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Variable Microwave Effects in the Synthesis of Ureidopyrimidinones: the Role of Heterogeneity

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Abstract:

Microwave-irradiated and conventionally heated nucleophilic additions of various C-6 substituted isocytosines (methyl, ethyl, isopropyl, and phenyl) to (di)isocyanates have been compared. As compared to conventional heating, the heterogeneous reaction mixtures showed higher reaction rates on using microwave heating. Variation of C-6 substituent, temperature, and amount of cosolvent influenced significantly the magnitude of these microwave effects. The magnitude of the microwave effect was governed by the solubility and the intrinsic reactivity of the variation in C-6 substitution on isocytosine. Presumably, the liquid layer near the solid surface is the area where selective heating by microwaves is occurring. As a consequence of locally higher temperatures, the solubility of the reactant as well as the rate coefficient of the reaction increase. Thus, higher reaction rates are observed than those corresponding with the measured bulk temperature. The observed microwave effects have a thermal rationale based on direct, fast, and selective heating, and the local heating effect is not found during conventional heating. This finding is crucial for a justified process scale-up scenario.

Introduction

Microwave irradiation can be very useful in chemical reactions and transfer of energy to reactions has led to better yields, improved selectivity, or even conversions otherwise impossible.[1−7] These combined observations have been assigned to beneficial microwave effects. The mechanistic background of these "effects" has been a subject of debate over the last two decades.[8−13] Microwave-enhanced reaction rates, when carefully compared with those derived from conventionally heated reaction mixtures, should be recognised as being due to either thermal or nonthermal mechanisms. Currently, most claimed nonthermal microwave "effects" have been renounced by elaborate studies and rejected as conclusions based on inaccurate temperature measurements and poor mixing.[5,14,15] Only a few examples seem to hold, and the matter of a true microwave effect still stands unresolved.[5,16] Therefore, each chemical reaction has to be evaluated separately to judge whether microwave heating is a suitable scaling-up tool and whether microwave heating is to be preferred over conventional heating during process scale-up.

While heating heterogeneous reaction mixtures with microwave irradiation the electromagnetic energy may be absorbed preferentially by one of the components in the mixture, resulting in considerable local temperature differences.[5,7,17,18] Recently, we reported on beneficial microwave effects where the magnitude of this effect was governed by the degree of heterogeneity in the reaction system.[19,20] The amount of cosolvent played a decisive role, and the microwave effect vanished completely in a homogeneous solution.

In the present study we report on the nucleophilic addition of isocytosines to isocyanates. The adducts are building blocks for 4-fold hydrogen-bonded supramolecular polymers. The reaction mixtures are heterogeneous during the complete course of the reaction because the starting materials (isocytosines) and end products are practically not soluble. The reaction mixtures were thought to be valuable candidates to enable elucidation of microwave effects and their physical and/or chemical origin.

Addition of an amine to an isocyanate leads to a urea functionality, see Scheme 1, which is capable of undergoing intermolecular hydrogen bonding.

In the case of 6-methylisocytosine (i.e., R = methyl) the product is a self-complementary ureidopyrimidinone (UPy) moiety that dimerizes by quadruple hydrogen bonding.[21−23] As

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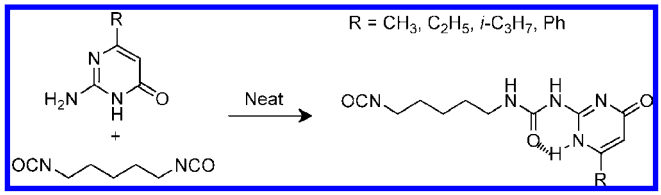
Scheme 1. **Nucleophilic addition of C-6-substituted isocytosines to hexamethylene diisocyanate**



a consequence, a bifunctional UPy may lead to a supramolecular polymer, see Figure 1, with potential applications in the fields of adhesives,[24] printing,[25] cosmetics,[26]> personal care,[27] and coatings.[28]

First, the monoaddition of 6-methylisocytosine to hexamethylene diisocyanate (HDI), the latter being in excess and acting as a solvent to afford a UPy-moiety, was thoroughly investigated. The influence of various reaction parameters and the addition of cosolvent on the reaction rate and (mono)selectivity was studied. The conversion−time histories for conventional (oil bath) heating were compared with those of microwave heating.

Influence of Temperature. A preliminary conventional heating study, focussing on the temperature dependency of the addition of 6-methylisocytosine to HDI, revealed the occurrence of mass transfer limitations for temperatures exceeding 100 °C.[29] Below 100 °C the monoadduct is selectively formed. Monoaddition, essential for further downstream chemistry, is rationalized by the limited solubility of 6-methylisocytosine in HDI and by the presence of a large excess of HDI. After monoaddition the product has an even lower solubility that prevents 2-fold addition.

Time−conversion histories were measured at three temperatures to find optimal conditions to reach complete conversion of isocytosine within a time span of 1−3 h, see Figure 2. This duration was selected from the prospect of further process scaling-up. For temperatures of 74 and 85 °C the reaction obeys approximately (pseudo) zero-order kinetics for conversions below 50%, see Figure 2. Note that at 100 °C the overall conversion changes approximately exponentially with time, i.e. ln $X \approx -t$. The substrate is sparingly soluble and hence is present in solution at a constant, very low concentration.

HDI, on the contrary, is as solvent and reactant initially present in 7.5 molar excess, and the concentration is, therefore, also approximately constant throughout the reaction. Unfortunately, an accurate value of the solubility of 6-methylisocytosine in the reaction mixture could not be determined (reaction!), and therefore, absolute values for the rate coefficient could not be calculated from the reaction rate equation, see eq 1.[30] However, as C_{iso} and C_{HDI} are approximately constant during the reaction, an estimation of the apparent activation energy[31] can be obtained

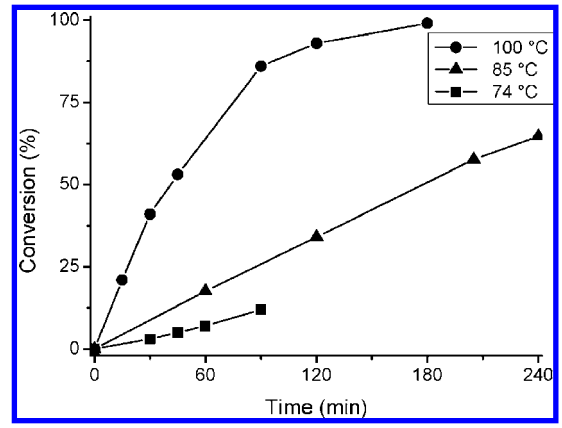


Figure 2. **Nucleophilic addition of 6-methylisocytosine to hexamethylene diisocyanate (7.5 equiv) at 74, 85, and 100 °C under neat conditions.**

Table 1. **Initial conversion rates ($[d(x)/d(t)]_{t=0}$) of nucleophilic addition of 6-methylisocytosine to HDI at various temperatures as a function of the weight fractions of cosolvent under conventional heating conditions**

		conversion rate		
entry	temperature (°C)	without cosolvent[a]	1 wt % NMP[a]	5 wt % NMP[a]
1	74	1.2	3.3	9.5
2	85	2.8	4.8	14.9
3	100	12.5	13.7	29.1

[a] Units are $10^{-3}\cdot min^{-1}$.

from the initial conversion rate, $[d(x)/d(t)]_{t=0}$ expressed in min^{-1}, see eq 2.

$$r = k_2 \cdot C_{iso} \cdot C_{HDI} \tag{1}$$

$$r = C_0 \cdot \frac{dx}{dt} = A' \cdot e^{-E_a/RT}$$
$$\ln\left(\frac{dx}{dt}\Big|_{t=0}\right) = \ln\left(\frac{A'}{C_0}\right) - \frac{E_{a,apparent}}{RT} \tag{2}$$

Note that C_0 is the total amount of moles of isocytosine per unit volume of reaction mixture at the start of the reaction, i.e. the recipe concentration of isocytosine. Assuming that the solubility of the cytosine (S_{iso}) obeys eq 3,

$$\ln\left(\frac{S_{iso}(T_2)}{S_{iso}(T_1)}\right) = -\frac{\Delta_{soln}H}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \tag{3}$$

the apparent activation energy can be equated as the sum of the heat of solution ($\Delta_{soln}H$) and the actual activation energy (E_a) in eq 4:

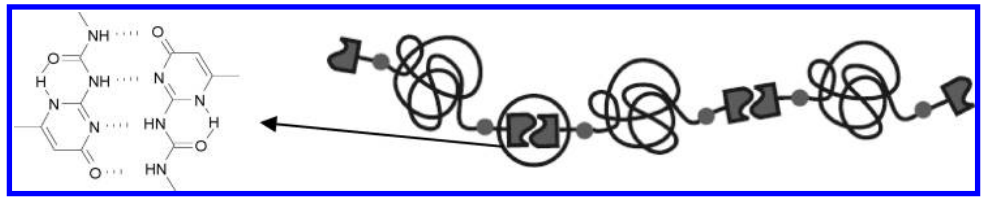


Figure 1. **Coupling of two ureidopyrimidinone (UPy) moieties to a polymer leads to a macromonomer for supramolecular polymerization.**

$$E_{a,apparent} = E_{act} + \Delta_{soln}H \quad (4)$$

An overview of the initial conversion rates depending on three temperatures is given in Table 1.

Influence of a Cosolvent. In an additional series of experiments it was found that the heterogeneity could be influenced by addition of the cosolvent *N*-methylpyrrolidinone (NMP). NMP was selected as a cosolvent on the basis of earlier work.[29] The results for some weight fractions of cosolvent NMP are collected in Table 1 and in Figure 3. The results in Figure 3 clearly demonstrate that a reduction of the heterogeneity leads, as expected, to higher conversion rates.

Scope with Various Substrates and Reagents. To broaden the scope of the addition of 6-methylisocytosine to HDI, three C-6-substituted isocytosines were synthesized, see Scheme 1.[32] Additionally, HDI was replaced in the reaction with 6-methylisocytosine by *n*-hexylisocyanate (HI), see Scheme 2.

The use of *n*-hexylisocyanate (HI, Scheme 2) automatically overcomes the possibility of 2-fold addition. With respect to the reaction with the diisocyanate, only a small change of the solubility of isocytosine and, therefore, probably of the conversion rate can be expected. During preliminary experimentation the addition of 6-methylisocytosine to HI revealed a significant influence of an impurity, causing poorly reproducible time−conversion histories. A striking difference in reaction rate was observed when using an aged and opened or a fresh bottle of HI. When HI from a fresh bottle was taken, the reaction needed considerably more time for completion than in the case of the aged and opened bottle. A solid precipitate in the aged bottle was identified as the water adduct *N*,*N*-dihexylurea, see Scheme 3.

The influence of water on the reaction as depicted in Scheme 3 was not detectable nor was the presence of an analogous impurity in HDI. At room temperature *N*,*N*-dihexylurea is a solid, but at the reaction temperatures used, it was molten, and the liquid *N*,*N*-dihexylurea acted as a cosolvent. When subsequently *N*,*N*-dihexylurea was added deliberately to the reaction of 6-methylisocytosine with HI, the reaction rates increased significantly, see Figure 4. Similar rate enhancements were observed with the addition of *N*-methylpyrrolidinone as a cosolvent.

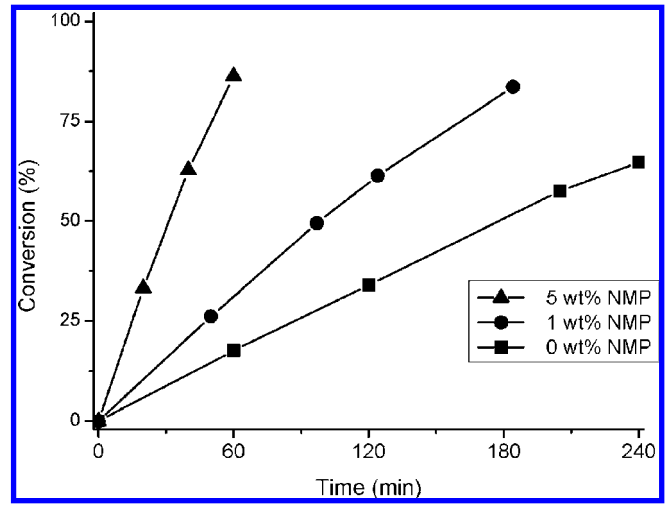
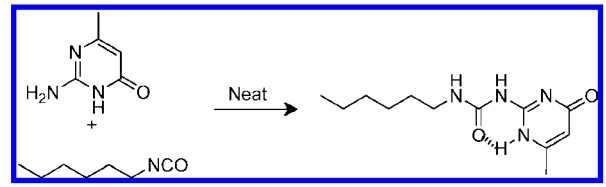
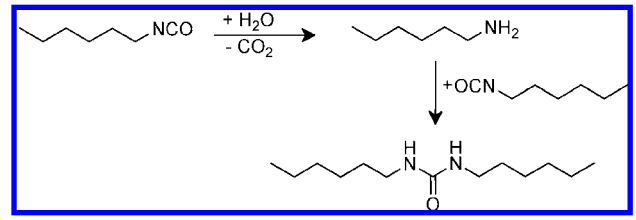


Figure 3. **Nucleophilic addition of 6-methylisocytosine to HDI in the presence of cosolvent (NMP) at 85 °C with conventional heating.**

Scheme 2. **Nucleophilic addition of 6-methylisocytosine to *n*-hexylisocyanate (HI)**



Scheme 3. **Reaction of *n*-hexylisocyanate (HI) with water (<0.5 equiv)**



Variation of the substituent at the C-6 position of isocytosine was expected to largely influence its solubility in HDI and, as a consequence, the overall reaction rate. Although the solubility could not be measured directly in HDI, the solubility was

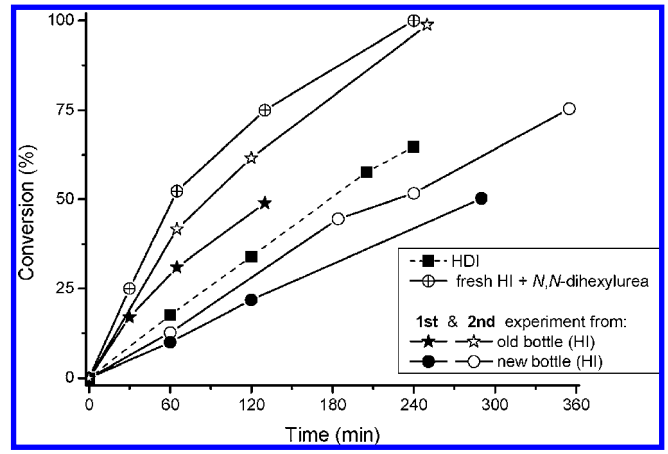


Figure 4. **Nucleophilic addition of 6-methylisocytosine to *n*-hexylisocyanate (HI) of different grades at 85 °C and the addition of 6-methylisocytosine to hexamethylene diisocyanate (HDI). *N*,*N*-dihexylurea was added to fresh HI.**

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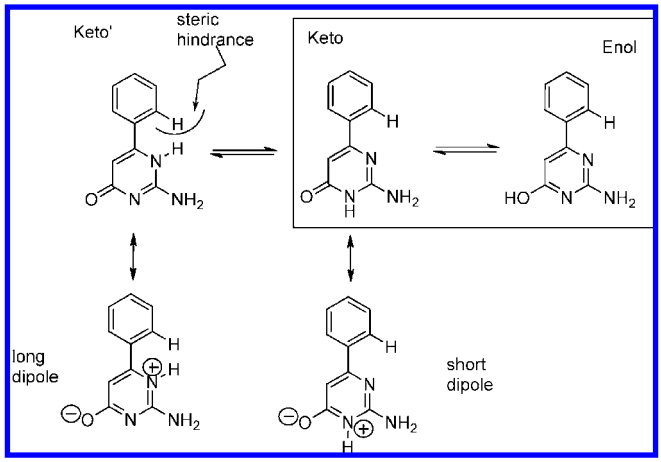
(29) Pranger, M. Ph.D. Eng-Thesis. Stan Ackermans Institute, Eindhoven University of Technology: The Netherlands, 2005.
(30) $E_{a,\ apparent}$ = apparent activation energy.
(31) Estimated apparent activation energy for the nucleophilic addition of 6-methylisocytosine to HDI without cosolvent, 1 wt % NMP, and 5 wt % NMP; 46, 60, and 98 kJ/mol, respectively.
(32) Liao, R.-F.; Lauher, J. W.; Fowler, F. W. *Tetrahedron* **1996**, *52*, 3153.

Table 2. **Solubilities of isocytosines with various substituents at the C-6 position and overall reaction rate of these isocytosines upon addition to HDI**

entry	substituent	sol. in DMA [mmol/L][a]	sol. in 1,4-dioxane [μmol/L][a]	overall reaction rate
1	methyl	0.17	<0.1	low
2	ethyl	0.56	10	medium
3	isopropyl	1.2	28	medium
4	phenyl	1.1	41	higher

[a] Solubility at 85 °C.

Scheme 4. **Keto−enol tautomerization of 6-phenylisocytosine**



categorized visually and measured in two other solvents, *N*,*N*-dimethylacetamide (DMA) and 1,4-dioxane.

The polarity of these solvents was chosen above (DMA) and below (1,4-dioxane) that of HDI. The results of the influence of various substituents at the C-6 position on the solubility in DMA and 1,4-dioxane and on the overall reaction rate in pure HDI are listed in Table 2. As can be derived from Table 2, ranking the various alkylated isocytosines with respect to solubility explains qualitatively the effects of the substituents on the reaction rate. It can be concluded that the isocytosines with the methyl, ethyl, and isopropyl substituents are in line. Surprisingly, the selectivity and reactivity of 6-phenylisocytosine differ significantly from those of 6-isopropylisocytosine with a comparable solubility in HDI. A plausible rationale for this behavior may relate either to the product solubility, or to the keto−enol tautomerization of the isocytosines that may influence the intrinsic reaction rate of the amine functionality, see Scheme 4.

The solubilities of the methyl, ethyl, isopropyl, and phenyl single addition products in 1,4-dioxane are <0.10, <0.10, 67, and 32 μmol/L at 85 °C, respectively. The higher the solubility of the single addition product, the lower the selectivity for monoaddition, potentially due to 2-fold addition, see Scheme 5. Thus, in the aliphatic series the reaction rate reflects the solubility of the isocytosines, and the selectivity for the monoaddition product increases in the order isopropyl < ethyl < methyl. 6-Phenylisocytosine, however, is exceptional since the solubility of the starting material is relatively high, whereas the monoadduct is less soluble than the starting material.

Scheme 5. **Single and 2-fold addition of 6-isopropylisocytosine to hexamethylene diisocyanate**

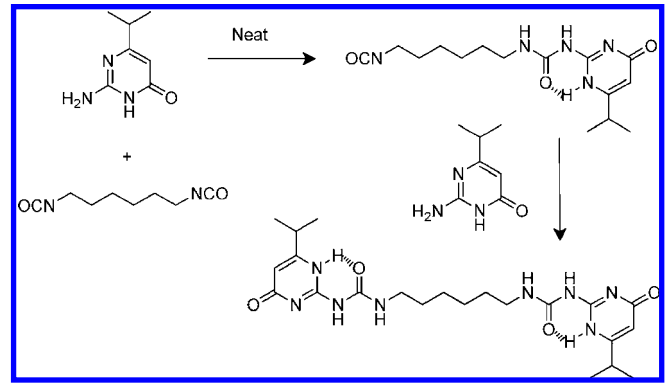


Table 3. **Some typical values of absorption bands in the IR spectra of 6-isopropylisocytosine and 6-phenylisocytosine**

entry	band type	6-isopropylisocytosine (cm^{-1})	6-phenylisocytosine (cm^{-1})
1	OH *stretch*	3333	3374
2	NH/NH_2 *stretch*	3072	3134
3	C=O *stretch*	1657	1668

In general, isocytosines may be represented by three interconverting tautomers, see Scheme 4. The aberrant profile of 6-phenylisocytosine may relate to its preference for the enol tautomer and the concomitant enhanced nucleophilicity of the amine function. To that end, extended Hückel calculations on the charge distribution for each tautomer were performed. Unfortunately, MM2[33] and MMFF94[33] models did not unequivocally rationalize the higher reaction rate of 6-phenylisocytosine compared to that of 6-isopropylisocytosine. However, an extended (IR) study on the keto−enol tautomerization for ureidopyrimidinones revealed a preference for the enol tautomer with electronegative substituents on the C-6 position.[34] IR-measurements showed indeed a higher absorption wavenumber for the NH_2 band (blue-shift/more nucleophilic) for 6-phenylisocytosine compared to 6-isopropylisocytosine, see Table 3. This difference in the location of the NH_2 band was not observed for the three alkyl analogues. Presumably, the amine function of 6-phenylisocytosine is more nucleophilic due to the more powerful electron-donating character of the phenyl moiety in comparison to the aliphatic C-6 substituted isocytosines.

Microwave Heating. Some reaction parameters (e.g., temperature or application of a cosolvent) have been altered in conventionally heated reactions of isocytosines with isocyanates, as described above. Comparing time−conversion histories of conventional (CH) and microwave (MW) heating allows recognition of any possible microwave effect if otherwise identical reaction conditions are selected. A quantification of a microwave effect follows from the ratio of the initial reaction rates of both heating methods, see eq 5.

$$f_{MW} = \frac{r_{ini;MW}}{r_{ini;CH}} \qquad (5)$$

(33) MM2 and MMFF94 are Molecular Mechanism and Merck Molecular Force Fields models.; Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490.
(34) Beijer, F. H., Ph.D. Thesis. Eindhoven University of Technology: The Netherlands, 1998.

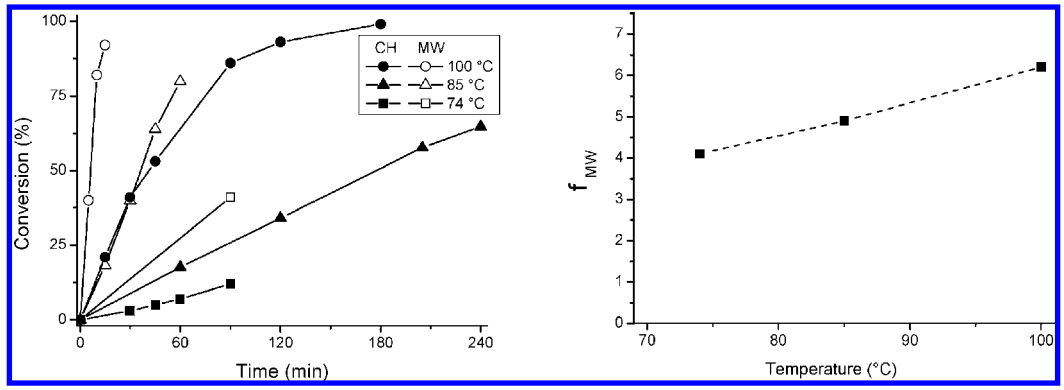


Figure 5. **(Left) Nucleophilic monoaddition of 6-methylisocytosine to hexamethylene diisocyanate at 74, 85, and 100 °C for conventional heating (CH) and microwave heating (MW). (Right) Effect of temperature on the microwave effect (f_{MW}).**

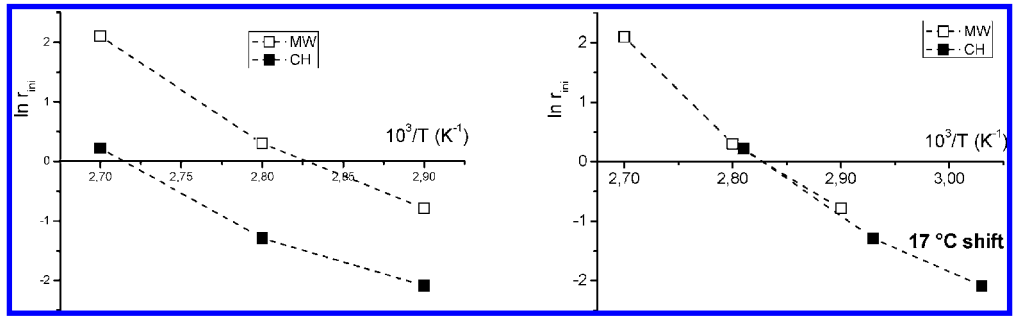


Figure 6. **(Left) Correlation between temperature and initial reaction rate for nucleophilic monoaddition of 6-methylisocytosine and hexamethylene diisocyanate using conventional and microwave heating. The estimated apparent activation energy is: 100 < *E* < 120 kJ/mol. Right: initial reaction rates of conventional heating when shifted with +17 °C to allow coincidence with those of the microwave-heated experiments.**

Influence of Temperature. Three experiments were conducted at 74, 85, 100 °C to convert 6-methylisocytosine with an excess of HDI under microwave heating conditions, see Figure 5. For microwave heating the initial reaction rates were significantly higher than for oil-bath heating. In the experiments the stirring speed and the temperature were kept as close as possible to those of the oil-bath heated experiments. Intriguingly, the ratio of the initial reaction rates of microwave to that of conventionally heated experiments increases when the temperature rises, in other words, a larger microwave effect with temperature, see Figure 5 (right).

The relationship between reaction rate and temperature as given by the Arrhenius equation could give more insight into the background of the difference between the conversion−time histories for conventional and microwave heating, the so-called microwave effect. Plotting the initial reaction rates, eq 2, against the reciprocal temperatures for the experiments with conventional and microwave heating shows that the slopes and by that $E_{a,apparent}$ ($= E_a + \Delta_{soln}H$) are only slightly different. A possible explanation for the observation given in Figure 6 (left) is that the locus of reaction, i.e. the liquid layer around the 6-methylisocytosine particles is under microwave-heated conditions at a significantly higher temperature than the bulk fluid. Shifting the reaction temperatures in the locus of reaction to a value of 17 °C higher than the bulk temperature leads to coinciding of the conventionally and microwave-heated reactions. Local heating of the liquid layer around the 6-methylisocytosine particles leads to a higher isocytosine concentration and a higher reaction rate. Changes in the actual activation energy E_a by applying microwave irradiation are very improbable. Changes of $E_{a,apparent}$ may originate from "solvent" effects on increasing the solubility of 6-methylisocytosine. Also effects of temperature on viscosity may influence the hydrodynamics around the particles and by that the observed temperature effects. The apparent activation energy, consisting of the sum of actual activation energy and heat of solution, remains the same for both heating techniques, although the pre-exponential factor seems to differ. Consequently, these results lead to the assumption that limitations in the rate-determining step are less pronounced under microwave irradiation.

Influence of the Cosolvent. As discussed above, see Figure 3, the results of the conventionally heated experiments demonstrated that the use of a cosolvent (e.g., NMP) gave higher reaction rates. The data depicted in Figure 7 (right) demonstrates that the microwave effect (f_{MW}) decreases with increasing weight fraction of NMP. Although NMP is absorbing microwaves quite well, the penetration depth is still sufficient.[35] Further addition of NMP to obtain a homogeneous solution was unrealistic. Replacing 6.5 equiv of HDI by NMP did not result in a homogeneous reaction mixture. It can be concluded that the addition of a cosolvent leads to a partial dissolution of 6-methylisocytosine and a concomitant vanishing microwave effect.

Scope with Various Substrates and Reagents. Heterogeneity can be changed as demonstrated by cosolvent addition, vide supra, as well as by variation of the reactants. This expands the scope of microwave-assisted addition of a series of 6-substituted isocytosines to hexamethylene diisocyanate, but it also gives more insight into the microwave effect.

(35) The penetration depth is in the order of a few centimeters (loss tangent is 0.275 for NMP; penetration at 2.45 GHz is therefore ~9 cm).

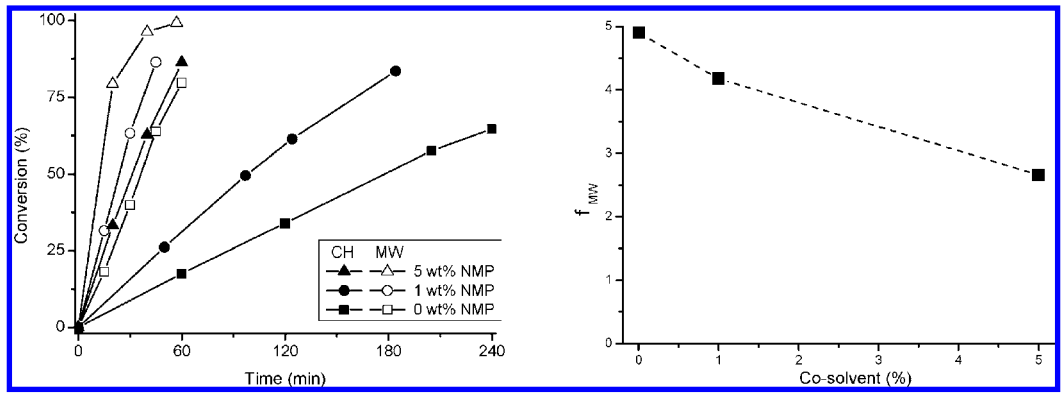


Figure 7. **(Left) Nucleophilic addition of 6-methylisocytosine to hexamethylene diisocyanate at 85 °C for conventional heating (CH) and microwave heating (MW): influence of the weight fraction of cosolvent NMP. (Right) Microwave effect as a function of weight fraction of NMP.**

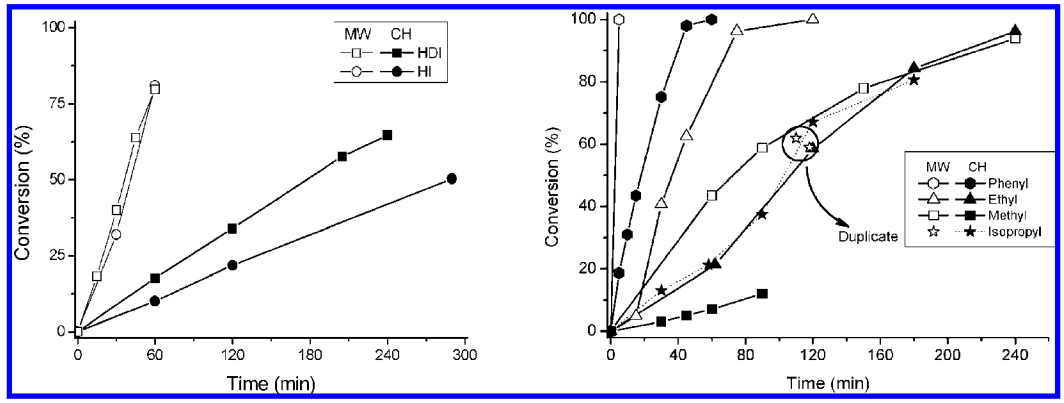


Figure 8. **(Left) nucleophilic addition of 6-methylisocytosine to hexylisocyanate (HI) and hexamethylene diisocyanate (HDI) at 85 °C for conventional heating (CH) and microwave heating (MW), respectively. (Right) Nucleophilic addition of several 6-substituted isocytosines to hexamethylene diisocyanate at 70 °C and for 6-methylisocytosine at 74 °C.**

Table 4. **Outcome of the nucleophilic addition of isocytosine with various substituents at C-6 to HDI: reactivity with microwave heating and microwave effect**

entry	substituent	solubility	reactivity	substituent	microwave effect[a]	
1	methyl	*low*	*low*	phenyl	*higher*	8.5
2	ethyl		*medium*	methyl		5.4
3	isopropyl		*low*	ethyl		2.8
4	phenyl	*higher*	*higher*	isopropyl	*low*	*nil*

[a] f_{MW} at 70 °C (and for 6-methylisocytosine at 74 °C).

The differences between both heating techniques are depicted in Figure 8 (left) for the monoadditions of 6-methylisocytosine to HDI and HI at 85 °C, showing a f_{MW} of 7.4 for HI and a f_{MW} of 4.9 for HDI. A possible explanation for the lower rates with HI in a conventionally heated reaction as compared to HDI might be the poorer solubility of 6-methylisocytosine in HI due to its lower polarity.

Variation of the substituents at C-6 in the substrate gives also large differences between conventional and microwave heating at 70 °C, see Figure 8 (right). The correlation between solubility and reactivity was in general predictable as explained earlier. However, the correlation between solubility and microwave effect is not completely in line with our expectations, see Table 4. A better correlation between heterogeneity and microwave effect (f_{MW}) for all four substrates can be made when the overall heterogeneity of the reaction mixture is considered for both substrate and product solubility during the initial stages of the conversion. Note that the solubility of the monoaddition product of the phenyl-substituted isocytosine in HDI is much lower than the solubility of the monoaddition product of the isopropyl-substituted product in HDI.

This might explain the strong microwave effect for 6-phenylisocytosine in contrast to the absence of a microwave effect for 6-isopropylisocytosine with a similar substrate solubility.

The reactivities of 6-ethyl- and 6-isopropylisocytosine are not significantly different for conventional heating, see Table 2. However, with microwave heating only the rate of 6-ethylisocytosine is enhanced. During the reaction of 6-isopropylisocytosine the solubility increases to such a level that no microwave effect could be generated anymore.

Discussion and Conclusion

All of the reactions discussed were faster (or in the case of 6-isopropylisocytosine, equally fast) when microwave heating was employed. Reducing the heterogeneity diminished the microwave effect. Solubility of the substrate is an important

factor, albeit the overall heterogeneity (considering substrate *and* product) allows perhaps a better prediction of a positive microwave effect. Our experiments could not demonstrate a microwave effect for homogeneous reactions, but heterogeneity alone is not sufficient to induce a microwave effect.[36] So far a beneficial microwave effect was only observed in solid−liquid systems with very low solubilities of the solid substrates, involving relatively fast reactions in the liquid layer around the isocytosine particles. It is exactly in these liquid layers where selective heating can occur.

In the case of the addition of 6-methylisocytosine to hexamethylene diisocyanate, 6-methylisocytosine slightly dissolves which results in an absorption enhancement of microwaves. Consequently, the temperature increases locally, leading to an even higher solubility and reaction rate. The occurrence of such a microwave effect at the interphase region was also demonstrated previously through modeling of a chemical conversion with microwave heating.[37−39]

In our cases neither the solid nor the liquids used were good microwave absorbers, which was demonstrated by simple heating experiments.[40] The effects cannot be measured locally by any sensor, but they are witnessed indirectly by higher reaction rates and higher pre-exponential factors. Figure 5 (left) illustrates an example, representing a conversion of 6-methylisocytosine for the conventionally heated experiment at 100 °C, that is almost similar to the microwave-heated reaction at 85 °C. When the reaction predominantly takes place in the liquid layer, then this layer conclusively has an average temperature of about 102 °C, but the bulk temperature is in fact measured to be 17 °C lower.

In conclusion, significant rate and productivity enhancements in the UPy-process starting from 6-methylcytosine have been found. These results provided a better understanding of an important microwave effect, offering the right scenario for a microwave-assisted process scale-up.

Experimental Section

All microwave-heated experiments were performed in a MicroSynth of Milestone srl, Italy with internal fibre-optic (type ATC-FO; fluoroptic probe) temperature measurement via a Teflon-coated ceramic well. In general, all reactions were temperature controlled with a set power maximum to obtain the thermal set-point. A maximal magnetic stirring speed in the microwave oven was applied. Control experiments using a pitched-blade overhead stirrer did not alter the presented results. During reaction, aliquots were taken and quenched in cold methyl *tert*-butyl ether (MTBE) (2 mL, 0 °C). The suspension was filtered and washed twice with cold MTBE (0.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed by ^{1}H NMR (conversion based on ratio isocytosine and product).

Nucleophilic Additions under Microwave Heating. *N-(6-Isocyanatohexyl)-N′-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)urea.* A 20-mL reaction tube was charged with 6-methylisocytosine[21] (0.75 g, 6.0 mmol) and hexane-1.6-diisocyanate (7.5 g, 44.6 mmol). The tube was flushed with argon and closed. Temperature was measured via a fibre-optic insert. The reaction mixture was heated at 85 °C with stirring for 2 h in the microwave oven (average power: 25 W/max: 200 W). Thereafter, the mixture was diluted with MTBE (15 mL), and after cooling the suspension was filtered and washed twice with MTBE (1.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed. Yield after workup: 1.39 g (79%); ^{1}H NMR (400 MHz) in $CDCl_3$/d-TFA (1/1 vol %) δ 6.3 (s, 1H, $\underline{CH}$═C−CH_3), 3.3 (t, 2H, NH−$\underline{CH_2}$), 3.2 (t, 2H, $\underline{CH_2}$−NCO), 2.5 (s, 3H, $\underline{CH_3}$−C═CH), 1.8 (m, 2H, NH−CH_2−$\underline{CH_2}$), 1.6 (m, 2H, $\underline{CH_2}$−CH_2−NCO), 1.5 (m, 4H, $(\underline{CH})_2$−$(CH_2)_2$−NCO).

N-(6-Isocyanatohexyl)-N′-(6-ethyl-4-oxo-1,4-dihydropyrimidin-2-yl)urea. A 20-mL reaction tube was charged with 6-ethylisocytosine[29] (0.84 g, 6.0 mmol) and hexane-1.6-diisocyanate (7.5 g, 44.6 mmol). The tube was flushed with argon and closed. Fibre-optic temperature control was measured via an insert. The reaction mixture was heated at 85 °C with stirring for 2 h in the microwave oven (average power: 25 W/max: 200 W). Thereafter, the mixture was diluted with MTBE (15 mL), and after cooling the suspension was filtered and washed twice with MTBE (1.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed. Yield: 1.29 g, 70%; ^{1}H NMR (400 MHz) in $CDCl_3$/d-TFA (1/1 vol %) δ 6.4 (s, 1H, $\underline{CH}$═C−C_3H_7), 3.4 (m, 2H, NH−$\underline{CH_2}$, 3.2 (m, 2H, $\underline{CH_2}$−NCO), 2.8 (q, 2H, $\underline{CH_2}$−C═CH), 1.8 (m, 2H, NH−CH_2−CH_2), 1.7 (m, 2H, $\underline{CH_2}$−CH_2−NCO), 1.5 (m, 4H, $(\underline{CH_2})_2$−$(CH_2)_2$−NCO), 1.4 (t, 3H, $\underline{CH_3}$−CH_2−C═CH).

N-(6-Isocyanatohexyl)-N′-(6-isopropyl-4-oxo-1,4-dihydropyrimidin-2-yl)urea. A 20-mL reaction tube was charged with 6-isopropylisocytosine[32] (0.92 g, 6.0 mmol) and hexane-1.6-diisocyanate (7.5 g, 44.6 mmol). The tube was flushed with argon and closed. Temperature was measured via an insert. The reaction mixture was heated at 85 °C with stirring for 2 h in the microwave oven (average power: 24 W/max: 70 W). Thereafter, the mixture was diluted with MTBE (15 mL), and after cooling the suspension was filtered and washed twice with MTBE (1.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed. Yield: 1.21 g, 63%; ^{1}H NMR (400 MHz) in $CDCl_3$/d-TFA (1/1 vol %) δ 6.4 (s, 1H, $\underline{CH}$═C−CH_3), 3.3 (t, 2H, NH−$\underline{CH_2}$), 3.2 (t, 2H, $\underline{CH_2}$−NCO), 3.0 (m, 1H, C_2H_6−$\underline{CH}$−C═CH), 1.8 (m, 2H, NH−CH_2−$\underline{CH_2}$), 1.6 (m, 2H, $\underline{CH_2}$−CH_2−NCO), 1.4 (m, 4H, $(\underline{CH_2})_2$−$(CH_2)_2$−NCO), 1.3 (d, 6H, $(\underline{CH_3})_2$−CH−C═CH).

N-(6-Isocyanatohexyl)-N′-(6-phenyl-4-oxo-1,4-dihydropyrimidin-2-yl)urea. A 20-mL reaction tube was charged with 6-phenylisocytosine[32] (1.12 g, 6.0 mmol) and hexane-1.6-diisocyanate (7.5 g, 44.6 mmol). The tube was flushed with argon and closed. Temperature was measured via an insert. The

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(40) It can generally be stated that solids are difficult to heat by microwave irradiation. For ice and water the loss tangents differ 3 orders of magnitude at 0 °C (ice: 0.00027, water 0.207). Both components (6-methylisocyosine and HDI) were separately heated in the microwave oven. 6-Methylisocyosine was dispersed in THF. The heating rate of this mixture was compared with that of pure THF. HDI was heated as such. In no case was significant heating observed with the use of a fibre-optic probe, showing that each individual component is a poor microwave absorber.

reaction mixture was heated at 85 °C with stirring for 2 h in the microwave oven (average power: 22 W/max: 120 W). Thereafter, the mixture was diluted with MTBE (15 mL), and after cooling the suspension was filtered and washed twice with MTBE (1.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed. Yield: 1.77 g, 83%; ^{1}H NMR (400 MHz) in $CDCl_3$/d-TFA (1/1 vol %) δ 7.6−7.8 (m, 5H, $\underline{C_6H_5}$−C═CH), 6.8 (s, 1H, CH═C−CH_3), 3.4 (t, 2H, NH−$\underline{CH_2}$), 3.2 (t, 2H, $\underline{CH_2}$−NCO), 1.8 (m, 2H, NH−CH_2−CH_2), 1.7 (m, 2H, $\underline{CH_2}$−CH_2−NCO), 1.5 (m, 4H, $(\underline{CH_2})_2$−$(CH_2)_2$−NCO).

N-Hexyl-N′-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)urea. A 20-mL reaction tube was charged with 6-methylisocytosine (0.75 g, 6.0 mmol) and hexylisocyanate (5.67 g, 44.6 mmol). The tube was flushed with argon and closed. Temperature was measured via an insert. The reaction mixture was heated at 85 °C with stirring for 4 h in a Milestone microwave oven (average power: 25 W/max: 200 W). Thereafter, the mixture was diluted with MTBE (15 mL), and after cooling the suspension was filtered and washed with MTBE (1.5 mL). The remaining solid was dried under reduced pressure at 40 °C and analyzed. Yield: 1.2 g, 73%; ^{1}H NMR (400 MHz) in $CDCl_3$/d-TFA (1/1 vol %) δ 6.3 (s, 1H, CH═C−CH_3), 3.3 (t, 2H, NH−$\underline{CH_2}$), 2.5 (s, 3H, $\underline{CH_3}$−C═CH), 1.8 (m, 2H, NH−CH_2−$\underline{CH_2}$), 1.5 (m, 6H, $(\underline{CH_2})_4$−$(CH_2)_2$−NH), 1.4 (t, 3H, CH_2−$\underline{CH_3}$).

Typical Procedure for All Oil-Bath-Heated Reactions. An analogous procedure was applied for the oil-bath experiment substituting microwave with oil-bath heating, except for the prolonged duration of the reactions.

N-(6-Isocyanatohexyl)-N′-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)urea. Conventionally heated experiment (4 h). Yield after workup: 1.55 g (88%) monosubstituted product.

The other C-6 substituted analogues have been monitored only in terms of conversion by ^{1}H NMR.

N,N′-Dihexylurea. A 20-mL reaction tube was charged with *n*-hexylamine (234 mg, 2.31 mmol), toluene (5 mL), and hexylisocyanate (280 mg, 2.2 mmol). The reaction mixture was refluxed for 2 h. Thereafter, the solvent was removed at 50 °C under reduced pressure. ^{1}H NMR (300 MHz) in $CDCl_3$ δ 4.3 (s, 1H, $\underline{NH}$−CO), 3.2 (t, 2H, CH_2−NH), 1.5 (m, 2H, $\underline{CH_2}$−CH_2−NH), 1.3 (m, 6H, $(\underline{CH_2})_3$−CH_3), 0.9 (t, 3H, −CH_3). GC−MS *m*/*z*: 228 (FW 228).

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