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Re-examination of Microwave-Induced Synthesis of Phthalimides

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Abstract—Solvent-free microwave reactions between phthalic anhydride and amino compounds need at least one liquid phase. The reaction occurs after melting of anhydride and subsequent solubilisation in amines. So, reactions between two solids may not take place and need the use of a high boiling point solvent. In all cases, excellent yields are obtained within short reaction times with products of high purity. © 2000 Elsevier Science Ltd. All rights reserved.

Imide derivatives constitute an important class of organic compounds with numerous uses in biology,[1] synthetic[2] and polymer chemistry.[3] Despite their wide applicability, available routes for their synthesis are limited. Generally most methods involve Lewis acid mediated condensation of an amine with maleic or phthalic anhydrides.[4] These methods are limited by low yields, by-product formation and harsh reaction conditions.[5]

Substantial improvements in amine additions to carbonyl compounds have been described using microwave (MW) irradiation[6] and this technique has been used in the one-pot synthesis of phthalimides by the condensation of functionalised amines with maleic or phthalic anhydride using a domestic microwave oven.[7a,8,9] Bose et al.[7a] reported that *N*-phthalimides of amino acids could be synthesized in good yields within few minutes by the microwave-assisted reaction of phthalic anhydride with amino acids in DMF. In contrast, these reactions had been carried out conventionally by refluxing the reagents in toluene for 1.5 h.[7b] It was concluded that the large rate enhancement was not only due to thermolysis implying that a specific (non-thermal) microwave effect was involved. The reaction of phthalic anhydride with glycine was later re-examined by Westaway and Gedye,[8] who found that the rate of the reaction was actually the same when carried out by MW or conventional heating in DMF at the same temperature. Hence it was concluded that the rate increase observed by Bose was due to a change in solvent and temperature when DMF was substituted for toluene.

Recently, a solvent-free procedure using $TaCl_5$–silica gel as catalyst has been described for the preparation of imides under microwave irradiation.[10]

Finally, Sandhu et al.[9] advocated the use of a more eco-friendly solvent-free system involving the reaction of equal amounts of anhydride and amines or amino acids in the absence of solvent in a domestic oven without any catalyst. In the case of the reaction of the anhydride with amino acids, a reaction between two solids was involved, for example between phthalic anhydride and glycine (Scheme 4). Unfortunately, no temperature measurements were reported.

These results are unexpected since no liquid phase was present. This prompted the present re-examination of the reaction using a monomode reactor with focused microwaves[11,12] and accurate temperature monitoring. To investigate the possibility of specific (non-thermal) effects, the microwave activated reactions would then be compared with similar reactions using conventional heating strictly under the same conditions.[13,14] Special attention would be given to:

(i) *The effect of the physical state of the reactants* by using phthalic anhydride (mp 131–134°C) and several amino compounds either liquid (benzylamine) or solids with low melting point (6-amino-1-hexanol, mp 56–58°C; *n*-octadecylamine, mp 55–57°C) where a liquid phase would be present, or with a rather high melting point (Glycine, mp 240°C) where no liquid phase would be expected.
(ii) *The possibility of intervention of specific MW effects*, by comparing reaction rates under microwave and conventional heating, using identical conditions except for the heating mode. In particular, it would be kept in mind that slower reactions are likely to show greater microwave rate enhancements than faster ones.[16]

Also, the reactions would be carried out in the absence or

Keywords: phthalic anhydride; microwave reactions; DMF; solvent-free reaction.

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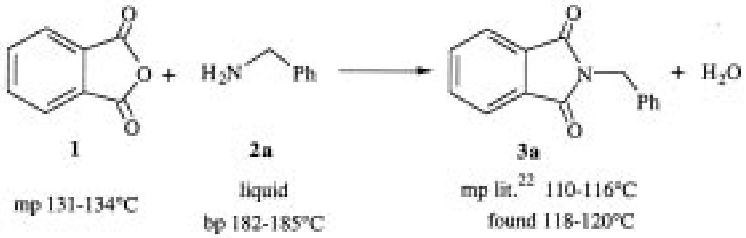


Scheme 1. Reaction with benzylamine **2a**.

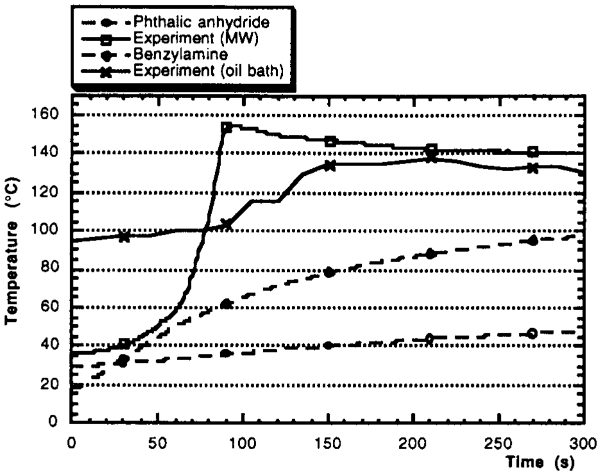


Figure 1. Thermal behaviour of **1** and **2a** alone and their mixture under MW irradiation.

presence of a solvent, either polar or non-polar. In the case of a polar solvent, although faster rates might be expected, any specific or non-thermal microwave effects would be masked due to absorption of microwaves by the solvent. On the other hand, the possibility of specific effects would appear to be greater in the presence of a non-polar solvent where only the reactants would absorb microwave irradiation.[15]

Results and Discussion

Prior to carrying out the reactions, the heating rate of each reactant was studied under MW irradiation to evaluate the thermal behaviour induced by MW absorption, which is mainly dependent on the polarity of the system.[17] It is noteworthy that a sharp increase in heating rate occurs around the melting points of the products, presumably due to an increase in polarity associated with the change from the solid to the liquid phase. Thus, the thermal MW effect is more pronounced with liquids than with solids. Reaction with benzylamine **2a** (Scheme 1).[18]

In the reaction of benzylamine with phthalic anhydride, both reactants are of low polarity and therefore slightly MW absorbent. As the polarity increases during the reaction[19] due to development of partial charges in the transition state compared with initial one, the solvent-free reaction shows a rapid rise in temperature to 150°C in less than 2 min (Fig. 1).

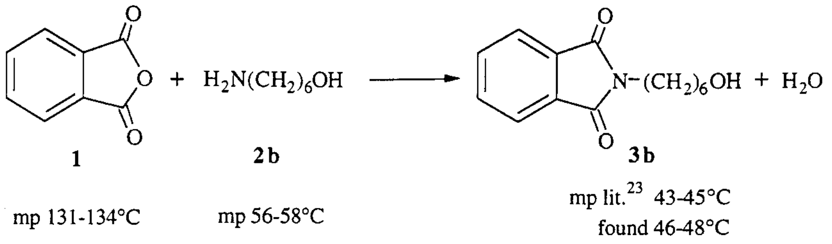
After 5 min of irradiation, a crude yield of 95% of **3a** was obtained (90% of pure product after recrystallisation from ethanol). Similar results were obtained under conventional heating (Δ) using a thermostated oil bath (5 min, 150°C). Therefore, in this case, there is no need for a solvent for the reaction and there is no evidence for a specific microwave effect (Entry 1, Table 1). Reaction with 6-amino-1-hexanol **2b** (Scheme 2).

The reaction with equivalent amounts of **1** and **2b** under MW activation in solvent-free conditions leads to a nearly quantitative yield (97% based on isolated products) within 2 min with a final temperature of 160°C (Fig. 2a). Heating in an oil bath gave only 47% yield under similar conditions of temperature and reaction time. The temperature–time

Table 1. Synthesis of phthalimides **3a**–**3d** under microwave activation (MW) or by conventional heating (Δ)

Entry	Compound	Solvent	Final temperature (°C)	Reaction time (min)	Yield (%) **3**[a]	
					MW	Δ
1	**2a**	None	150	5	95 (90)	95 (90)
2	**2b**	None	160	2	99 (97)	60 (47)
3		None	160	10	99 (97)	85
4		Mesitylene	160	10	97	60
5	**2c**	None	150	15	95 (90)	93 (92)
6		None	120	15	75	73
7		Xylenes	120	15	75	71
8	**2d**	None	85	10	0	
9		Toluene	110	10	0	
10		Xylenes	135	10	(90)	(89)
11		DMF	150	10	(81)	(77)

[a] Yield evaluated by GC using an internal standard; yield in isolated product in brackets.



Scheme 2. Reaction with 6-amino-1-hexanol **2b**.

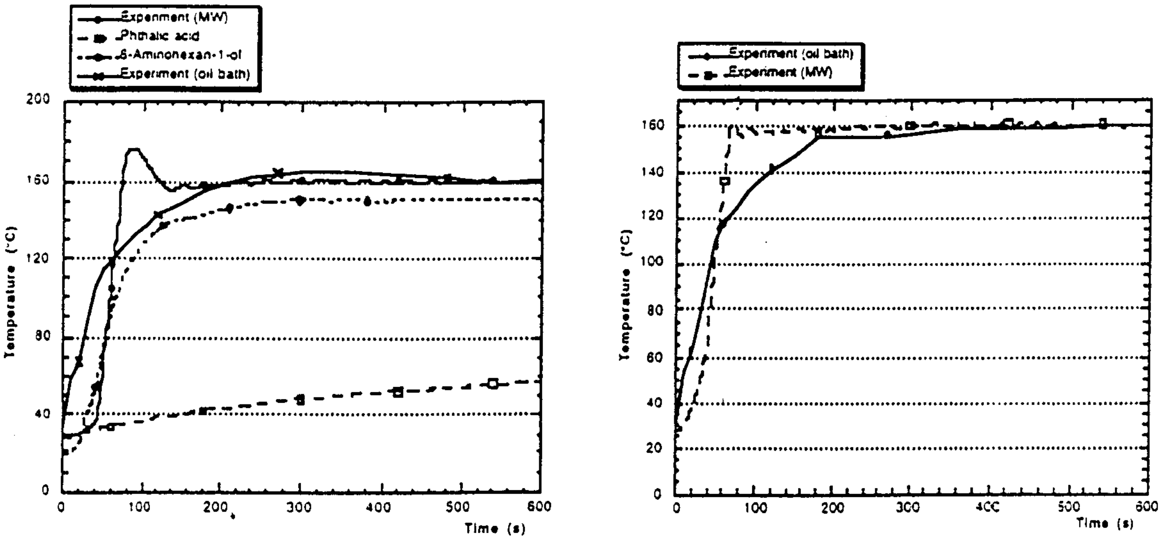
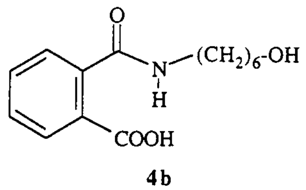


Figure 2. (a) Thermal behaviour of **1** and **2b** alone and their mixture under MW irradiation and in oil bath. (b) Thermal behaviour of the mixture of **1** and **2b** in mesitylene under MW irradiation and in oil bath.

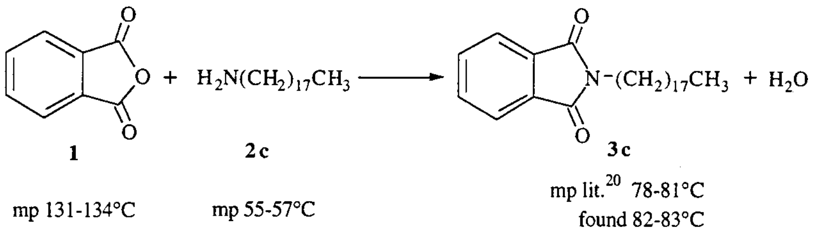
profiles for the reactions of **1** and **2b** under solvent-free conditions and in mesitylene are shown in Fig. 2a and b. Under classical heating, the yield can be enhanced up to 85% by increasing the reaction time to 10 min. The yields of reactions conducted in mesitylene are lower particularly under classical heating (Entry 4, Table 1).

It is noteworthy that the reaction is chemoselective and occurs specifically with the amino moiety. The starting materials are completely converted into products in a very short time (less than 2 min). When yields are not quantitative, the complement to 100% is constituted by the intermediate **4b**. This compound was characterised by its ^{1}H NMR spectrum and by its easy transformation into its methyl ester by reaction with diazomethane.



4b

In this case, *a solvent is not necessary and there is a substantial rate enhancement in the MW heated reaction* (Entry 2, Table 1), presumably because of the higher polarity of the amino alcohol **2b** and its ability to interact strongly with the microwaves. Thus there appears to be evidence for



Scheme 3. Reaction with *n*-octadecylamine **2c**.

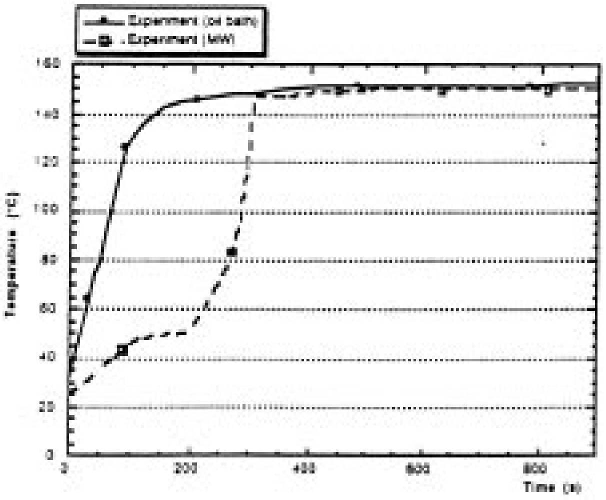
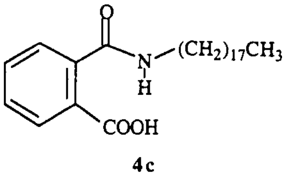


Figure 3. Thermal behaviour of the mixture of **1** and **2c** under MW irradiation and in oil bath.

a specific microwave in solvent-free media or in mesitylene which could be explained either by modifications of activation parameters ($\Delta S^{\#}$) or hot-spots in the reaction mixture. It should be noted, however, that it was difficult to achieve an identical temperature profile under MW and oil-bath heating. Typically, as shown in Fig. 2a and b, the heating rate of the MW reaction is initially lower than that of the oil-bath reaction, but then increases rapidly to reach a temperature of about 40°C, higher than the classically heated mixture after about 80 s. Hence it is also possible that the microwave effect could be a thermal one. Reaction with *n*-octadecylamine **2c** (Scheme 3).

N-Octadecylphthalimide **3c** is obtained in 90–92% yield by heating at 150°C in solvent-free conditions, whatever the activation mode is (Entry 5, Table 1) (Fig. 3).

At lower temperature (120°C), yields decrease to 73–75% without any specific influence of microwave or solvent (Entries 6 and 7, Table 1). Conversions are total and the complement to 100% is constituted by the amide acid **4c**, which is characterized by ^{1}H NMR.



4c

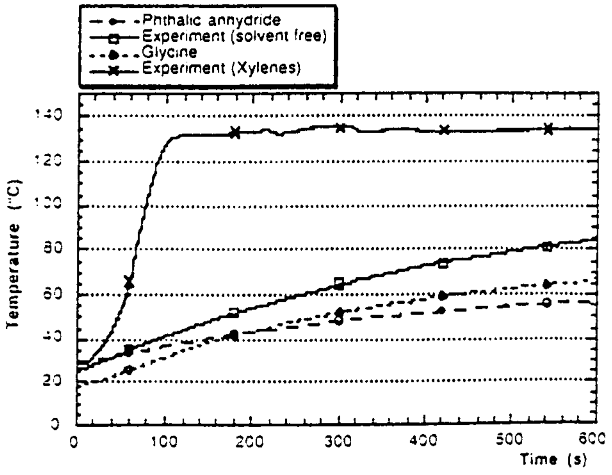


Figure 4. Thermal behaviour of **1** and **2d** alone and their mixture under MW irradiation.

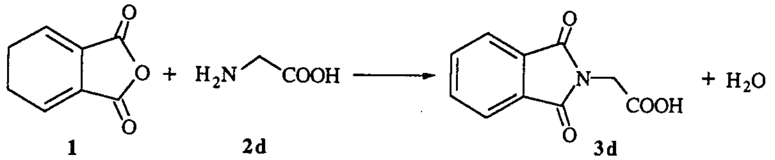
Reaction with glycine **2d** (Scheme 4). In contrast with Sandhu's observation, *the reaction between the solids **1** and **2d** does not occur in the absence of solvent even after 10 min* (Entry 8, Table 1). This could explain the much lower melting point of Sandhu's product compared with literature value for phthaloylglycine (mp[9] 110–111°C instead of 195°C[21]) (Scheme 4). The mixture remains solid since the temperature of the two reactants reaches only 55°C for **1** and 65°C for **2d** (Fig. 4).

Adding a high boiling point solvent, either polar (DMF) or non-polar (xylenes) allows a rise in temperature up to melting point of phthalic anhydride (131–134°C) (Fig. 5a and b). This causes the reactants to dissolve in the solvent and the reaction can occur in homogeneous medium with satisfactory yields (Entries 10 and 11; Table 1) (Fig. 4).

Some attempts were performed with maleic anhydride (mp=54–56°C) either in the absence or in the presence of solvent (xylene, tetralin). Within 3 min under MW (max. temperature=188°C), the conversion is total. *N*-Carboxymethylmaleimide **5** is contaminated with more polar by-products difficult to be separated after extraction with methanol. The treatment indicated by Sandhu[9] is not appropriated as **5** is effectively insoluble in chloroform (Scheme 5).

Conclusion

This study has established that *the solvent-free MW reactions need at least one liquid reactant*. This is possible if a liquid reactant (case **2a**) or a solid with low melting point able to melt rapidly (cases **2b** and **2c**) is used, giving a polar liquid which is more prone to MW absorption. In these



1 mp 131-134°C

2d mp 240°C

3d mp lit.[21] 195°C found 194-197°C

Scheme 4. Reaction with glycine **2d**.

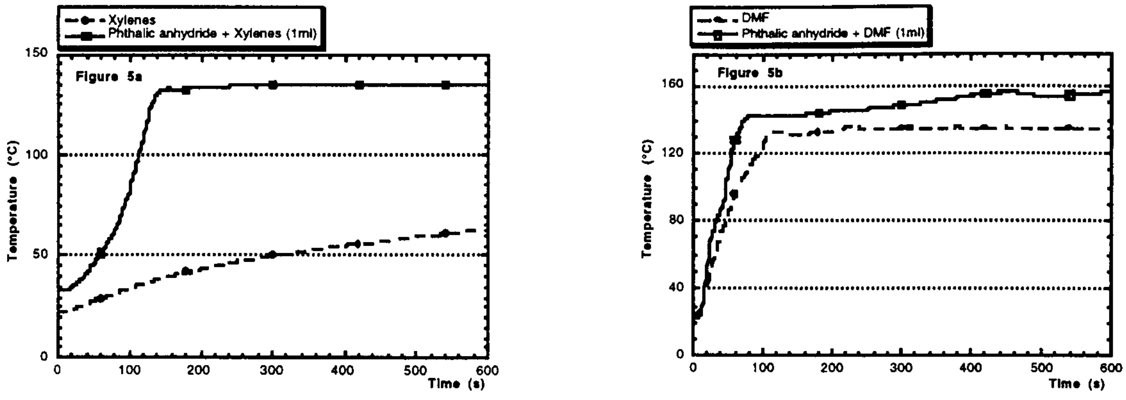
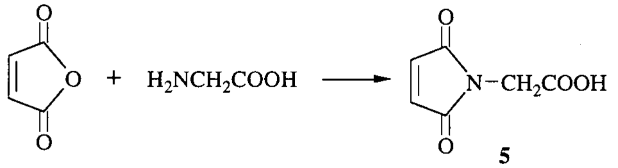


Figure 5. Thermal behaviour of solvent and phthalic anhydride in this solvent under MW irradiation: (a) xylenes; (b) DMF.



Scheme 5. Reaction of maleic anhydride with glycine.

cases, the temperature may be over 135°C and the reaction can occur after melting and solubilisation of phthalic anhydride in the amines. If this situation is not involved (i.e. in reactions between two solids) the reaction may not take place and requires the use of a high boiling point solvent. In all cases, excellent yields of phthalimides (>90%) are obtained from the reaction of phthalic anhydride with amino compounds within short reaction times (5–10 min) giving products of high purity.

Experimental

Microwave experiments were performed in a Synthewave 402® monomode reactor from Prolabo Company. All reactions were conducted in a specially adapted cylindrical Pyrex vessel. The mixtures were heated into the monomode reactor at temperatures and for reaction times as indicated in the table or in the figures. Continuous mechanical stirring provided a good homogeneity of materials. The temperature was controlled throughout the reaction and evaluated by an infrared detector that indicated the surface temperature (IR detector was calibrated by according the emissivity factor using an optical fibre inside the reaction mixture). A computer system was used for automatic control of the irradiation (power and temperature) as well as data processing.

NMR spectra were recorded on Bruker AC 250 in solutions with TMS as reference. Melting points were determined on a Büchi melting point apparatus and are uncorrected.

Crude products were analysed by capillary gas chromatography (column CP Sil 5CB, 25 m) and the data are shown in Table 2.

In a typical reaction, 9.15 mmol of benzylamine **2a** (1 ml) and 9.15 mmol of phthalic anhydride **1** (1.35 g) were introduced into a Pyrex flask, and then submitted to microwave irradiation under conditions of time and temperature as indicated. At the end of the irradiation, the reaction mixture was cooled to room temperature. The crude solid was recrystallised from ethanol to afford 1.95 g (8.23 mmol, 90%) of pure **3a** as white crystals.

In the case of **2b**, **2c** and **2d**, the same amounts of starting materials were used. For the reactions carried out with solvent, 2 mL of this solvent was used. At the end of irradiation, the reaction mixtures were cooled and extracted with acetone. The extracts were evaporated under reduced pressure, analysed by GC (with internal standard) and purified by chromatography on silica gel using pentane/diethyl ether as eluant. Details of the NMR analysis of the products are as follows:

***N*-Benzylphthalimide 3a:** mp 118–120°C (lit.[22] mp 110–116°C); ^{1}H NMR δ ($CDCl_3$, 250 MHz) 4.83 (s, 2H, PhCH_2N), 7.24–7.33 (m, 3H, ArH), 7.39–7.46 (m, 2H, ArH), 7.66–7.77 (m, 2H, ArH (Pht)), 7.79–7.85 (m, 2H, ArH (Pht)); ^{13}C NMR δ ($CDCl_3$, 62.9 MHz) 41.5 (PhCH_2N), 123.3, 127.8, 128.6, 133.9 (C Ar), 168.2 (C=O).

6-Phthalimidohexan-1-ol 3b: mp 46–48°C (from: ethyl acetate/hexane) (lit.[23] mp 43–45°C); ^{1}H NMR δ (DMSO d_6, 250 MHz) 1.30 (m, 4H, C_4H and C_3H), 1.40 and 1.58 (2 m, 4H, C_5H and C_2H), 3.37 (dt, 2H, C_1H, $J_{1\text{-}2}$=$J_{1\text{-OH}}$=6.4 Hz), 3.56 (t, 2H, C_6H, J=7.2 Hz), 4.38 (t, 1H, OH), 7.77–7.94 (m, 4H, ArH (Pht)); ^{13}C NMR δ ($CDCl_3$, 62.9 MHz) 25.1, 26.4, 28.4 (C_5, C_4 and C_3), 32.4 (C_2), 37.7 (C_6), 62.4 (C_1), 123.0, 133.8 (C Ar), 168.4 (C=O).

Table 2. GC analysis

Compound	Temperature programation	Retention time (min)	Internal standard	Retention time of the internal standard (min)
3b	140–260°C with 10°C/min	8.4	Diethyl phthalate	3.7
3c	280°C	6.3	2-Ethylhexyl phthalate	3.0

N-(6-Hydroxy-hexyl)phthalamic acid 4b: ^{1}H NMR δ (DMSO d_6, 250 MHz) 1.30 (m, 4H, C_4H and C_3H), 1.40 and 1.58 (2 m, 4H, C_5H and C_2H), 2.78 (dt, 2H, C_6H, $J_{6\text{-}5}=J_{6\text{-NH}}=6.9$ Hz), 3.37 (dt, 2H, C_1H, $J_{1\text{-}2}=J_{1\text{-OH}}=7.1$ Hz), 4.38 (t, 1H, OH), 6.12 (s, 1H, NH), 7.50 and 8.16 (m, 4H, ArH (Pht)).

N-Octadecylphthalimide 3c: mp 82–83°C (lit.[20] mp 78–81°C); ^{1}H NMR δ ($CDCl_3$, 250 MHz) 0.85 (t, 3H, $C_{18}H$, $J=6.0$ Hz), 1.17–1.42 (m, 28H, C_3H to $C_{17}H$), 1.65 (m, 2H, C_2H), 3.68 (t, 2H, C_1H, $J=7.4$ Hz), 7.67–7.78 (m, 2H, ArH (Pht)), 7.8–7.9 (m, 2H, ArH (Pht)).

N-Octadecylphthalamic acid 4c: ^{1}H NMR δ ($CDCl_3$, 250 MHz) 0.85 (t, 3H, $C_{18}H$, $J=6.0$ Hz), 1.17–1.42 (m, 30H, C_3H to $C_{17}H$), 1.65 (m, 2H, C_2H), 3.35 (dt, 2H, C_1H, $J_{1\text{-NH}}=J_{1\text{-}2}=7.4$ Hz), 6.60 (t, 1H, NH), 7.42 and 7.91 (m, 4H, ArH (Pht)).

N-Phthaloylglycine 3d: mp 194–197°C (from: ethyl acetate/hexane) (lit.[21] mp 195°C); ^{1}H NMR δ (Acetone d_6, 250 MHz) 4.43 (s, 2H, HOOC–CH_2–N), 7.90 (m, 4H, ArH (Pht)); ^{13}C NMR δ (Acetone d_6, 62.9 MHz) 39.1 (CH_2), 124.0, 132.8 and 135.3 (C Ar), 168.0 and 168.9 (COOH and C=O).

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