

Direct Synthesis of a 1,3-bis(*m*-nitrophenyl) Urea in Three Polymorphic Forms, Identified by FTIR Spectroscopy and Optical Microscopy

Monika Simon*, Ana Maria Raduta*, Aurel Raduta**, Carol Csunderlik*

*Department of Applied Chemistry and Organic and Natural Compounds Engineering, "POLITEHNICA" University of Timisoara, Industrial Chemistry and Environmental Engineering Faculty, 300006 Timisoara, Romania
Phone: (0040) 256-404233, Fax: (0040) 256-403060, e-mail akinomis@yahoo.com

**Department of Materials Science and Thermic Treatment, "POLITEHNICA" University of Timisoara, Faculty of Mechanics, 300222 Timisoara, Romania
Phone: (0040) 256-403645, Fax: (0040) 256-403523

Abstract: 1,3-Bis(*m*-nitrophenyl)urea (MNPU) was identified as having three different nonsolvated polymorphs (α form, yellow prisms; β and δ forms, white needles), one monohydrate (γ form, yellow plates) and many others as cocrystal complexes with various hydrogen bond acceptors. When the main polymorphs were characterized by IR spectroscopy, major differences were noticed in their IR spectra: α has $\nu_{C=O} = 1710 \text{ cm}^{-1}$, β has $\nu_{C=O} = 1660 \text{ cm}^{-1}$, δ has $\nu_{C=O} = 1674 \text{ cm}^{-1}$ and γ has $\nu_{C=O} = 1707 \text{ cm}^{-1}$. While investigating the reactivity of some reagents as potential replacements of the toxic phosgene, we discovered that bis(*o*-nitrophenyl)carbonate (DONPC) can be efficiently used in the synthesis of symmetrical *N,N'*-diaryl ureas. MNPU, like other diaryl ureas synthesised by this method, was isolated from reaction mixture (solvent toluene) by precipitation. Here we report a study of polymorphic forms obtained directly from reaction mixture when DONPC was treated with *m*-nitroaniline under various conditions. The products were analysed by IR spectroscopy and optical microscopy and both α and β forms were shown to be obtained. Another form with a previously unreported IR spectrum was identified by analysing the precipitate formed under particular conditions.

Keywords: bis(*o*-nitrophenyl)carbonate, 1,3-bis(*m*-nitrophenyl)urea, polymorphs, IR spectroscopy, optical microscopy

1. Introduction

A polymorph is a solid crystalline phase of a given compound with at least two different arrangements of the molecules of that compound in the solid state. The crystal structure adopted by a given compound when it is crystallized normally exerts a profound effect on the solid-state properties of that system. For a given material, the heat capacity, conductivity, volume, density, diffusivity, crystal hardness, crystal shape and color, refractive index, eletrolytic conductivity, melting or sublimation properties, latent heat of fusion, heat of solution, solubility, dissolution rate, enthalpy of transitions, phase diagrams, stability, hygroscopicity, and rates of reactions are all determined primarily by the nature of the crystal structure. [1]

Many organic and pharmaceutical compounds often exist in more than one polymorphic form, and investigation of the polymorphism is important to understand how the different crystalline affect the physicochemical behaviour and bioavailability of a drug[2].

1,3-Bis(*m*-nitrophenyl) urea (MNPU) was first reported by Groth in 1906 as having three visually distinguishable polymorphic forms: α (yellow prisms), β (white needles) and γ (yellow plates)[3].

Nearly a century later Etter *et al.* [4-6] reported the first crystal structures for the α ($P2_1/c$: $a = 11.495 \text{ \AA}$, $b = 13.816 \text{ \AA}$, $c = 8.307 \text{ \AA}$, $\beta = 91.92^\circ$) and β ($C2$: $a =$

20.95 \AA , $b = 7.412 \text{ \AA}$, $c = 6.715 \text{ \AA}$, $\beta = 104.96^\circ$) forms as part of a larger study on the hydrogen-bonding patterns and cocrystallization behaviour of diaryl ureas.

Recently, Bernstein *et al.* [7] has demonstrated by X-ray diffraction that the γ form is in fact a monohydrate ($C2$: $a = 24.744 \text{ \AA}$, $b = 7.380 \text{ \AA}$, $c = 3.736 \text{ \AA}$, $\beta = 96.39^\circ$, and also discovered a new form designated δ ($P2_1/c$: $a = 4.686 \text{ \AA}$, $b = 18.427 \text{ \AA}$, $c = 17.72 \text{ \AA}$, $\beta = 90.5^\circ$) which crystallizes as white needles.

Single-crystal X-ray diffraction studies indicate that the three anhydrous form are conformational polymorphs, distinguished by the relative orientation of the *m*-nitro groups with respect to the carbonyl: α , anti-anti [6]; β and γ (monohydrate), syn-syn [6,7] and δ , syn-anti [7]

The different forms were also characterized by X-ray powder diffraction, FT-IR spectroscopy, hot-stage microscopy (HSM), differential scanning calorimetry (DSC), solid-state NMR and thermogravimetric analysis [5-7].

In the IR spectra is has been noticed that the N-H and C=O stretching vibration bands, which are very sensitive to hydrogen bonding, show significant differences between the four forms: α has $\nu_{N-H} = 3388 \text{ cm}^{-1}$ and $\nu_{C=O} = 1710 \text{ cm}^{-1}$, β has $\nu_{N-H} = 3328 \text{ cm}^{-1}$ and $\nu_{C=O} = 1661 \text{ cm}^{-1}$, δ has $\nu_{N-H} = 3357 \text{ cm}^{-1}$ and $\nu_{C=O} = 1674 \text{ cm}^{-1}$, and γ has $\nu_{N-H} = 3357 \text{ cm}^{-1}$ and $\nu_{C=O} = 1707 \text{ cm}^{-1}$. [7]

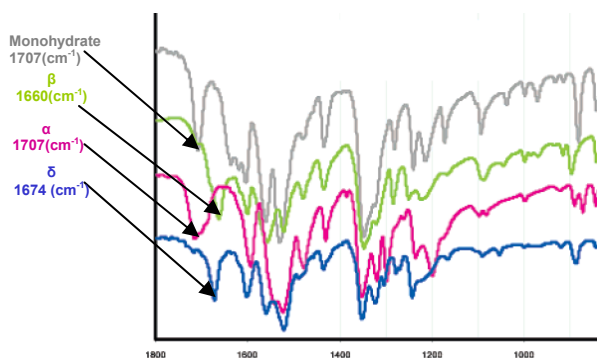
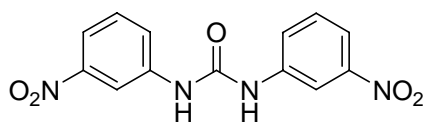


Fig. 1. Solid FT-IR spectra (KBr disk) of the four known forms [7]

While investigating the reactivity of some reagents in order to replace the toxic phosgene[8] in its reactions, we discovered that bis(*o*-nitrophenyl)carbonate (DONPC) can be efficiently used in the synthesis of symmetrical *N,N*-diaryl ureas [9].

Here we report a study of polymorphic forms obtained directly from the reaction mixture when DONPC is treated with *m*-nitroaniline in various conditions. The products were analysed by IR spectroscopy and optical microscopy. In addition to α and β forms, we identified by IR spectroscopy a new possible polymorph.



MNPU

2. Experimental

Melting points were determined on Boetius apparatus (Carl Zeiss Jena). The IR spectra were recorded in KBr disk with a Jasco FT/IR-430 instrument. TLC analyses were carried out on pre-coated plates of silica gel 60 F₂₅₄(Merk). To visualize spots the plates were exposed under a UV 254 lamp. The ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker Avance AC 200. Crystal images were obtained with a stereo microscope Olympus SZX 7. Bis(*o*-nitrophenyl)carbonate was obtained by the method described [10]. *m*-Nitroaniline, 4-(dimethylamino)pyridine, toluene and dichloromethane were purchased from chemical suppliers and used without further purification.

General Procedure for the preparation of 1,3-bis(*m*-nitrophenyl) urea (MNPU). To a solution of bis(*o*-nitrophenyl)carbonate (0.2 g, 0.658 mmol) in 10 mL solvent (toluene, dichloromethane) the *m*-nitroaniline (2.1 equiv) and 4-(dimethylamino)pyridine (0.1 equiv) were added. The reaction mixture was maintained at a specific temperature for a determined time period (Table 1) and the

solid crystallin precipitate formed was filtered and washed with cold solvent. After 2h at room temperature MNPU, was obtained in 49% yield as a yellowish precipitate with mp 237-242°C; $\nu_{C=O}(cm^{-1})= 1685$; $\delta_H(DMSO-d_6)$ 7.57 (t, 2H), 7.75-7.87 (m, 4H), 8.56 (s, 2H), 9.40 (s, 2NH); $\delta_C(DMSO-d_6)$ 112.5, 116.6, 124.6, 130.0, 140.6, 148.1, 152.4 {Lit. $\delta_H(DMSO-d_6)$ 7.57 (t, 2H), 7.75-7.87 (m, 4H), 8.56 (s, 2H), 9.40 (s, 2NH); $\delta_C(DMSO-d_6)$ 112.5, 116.6, 124.6, 130.0, 140.6, 148.1, 152.4 [9].

3. Results and discussion

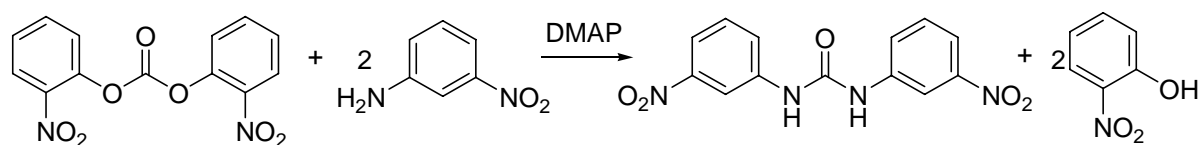
1,3-Bis(*m*-nitrophenyl) urea (MNPU) has previously been prepared using a standard method involving the reaction of *m*-nitrophenyl isocyanate with *m*-nitroaniline in benzene. [5,7,11] The product crystallized in α form after 24h at room temperature [5] and was recrystallised from various solvents leading to the formation of other polymorphs [6,7,11].

While investigating a new method for synthesis of *N,N*-diaryl ureas, which consists in treating of bis(*o*-nitrophenyl) carbonate with various aromatic amines in presence of 4-(dimethylamino)pyridine (DMAP), in toluene, we obtained 1,3-bis(*m*-nitrophenyl) urea (MNPU) (Scheme 1) in three polymorphic forms directly from synthesis depending on the reaction conditions employed. Because MNPU has low solubility in toluene, its isolation from reaction mixture is successfully achieved by precipitation.

One form, which crystallized in highest yield (88%) after 50h at room temperature, had in the IR spectrum the carbonyl stretching band at 1660 cm^{-1} [9]. From the IR spectrum it was apparent that the β form was obtained.

When the precipitate formed was isolated after 2h at room temperature, a yellowish product was obtained having a different IR spectrum from those already reported [7] (Figure 1). The major difference is the characteristic band of the carbonyl group which appeared, in this case, at 1685 cm^{-1} (Figure 2a). We initially believed this product to be *N*-(*m*-nitrophenyl)-*o*-nitrophenyl carbamate, which is normally formed as an intermediate, but the ¹H-NMR and ¹³C-NMR spectra showed that its chemical shifts are those characteristic of MNPU. Because this product was obtained only in 49% yield the filtrate remaining after removal of the precipitate was refluxed for 1h in order to increase the reaction rate. A white needle precipitate was separated after the second filtration. The IR spectrum revealed that it was the β form with its carbonyl stretching band at 1660 cm^{-1} (Figure 1b).

It is known that the β form, when heated undergoes a phase change to the α [7]. In our study we intended to obtain this polymorph by refluxing in toluene the white needle crystals obtained earlier.



Scheme 1

TABLE 1. Synthesis of MNPU under various conditions

No	Reaction Conditions	Time [h]	$\nu_{C=O}$ [cm ⁻¹]
1.	TL/r.t./stirring	2	1685
2.	TL/50°C/stirring	3	1660
3.	CH ₂ Cl ₂ /r.t./stirring	78	1685i, 1660m, 1707
4.	TL/reflux	1/6	1685i, 1660m
5.	TL/reflux	5	1707
6.	TL/r.t./DoNFC: mNA 1:1.1/stirring	2	1685i, 1660m
7.	TL/ 5°C/ DoNFC: mNA 1:1.1	24	1685i, 1660w

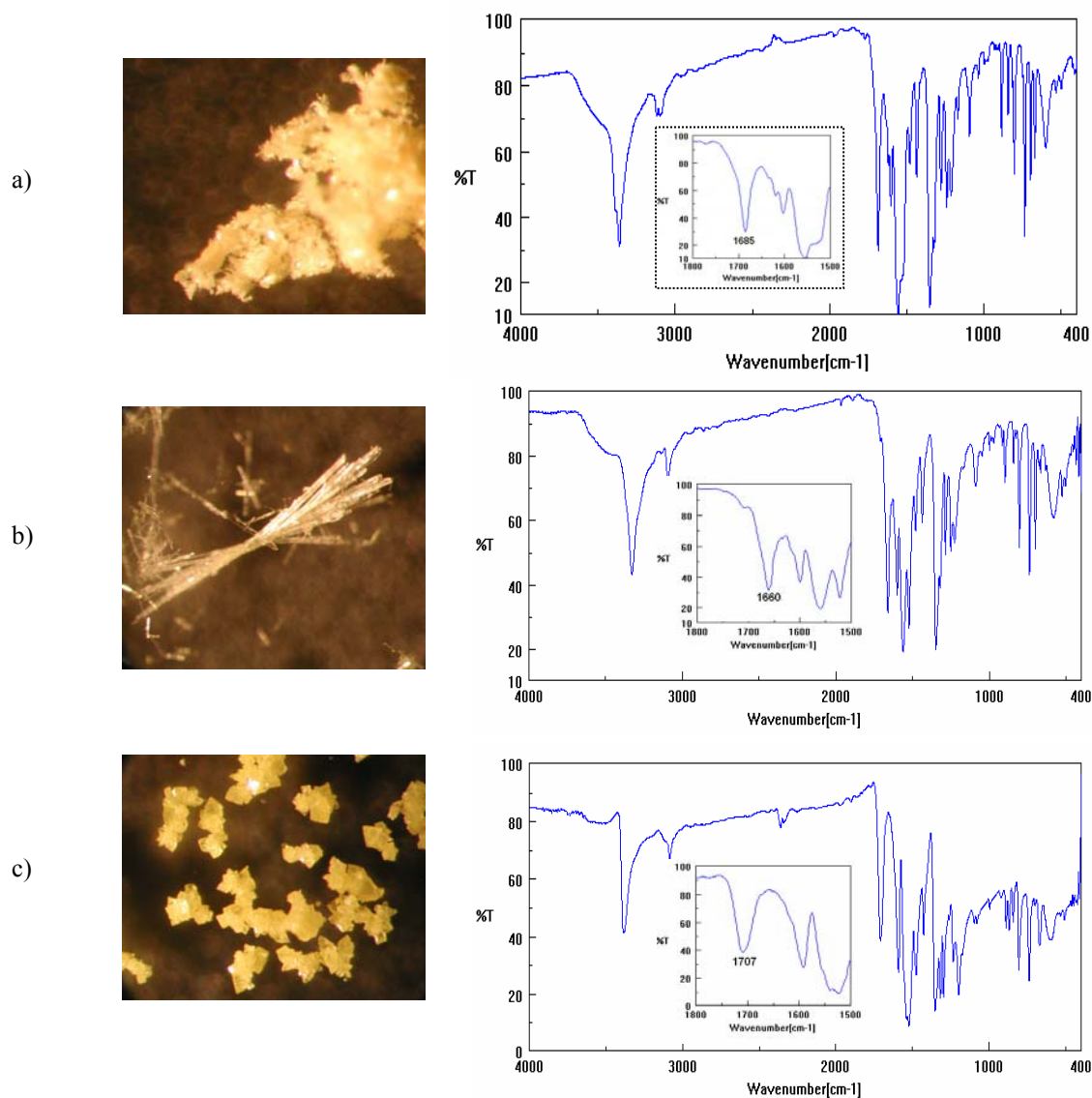


Fig. 2. Crystals of MNPU seen with a stereo microscope Olympus SZX 7 (on left) and the IR spectra (KBr disk) recorded on a Jasco FT/IR-430 spectrometer (right). a) unown form; b) β polymorph; c) α polymorph.

After 5 h under reflux conditions, the color and shape obtained were different. Using an optical microscope we showed that the urea had crystallized in a yellow prism form

(Figure 1c) and IR spectroscopy confirmed that the α polymorph had been obtained, the carbonyl absorption band being at 1707cm⁻¹. (Figure 1c)

A mixture of α and β form was analyzed by IR spectroscopy in order to verify, as was supposed, that the unknown form is actually a mixture of them, but in the IR spectrum two distinct carbonyl bands appear at the same wavenumber as those already mentioned (Figure 3).

From these investigations we concluded that MNPU could presents as new polymorph.

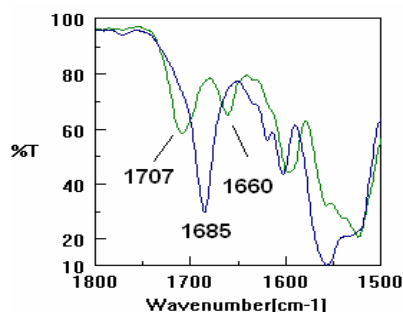


Fig. 3. Comparison between IR spectra of unknown form and a mixture of α and β polymorphs.

In further studies, various reaction conditions were employed for obtaining MNPU to see in what other situation the unknown form could be also obtained (Table 1).

In toluene, at room temperature, with stirring, after 2 h a product with an intense band at 1685 cm^{-1} was obtained. At $50\text{ }^{\circ}\text{C}$, and after 3 h the precipitate had an IR absorption band at 1660 cm^{-1} . After 10 min of reflux, the precipitate separated is a mixture of the β and the unknown form, the latter being present in larger proportion. We increased the time to 5 h and only the most stable form, the α , was obtained. In dichloromethane, after 3 days at room temperature α , β and the form with band at 1685 cm^{-1} precipitated together. When the molar ratio of reagents DONFC: mNA was changed to 1:1.1, after 2 h a mixture of the β and unknown polymorph precipitated again. When the reaction was repeated at 5°C at the same molar ratio, after one day, the major polymorph obtained had the carbonyl stretching band at 1685 , with a weak band at 1660 cm^{-1} also being observed.

These results demonstrate that the temperature, reaction time, molar ratio and solvent affect the formation of the polymorph. Lower temperature and shorter reaction time favor the precipitation of the unknown form, whereas the higher temperature and longer reaction time lead to α polymorph precipitation. When lower temperature and longer time or higher temperature and shorter time are employed the β form is obtained. Thus, the unknown form is kinetically favoured (it is first formed in the crystallization process) but it seems to be metastable

because in contact with the solution it is transformed to the β form. The transformation of a metastable polymorph to a stable one in solution has sometimes been reported [2].

No δ polymorph was observed in our study. Swift *et al* [11] have also reported their failure to obtain this form.

The recrystallisation of the forms obtained from ethanol, ethyl acetate, or acetone lead to the formation of only the α , β and γ polymorphs.

4. Conclusions

We have demonstrated that MNPU can be obtained from *bis(o-nitrophenyl)carbonate* and *m-nitroaniline* directly in different polymorphic forms as a function of the reaction conditions employed. The α and β forms and a new unreported one precipitated successfully directly from the reaction mixture.

In order to determine the true nature of the new polymorph we intend to analyze it by X-ray powder diffraction and to obtain monocrystals for structure characterization.

Acknowledgment

This paper is part of the "Grant A Cod CNCSIS 135/10/2006" project at the "POLITEHNICA" University of Timișoara, Industrial Chemistry and Environmental Engineering Faculty, and was financially supported by CNCSIS.

References

- Bernstein, J. *Polymorphism in Molecular Crystals*, Oxford University Press: New York, **2002**
- Wang, X.; Kirwan, D. J. *Cryst. Growth Des.*, **2006**, 6(10), 2228.
- Groth, P. *An Introduction to Chemical Crystallography*; Wiley: New York, **1906**
- Etter, M. C.; Panuto, T. W. *J. Am. Chem. Soc.*, **1988**, 110, 5896.
- Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panuto, T. *J. Am. Chem. Soc.*, **1990**, 112, 8415.
- Huang, K.-S.; Britton, D.; Etter, M. C.; Byrn, S. R. *J. Mater. Chem.*, **1995**, 5(3), 379.
- Rafilovich, M.; Bernstein, J.; Harris, R. K.; Apperley, D. C. *Cryst. Growth Des.*, **2005**, 5(6), 2197.
- a) Ryan, T.A.; Ryan, C.; Seddon, E.A.; Seddon, K.R. *Phosgene and Related Carbonyl Halide*, Elsevier: Amsterdam, **1996**; b) Cotarca, L.; Eckert, H. *Phosgenations- A Handbook*, Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2003**.
- Simon, M.; Micle, A.; Turoczi, M. C.; Badea, V.; Csunderlik, C., *Rev. Chim.*, **2006**, 57(4), 383
- a) Simon, M.; Csunderlik, C.; Tirnavanu, A., *Rev. Chim.*, **2001**, 52 (7-8), 371. Simon, M.; Csunderlik, C.; Jones, G. P.; Neda, I.; Fischer, A. K., *Acta. Cryst.* **2003**, E59, o688.
- Hiremath, R.; Basile, J. A.; Varney, S. W.; Swift, J. A. *J. Am. Chem. Soc.*, **2005**, 127, 18321.