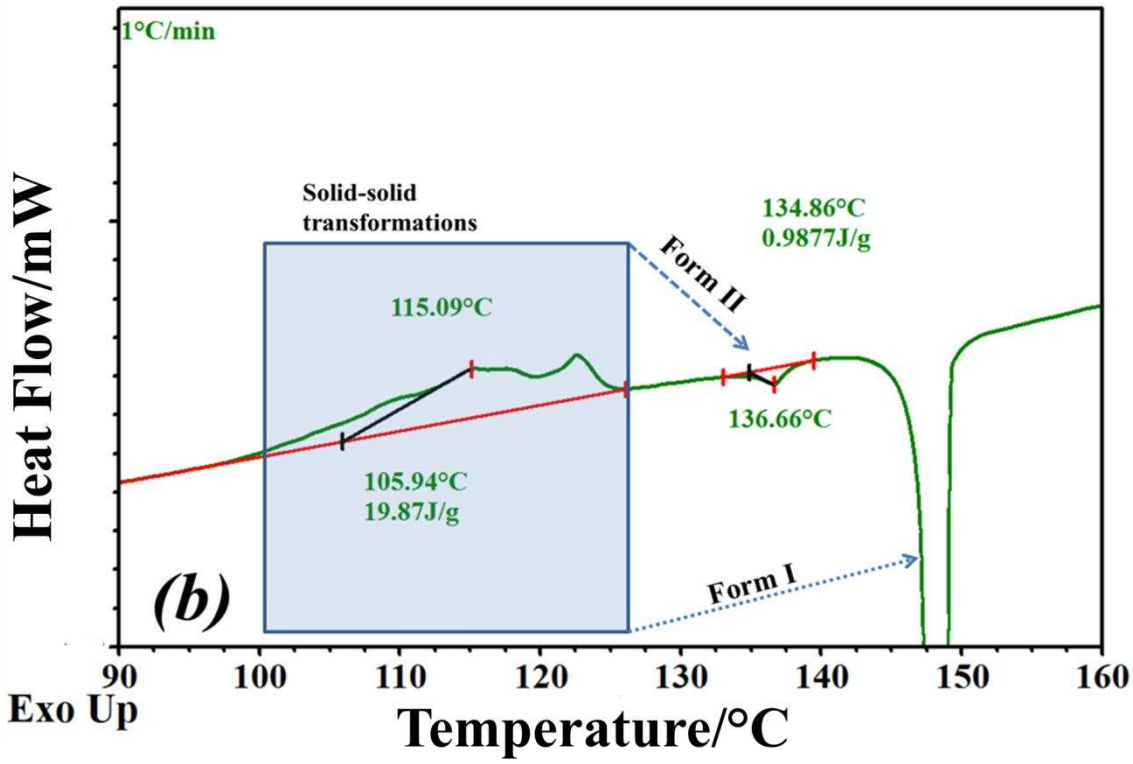


Fig. 6 (a) DSC curve overlay of 4-MBA (1) heated at various heating rates after cooling at a rate of 10°Cmin^{-1} and (b) HSM images of key transitions observed for 4-MBA (1) when heated at 10°Cmin^{-1} between 25 and 170°C. Starting material (Form II) was prepared by melting the initial sample and cooling over liquid nitrogen before being examined by HSM.


1°C/min
10
mW
5°C/min
10°C/min
20°C/min
30°C/min
40°C/min
Heat Flow/mW
(a)
0
50
100
150
200
Exo Up
Temperature/°C


1°C/min
Solid-solid
transformations
134.86°C
0.9877J/g
Form II
115.09°C
136.66°C
105.94°C
19.87J/g
Form I
(b)
Heat Flow/mW
90
100
110
120
130
140
150
160
Exo Up
Temperature/°C

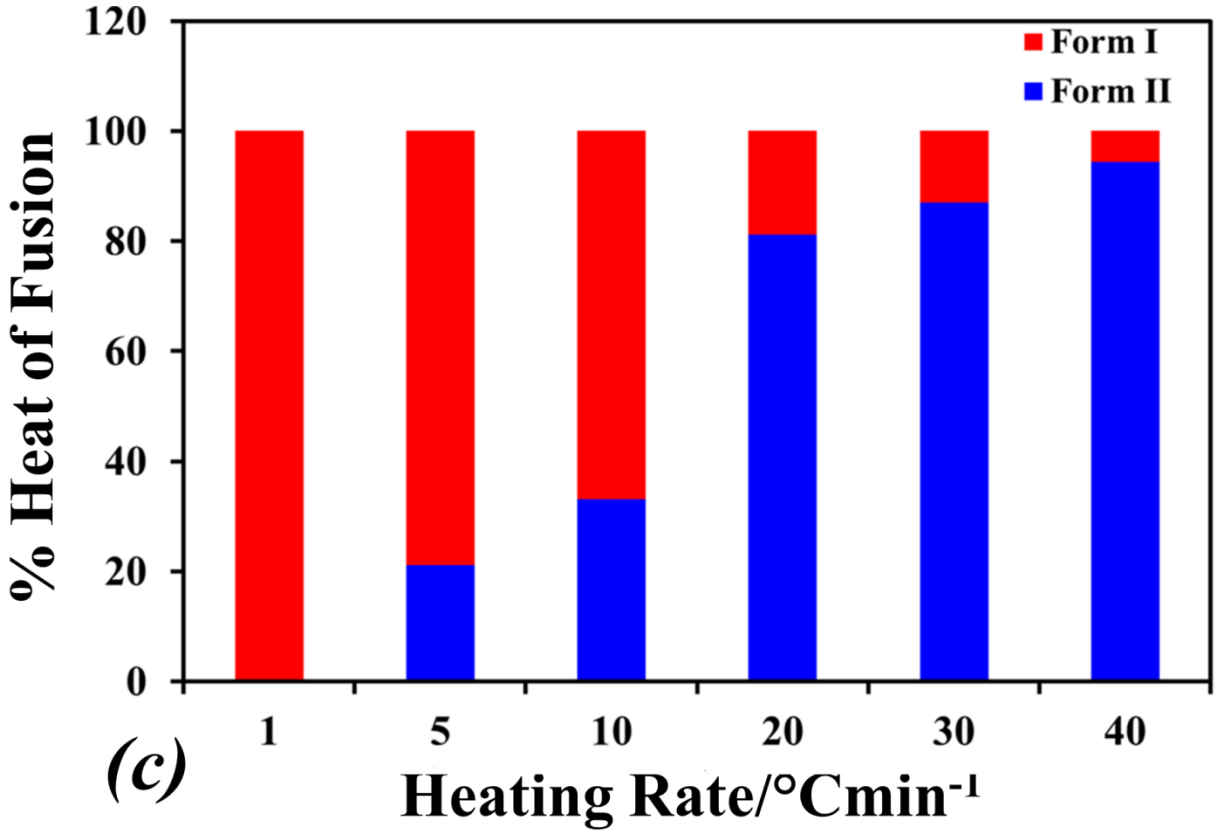
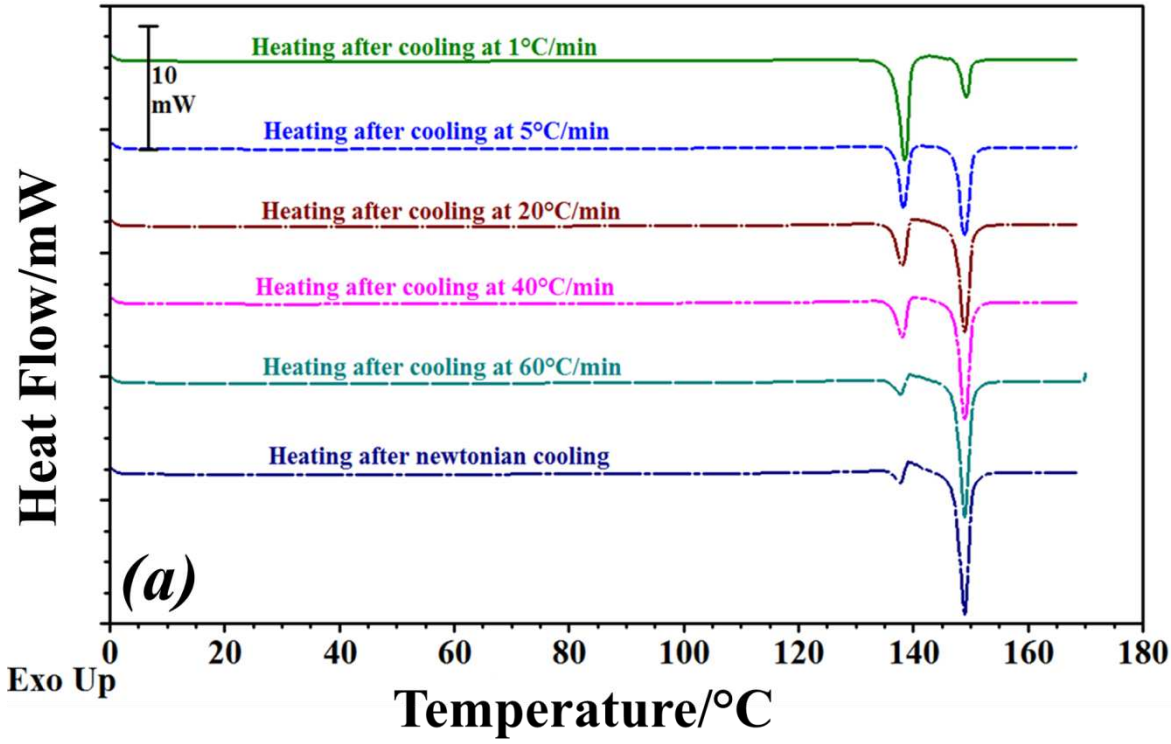
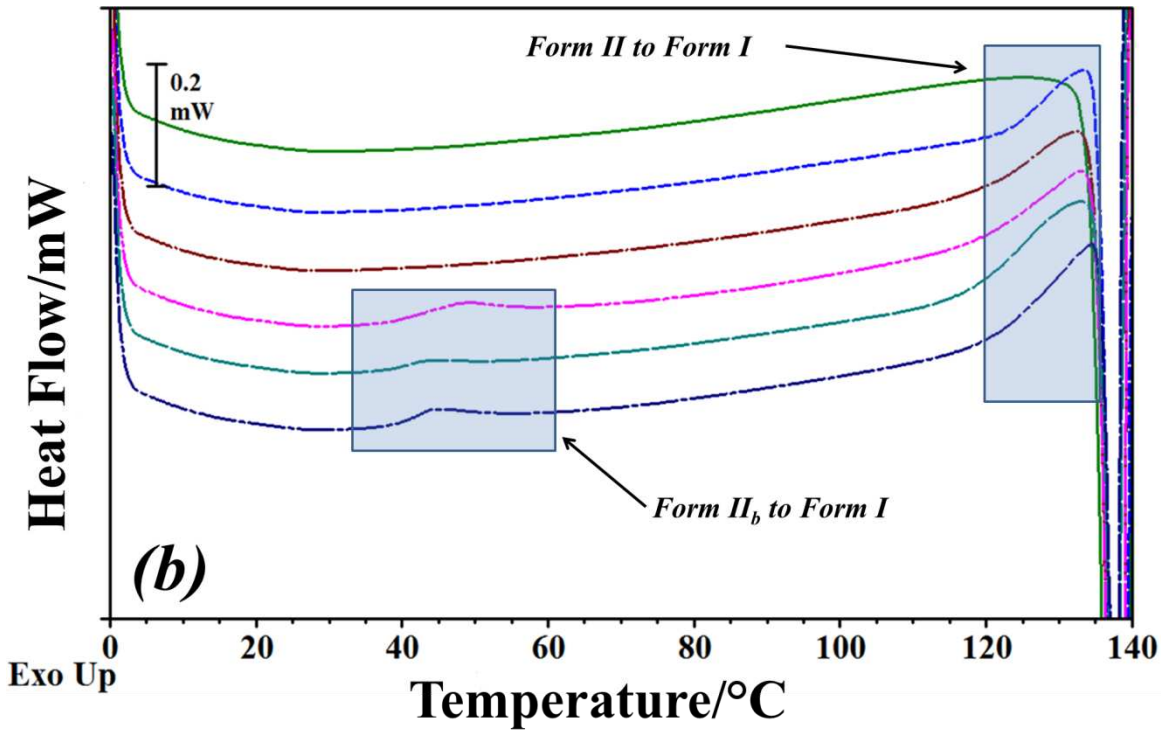
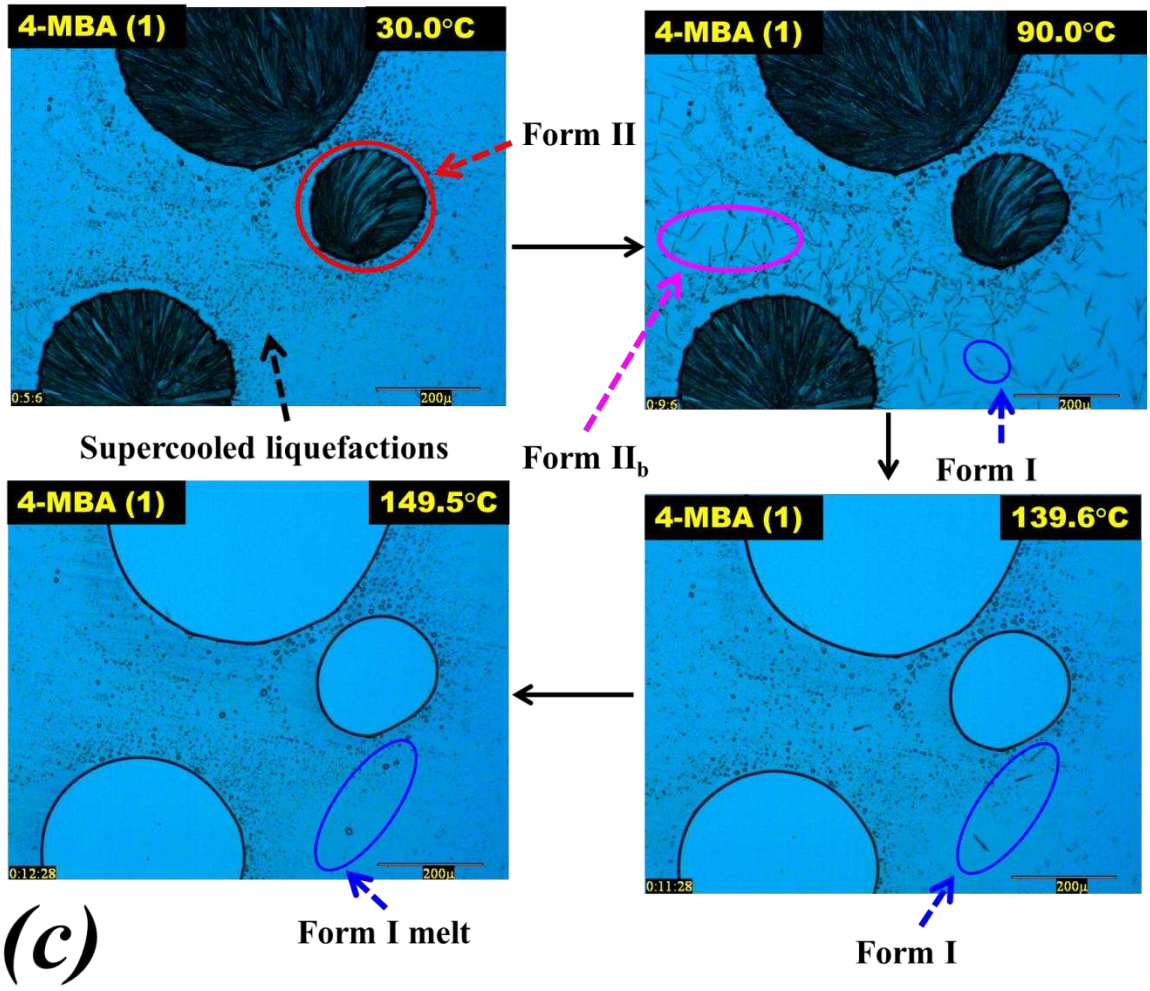


Fig. 7. (a) DSC curve of 4-MBA (1) at different heating rates (1 to 40°Cmin^{-1}) after cooling at 10°Cmin^{-1}, (b) expanded area of the DSC curve obtained at 1°°Cmin^{-1} heating rate and (c) the fractional contribution of the heat of fusion of Form II and Form I to the total heat of fusion as a function of heating rate.


Heating after cooling at 1°C/min
10 mW
Heating after cooling at 5°C/min
Heating after cooling at 20°C/min
Heating after cooling at 40°C/min
Heating after cooling at 60°C/min
Heating after newtonian cooling
(a)
Heat Flow/mW
Exo Up
0
20
40
60
80
100
120
140
160
180
Temperature/°C


Form II to Form I
0.2 mW
Form II$_b$ to Form I
(b)
Heat Flow/mW
Exo Up
0
20
40
60
80
100
120
140
Temperature/°C


4-MBA (1)
30.0°C
Form II
Supercooled liquefactions
4-MBA (1)
90.0°C
Form II$_b$
Form I
4-MBA (1)
149.5°C
Form I melt
4-MBA (1)
139.6°C
Form I
(c)

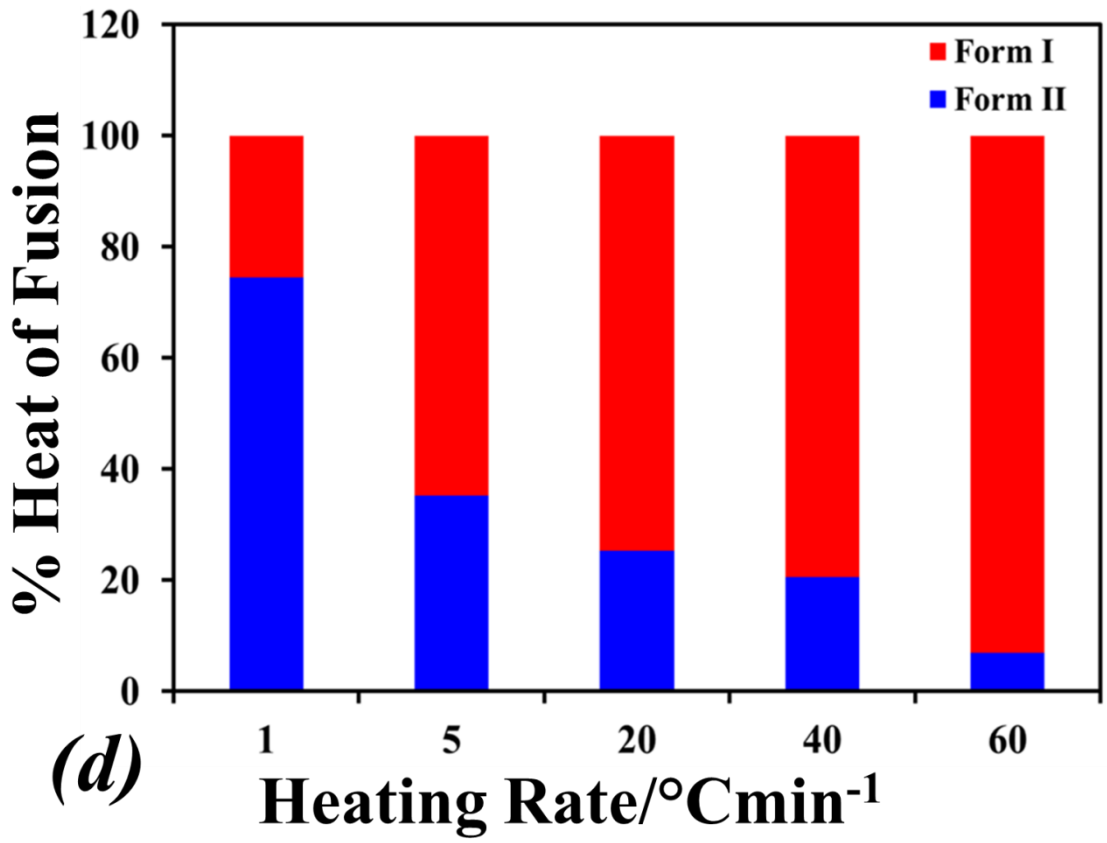
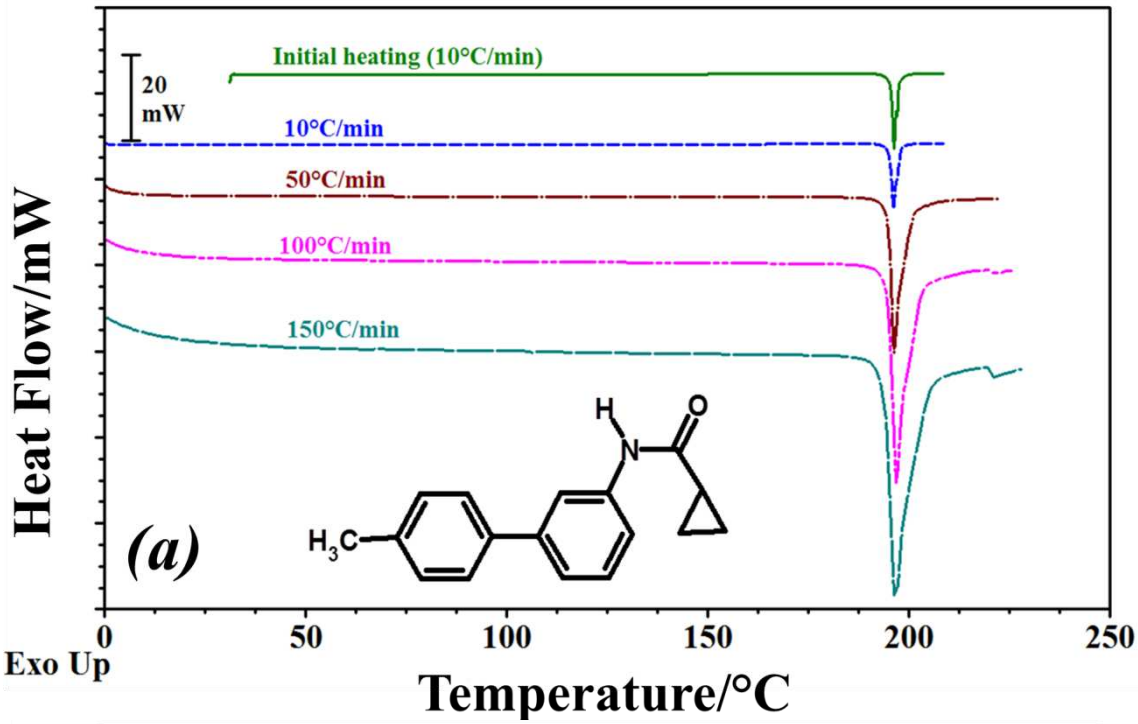
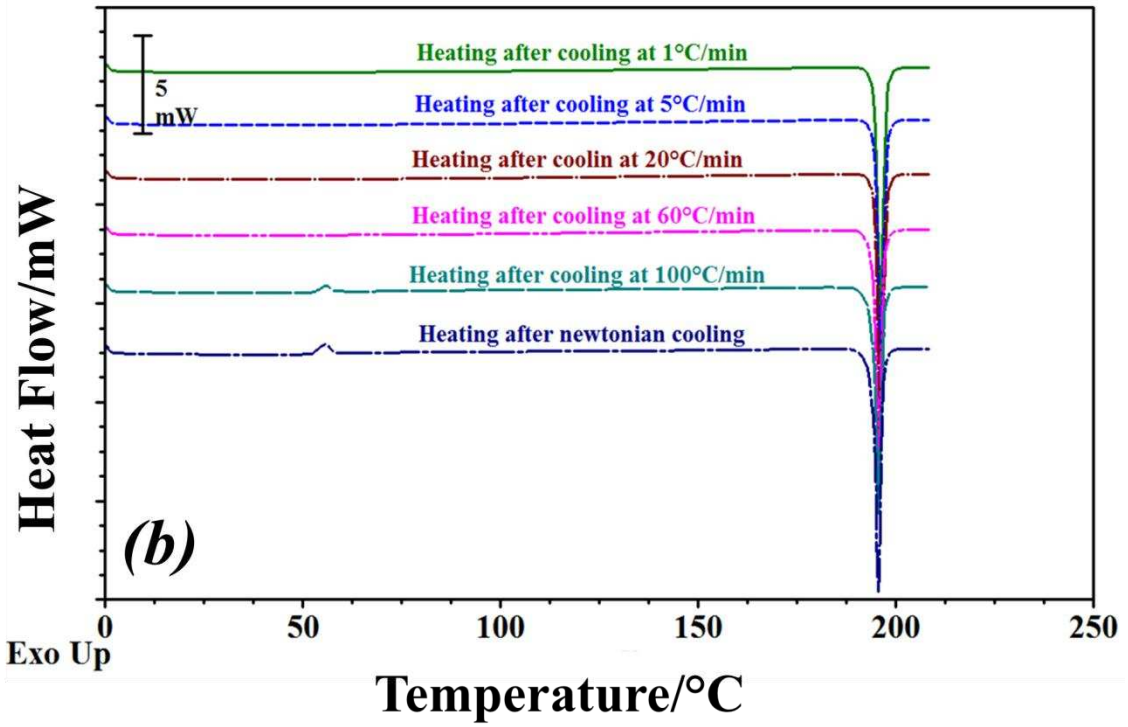


Fig. 8. (a) DSC curve of 4-MBA (1) obtained at a heating rate of 10°Cmin^{-1} after cooling at various rates (see graph for details), (b) expanded area of the DSC curve obtained at different heating rates, (c) HSM images of key transitions observed for 4-MBA (1) when heated at 10°Cmin^{-1} between 25 and 170°C after Newtonian cooling of the melt and (d) the fractional contribution of the melting enthalpies of Form II and Form I to the total heat of fusion as a function of cooling rate.


Initial heating (10°C/min)
20 mW
10°C/min
50°C/min
100°C/min
150°C/min
H
O
N
H3C
(a)
Heat Flow/mW
Exo Up
0
50
100
150
200
250
Temperature/°C


Heating after cooling at 1°C/min
5 mW
Heating after cooling at 5°C/min
Heating after coolin at 20°C/min
Heating after cooling at 60°C/min
Heating after cooling at 100°C/min
Heating after newtonian cooling
(b)
Heat Flow/mW
Exo Up
0
50
100
150
200
250
Temperature/°C

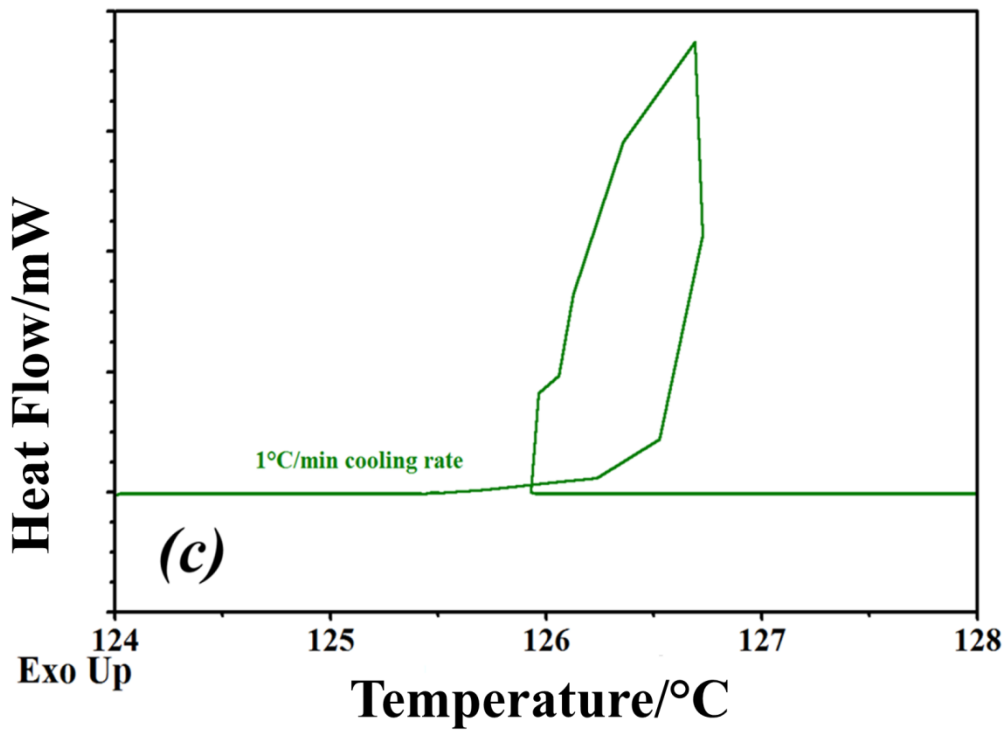
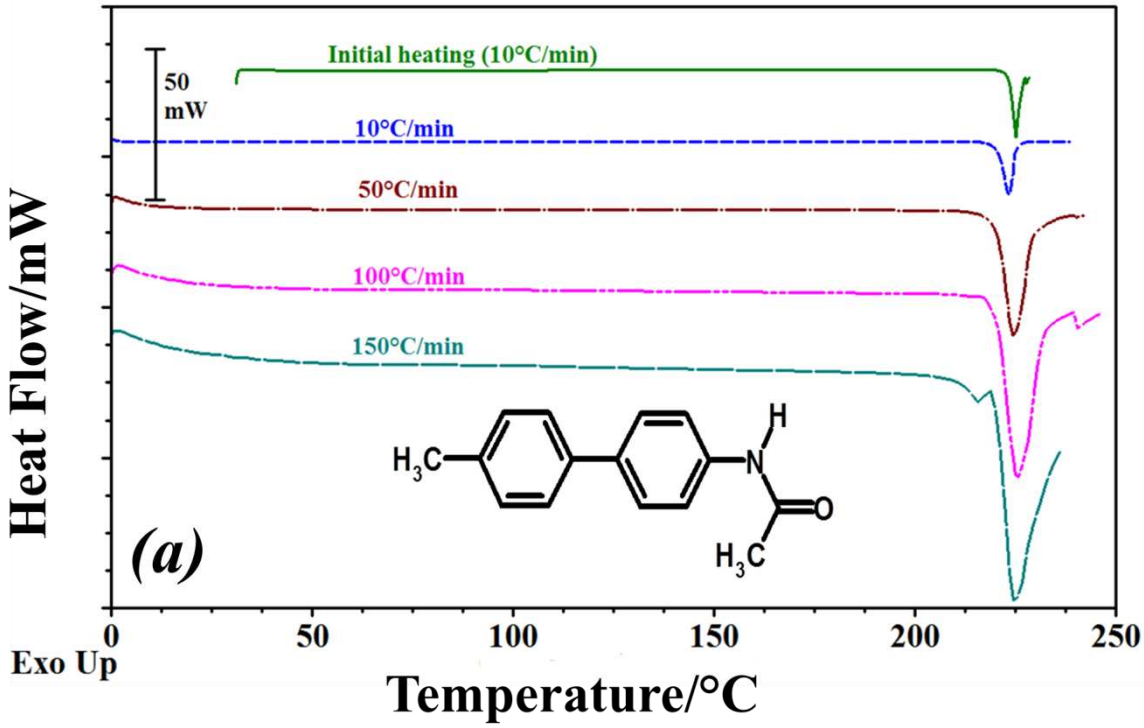
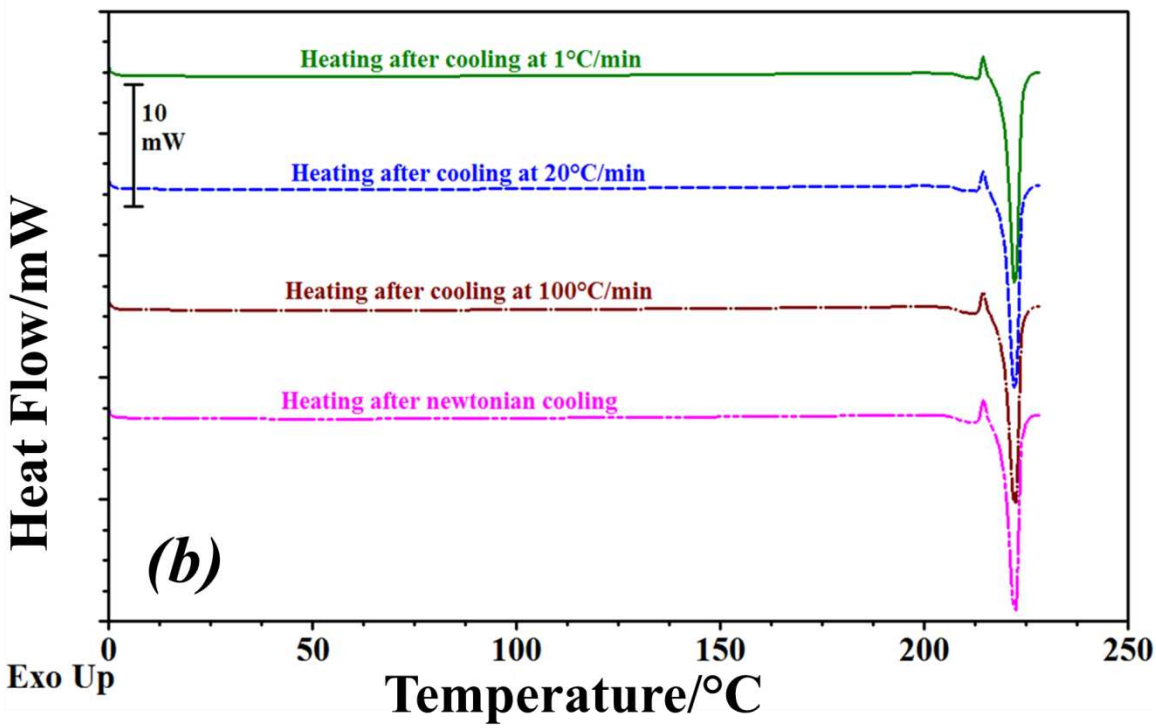


Fig. 9. (a) DSC curves of 4-MBA (2), (a) at various heating rates after cooling at 10°Cmin^{-1}, (b) at a heating rate of 10°Cmin^{-1} after cooling at various cooling rates (see graph for details) and (c) expanded area of the DSC curves obtained at a cooling rate of 1°Cmin^{-1}.





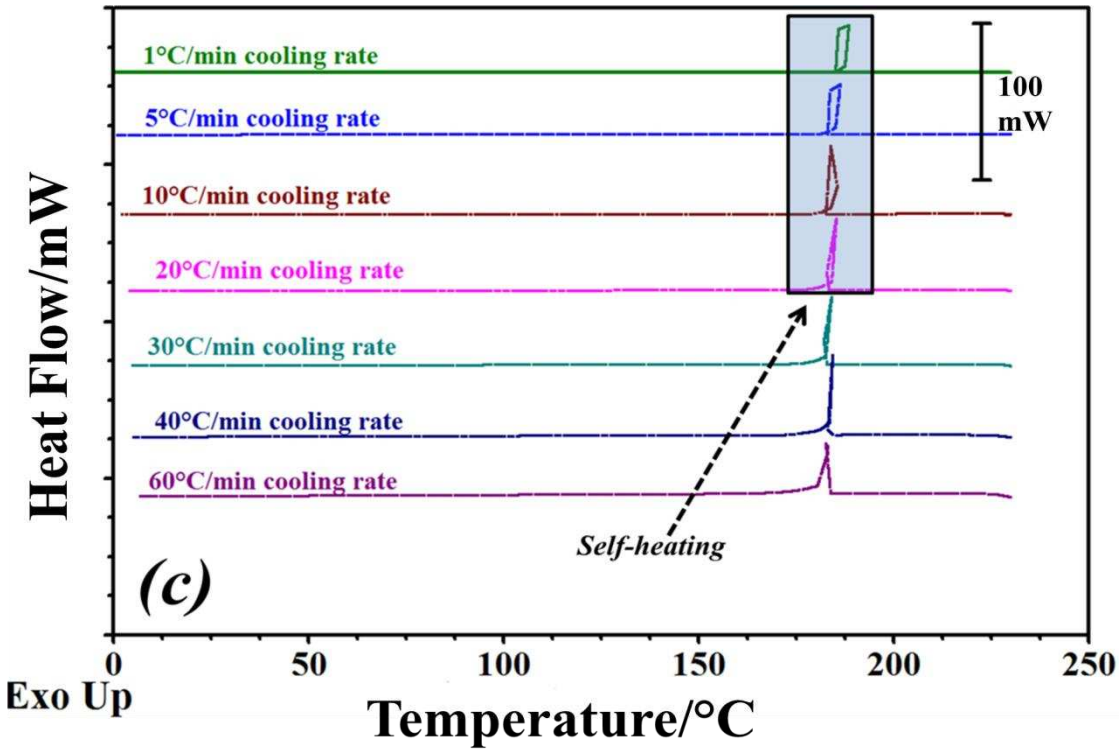
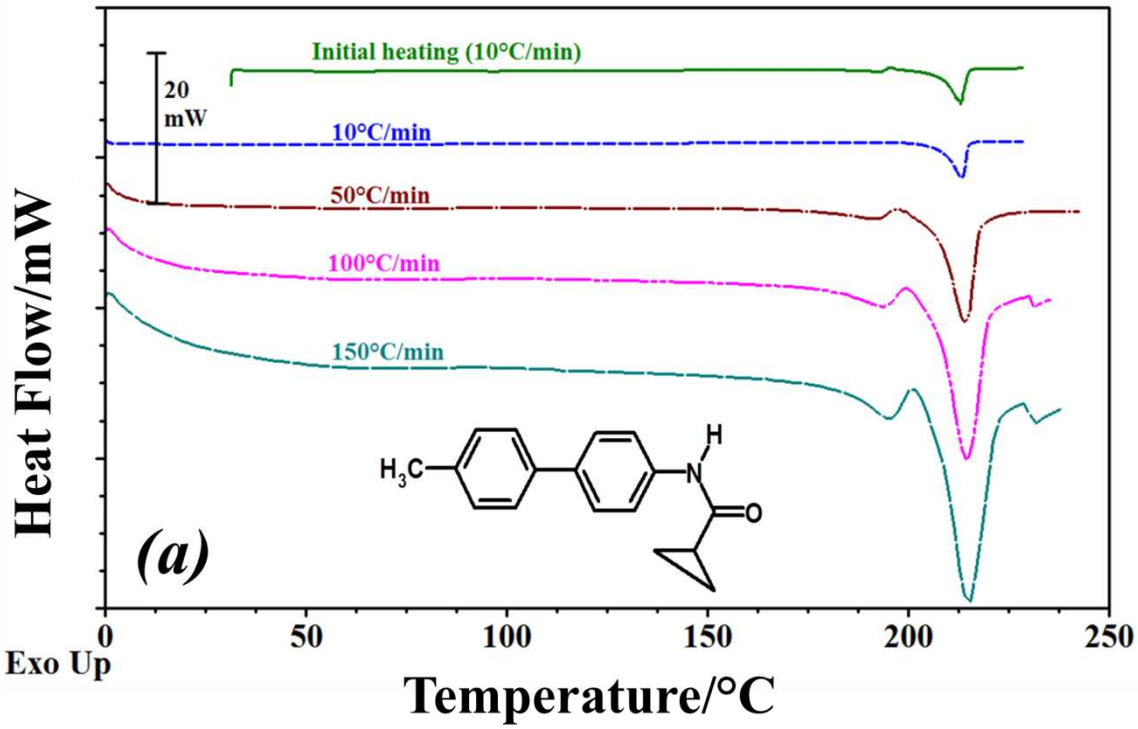
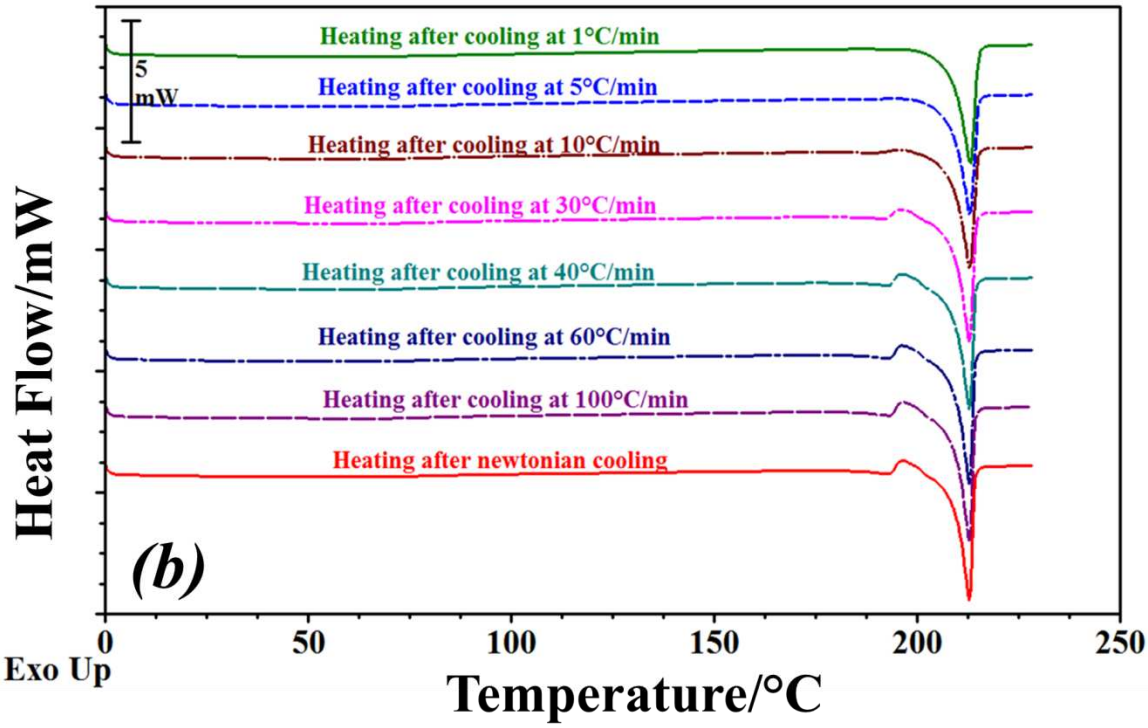


Fig. 10. (a) DSC curves of 4-MBA (3), (a) at various heating rates after cooling at 10°Cmin^{-1}, (b) at a heating rate of 10°Cmin^{-1} after cooling at various cooling rates and (c) DSC curves obtained at different cooling rates.


Initial heating (10°C/min)
20 mW
10°C/min
50°C/min
100°C/min
150°C/min
H3C
H
N
O
(a)
Heat Flow/mW
Exo Up
0
50
100
150
200
250
Temperature/°C


Heating after cooling at 1°C/min
5 mW
Heating after cooling at 5°C/min
Heating after cooling at 10°C/min
Heating after cooling at 30°C/min
Heating after cooling at 40°C/min
Heating after cooling at 60°C/min
Heating after cooling at 100°C/min
Heating after newtonian cooling
(b)
Heat Flow/mW
Exo Up
0
50
100
150
200
250
Temperature/°C

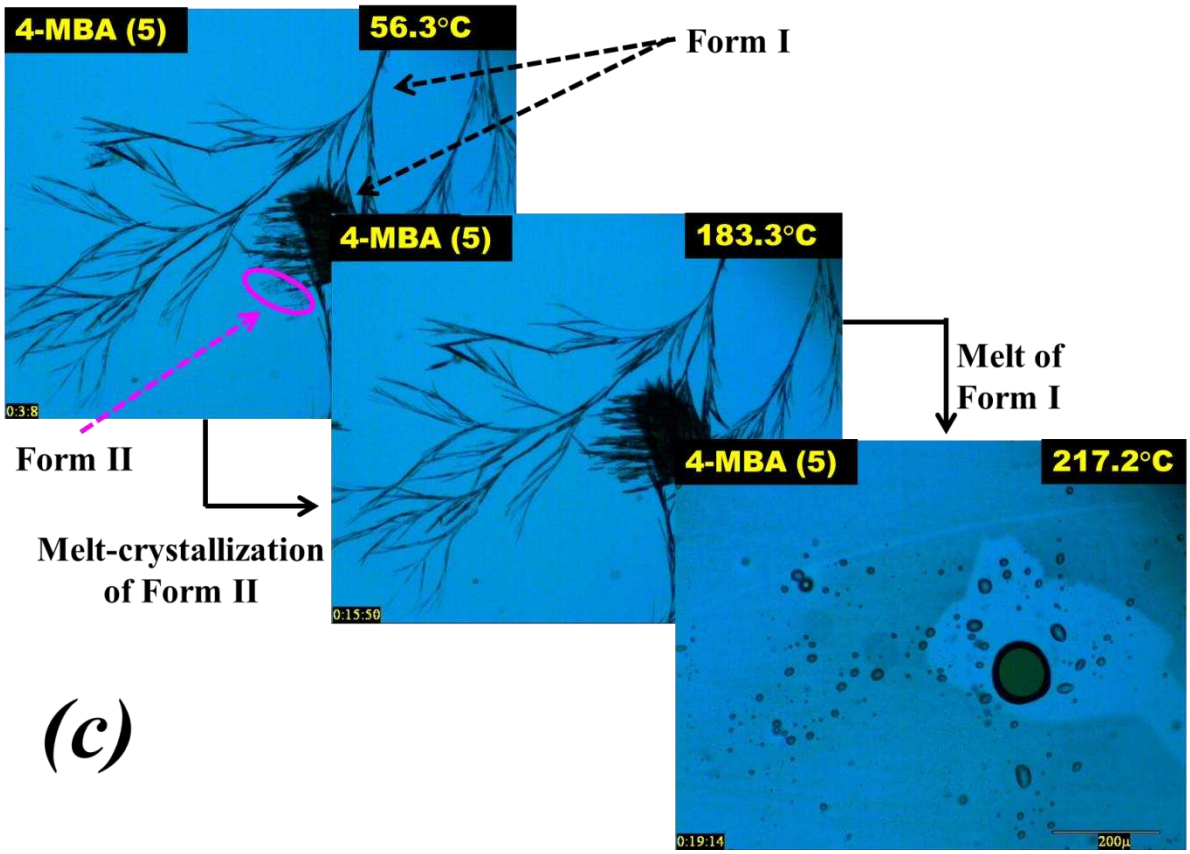


Fig. 11. (a) DSC curves of 4-MBA (5) obtained at different heating rates after cooling at 10°Cmin^{-1}, (b) at a heating rate of 10°Cmin^{-1} after cooling at various cooling rates and (c) HSM images of key transitions observed for 4-MBA (5) when heated at 10°Cmin^{-1} between 25 and 250°C after Newtonian cooling of the melt in the HSM.

Table 1. Molecular structures of the 4-methyl-biphenylamide derivatives.

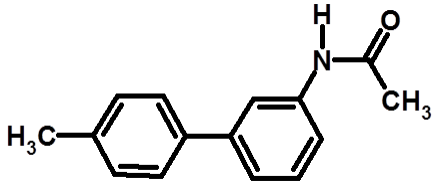
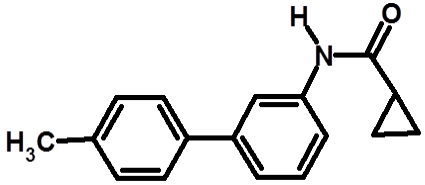
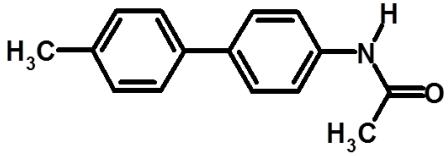
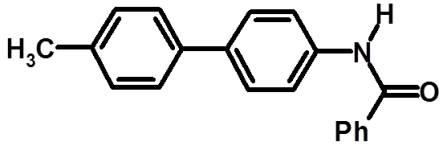
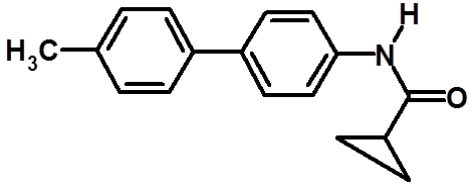
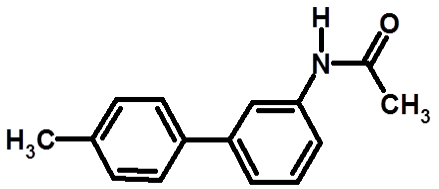
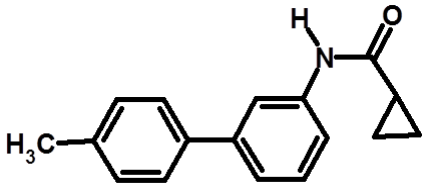
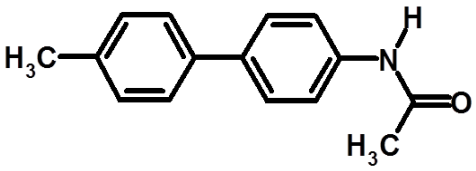
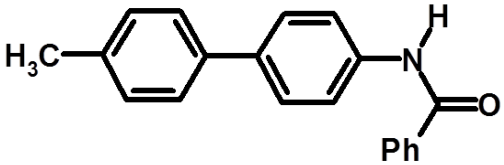
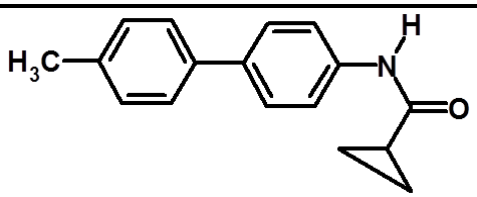
Sample ID	Sample name	Baltus et al, (2012) compound reference	Molecular structure
4-MBA (1)	**N-(4'-Methylbiphenyl-3-yl)acetamide**	**(6i)**	
4-MBA (2)	**N-(4'-Methylbiphenyl-3-yl) cyclopropanecarboxamide**	**(6h)**	
4-MBA (3)	**N-(4'-Methylbiphenyl-4-yl)acetamide**	**(6b)**	
4-MBA (4)	**N-(4'-Methylbiphenyl-4-yl)benzamide**	**(6e)**	
4-MBA (5)	**N-(4'-Methylbiphenyl-4-yl)cyclopropanecarboxamide**	**(6a)**	

Table 2. Fractional weight changes (ΔW (%)) and peak temperatures for processes detected by TG for the 4-methyl-biphenylamide derivatives.

	1st process		2nd Process		Total
Sample	**ΔW/%**	**Peak temperature/°C**	**ΔW/%**	**Peak temperature/°C**	**ΔW/%**
4-MBA (1)	100	322 ± 1	-	-	100
4-MBA (2)	100	341 ± 1	-	-	100
4-MBA (3)	100	331 ± 1	-	-	100
4-MBA (4)	100	380 ± 1	-	-	100
4-MBA (5)	2.5 ± 0.3	194 ± 1	98 ± 0.5	347 ± 1	100

Table 3. Apparent activation energies (n = 2) obtained for the 4-methyl-biphenylamide derivatives using MTG.

Sample	Structure	E_a (kJmol^{-1})
4-MBA (1)		**75 ± 7**
4-MBA (2)		**78 ± 5**
4-MBA (3)		**97 ± 12**
4-MBA (4)		**90 ± 8**
4-MBA (5)		**99 ± 14**