# Rapid access to reactive polymer-supported isocyanates

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**Abstract**—Isocyanate resins are used in polymer assisted solution-phase synthesis, however, their use is limited by their high cost and often unfavourable reaction profiles. Here a route to prepare efficient supported isocyanate resins from aminomethyl resin and inexpensive diisocyanates is reported and compared to commercially available isocyanate resins.
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Combinatorial and high-throughout synthesis methods allow the generation of thousands of compounds in a very time efficient manner.[1] Some of these HT methods often rely on the intermediary of polystyrene gel-type resins,[2,3] despite the fact that solid phase organic synthesis has a number of inherent limitations due to the nature of the solid support, such as the nontrivial transposition of well-known homogeneous reactions onto a solid support, the limitation of solvent choice and the impracticability of using conventional analysis methods.[4] Some of these problems have been solved, in part, by the use of solid supported reagents and catalysts,[5] where rather than immobilising the target and using reagents in solution, the target molecules stay in solution and the reagents are bound onto the polymer support which can then be used in excess and removed by simple filtration.

During scavenging reactions[6] with commercial polymer-supported isocyanates, many drawbacks, such as their relatively high cost and poor reactivity, become evident. The toxicity of phosgene and its equivalents,[7] used for the preparation of these resins[8] led to studies to find an alternative and to the immobilisation of a number of difunctionalised isocyanates onto a variety of aminomethyl resins.

A number of diisocyanates were investigated and these included *m*-xylene diisocyanate (MXD) **2**, methylene di-phenylene diisocyanate (MDI) **3** and phenyl diisocyanate (PDI) **4** (Scheme 1).[9]
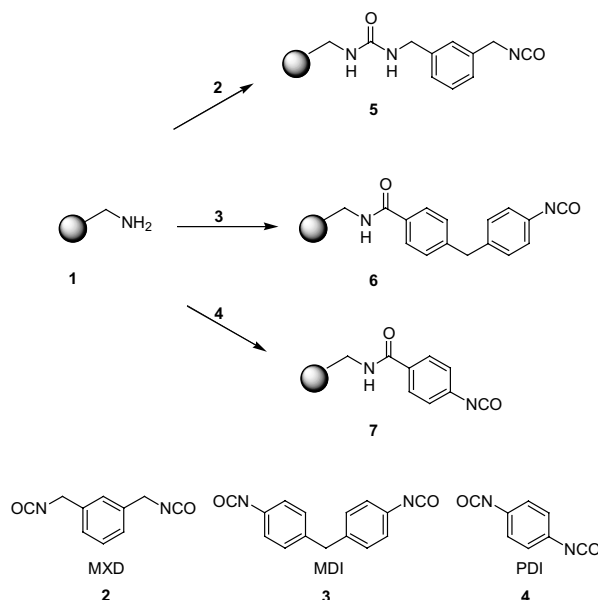
**Scheme 1.** Reaction of diisocyanates with aminomethyl resin and the synthesis of polymer-supported isocyanates.

Thus aminomethyl gel-type resins were treated with solutions of the diisocyanates in *N*-methyl-2-pyrrolidone (NMP), with microwave heating, and after a negative ninhydrin test,[10] showed a strong absorbance at $2259 \, cm^{-1}$ characteristic of an isocyanate moiety.

Resin loadings were determined by Br microanalysis of the polymer-supported urea after reaction of the resin with an excess of 4-bromobenzylamine,[8] or by treatment of the resins with a solution of 4-chlorobenzylamine and
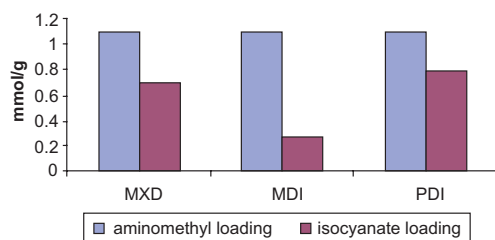
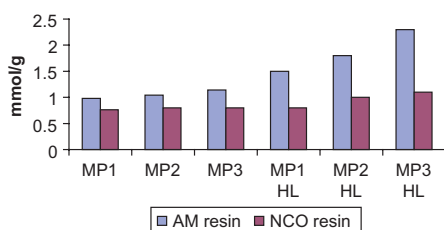**Figure 1.** Investigation of loading on isocyanate gel-type resins.



**Figure 2.** Loadings comparison of aminomethyl and isocyanate macroporous resin (MP) synthesised using PDI.

quantification by difference using GC. Good conversions were obtained as shown in Figure 1 with PDI proving to be the most efficient.

PDI was therefore used to prepare a resin library of macroporous polystyrene isocyanate supports and gave, in all cases, good conversions with the rigid macroporous nature[11,12] of such resins reducing any potential cross-linking (Fig. 2).

The supports prepared were tested for scavenging efficiency and compared to commercial methyl isocyanate resins (Novabiochem methyl isocyanate resin 2.5 mmol/g and Sigma–Aldrich methyl isocyanate resins 1.87 mmol/g).[10]

Table 1 and Figures 3–5 show the scavenging efficiency of the various resins. The experimental data all fitted the equation: $A = A_0 + a e^{-kt}$ as expected (pseudo first order reaction, where $k$ describes resin reactivity, and $A_0$, describes the scavenger efficiency of the resin.

The gel-type isocyanate resins developed here showed better reactivity compared to commercially available methyl isocyanate resins (Fig. 3). Macroporous resins (Figs. 4 and 5) showed slightly reduced kinetics com-
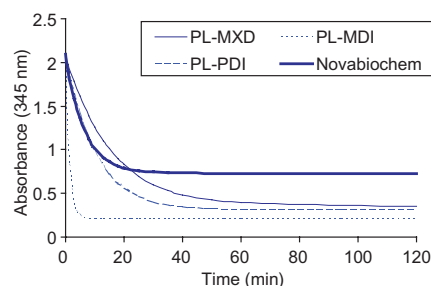
**Table 1.** Isocyanate resin kinetic parameters

| Resin | $A_0$ | $a$ | $k$ |
|---|---|---|---|
| NovaBiochem | 0.73 | 1.35 | 0.15 |
| Sigma–Aldrich | 0.43 | 1.44 | 0.10 |
| PL-MXD | 0.35 | 1.73 | 0.06 |
| PL-MDI | 0.21 | 1.88 | 0.08 |
| PL-PDI | 0.32 | 1.77 | 0.09 |
| MP1 | 1.06 | 0.8 | 0.003 |
| MP2 | — | — | — |
| MP3 | 0.4 | 1.45 | 0.007 |
| HL MP1 | 0.29 | 1.57 | 0.01 |
| HL MP2 | 0.19 | 1.67 | 0.034 |
| HL MP3 | 0.68 | 1.17 | 0.006 |



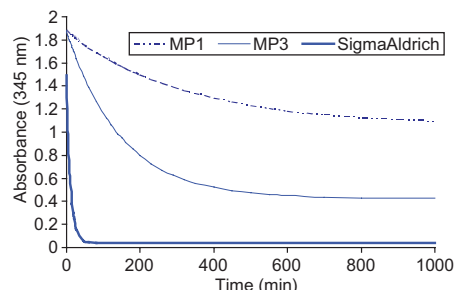**Figure 3.** Kinetic studies on gel-type isocyanate resins.



**Figure 4.** Kinetic studies on macroporous-type isocyanate resins (MP1 and MP3) and comparison with an equivalent commercial gel-type resin.
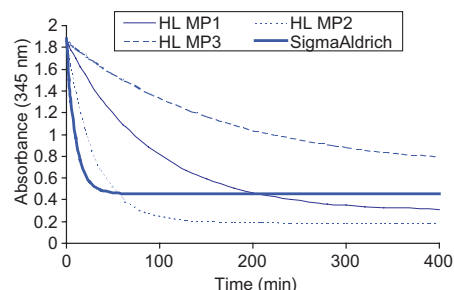


**Figure 5.** Kinetic studies on the macroporous-type isocyanate resins HL MP1, HL MP2 and HL MP3 and comparison with a commercial gel-type resin.

pared to gel-type resins, but generally showed much better scavenging efficiency (smaller $A_0$ value) as well as having the advantage of not suffering from the same solvent limitations as their gel-type counterparts, allowing them to be used efficiently in a wide range of solvents.

The gel-type isocyanate resin was used for the purification of a small library of amides generated using commercially available polymer supported DCC (Novabiochem) and 1.5 equiv excess of amine with respect to the carboxylic acids. The results are summarised in Table 2.

The polymer-supported isocyanates prepared by reacting aminomethyl resins and bis-isocyanates thus have major advantages over commercial materials, being inexpensive to prepare and highly reactive, showing better reaction kinetics and efficiency than classical methyl isocyanate resins.

**Table 2.** Synthesis of an amide library purified by isocyanate scavenging

| Amide | Yield (%) | Conversion (%) | Amine scavenged (%) |
|---|---|---|---|
|  | 40 | 100 | 100 |
|  | 66 | 100 | **100** |
|  | 43 | 77 | **56** |
|  | 55 | 100 | 100 |
|  | 49 | 100 | 100 |
|  | 37 | 68 | **63** |
|  | 32 | 100 | 100 |
|  | 33 | 50 | **100** |
|  | 48 | 66 | 100 |

Yields were determined gravimetrically. Conversions and purities were measured by LC/MS. **1** or **2** equivalents of isocyanate resin (with respect to the carboxylic acid) were used in the purification step.

## 1. General synthesis of polymer-supported isocyanate (macroporous-type) (9)

PDI **6** (35.2, 0.22 mmol) was dissolved in NMP (3 mL, anhydrous) and added to aminomethyl resin (100 mg, 0.1 mmol) previously swollen in the same solvent. The suspension was shaken under nitrogen for 1 h. Completion of the reaction was verified by a ninhydrin test. The resin was filtered and washed with NMP (5 mL × 3), DCM (5 mL × 3) and dried in vacuum at 40 °C for 24 h.

## 2. General synthesis of polymer-supported isocyanate: microwave assisted synthesis (gel-type)

Polymer labs aminomethyl resin (1.1 mmol/g, 100 g, 0.11 mmol) was swollen in anhydrous NMP (3 mL) in a 5 mL microwave vial. PDI (35.2 mg, 0.22 mmol) was dissolved in anhydrous NMP (2 mL) and added to the resin under sonication. The microwave vial was sealed and irradiated for 5 min at 100 °C. The resin was filtered

and washed with NMP (5 mL × 3), DCM (5 mL × 3) and dried in vacuum at 40 °C for 24 h.

## 3. Kinetic evaluation of isocyanate resins

1-Pyrene methylamine hydrochloride (3.8 mg, 0.014 mmol) was dissolved in triethylamine/DCM 1:99 (50 mL). 2.5 mL (35 μmol) of this solution were added to the isocyanate resin (12 equiv) previously weighed into quartz UV cells. Measurement of absorbance (345 nm) versus time allowed determination of the kinetic parameters.

## References and notes

1. Lebl, M *J. Comb. Chem.* **1999**, *1*, 3–24.
2. Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.
3. Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, *1*, 3293–3320.
4. Akelah, A.; Sherrington, D. C. *Chem. Rev.* **1981**, *81*, 557–587.
5. Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I. T. S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195.
6. Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193–7196.
7. Budavari, S. In *The Merck Index. An Encyclopedia of Chemicals, Drugs and Biologicals*; Merck Ed.; Rahway: NJ, 1996.
8. Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882–4886.
9. Barrett, A. G. M.; Smith, M. L.; Zecri, F. J. *Chem. Commun.* **1998**, 2317–2318.
10. Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.
11. Galaffu, N.; Bradley, M. Polymer-Supported Reagents. In *Encylopedia of Polymer Science and Technology*; Kroschwitz, J. I., Ed.; John Wiley & Sons: Hoboken, NJ, 2004; Vol. 11, pp 134–163.
12. Macroporous resins (45–75 μm) were synthesised using 40% (M) cross-linking.

| Resin ID | Loading (mmol/g) | Porogen type | | Porogen (%) |
|---|---|---|---|---|
| | | Toluene | Heptane | |
| MP1 | 0.98 | 9 | 1 | 200 |
| MP2 | 1.04 | 1 | 0 | 300 |
| MP3 | 1.12 | 1 | 0 | 300 |
| HL MP1 | 1.5 | 9 | 1 | 200 |
| HL MP2 | 1.8 | 1 | 0 | 300 |
| HL MP3 | 2.3 | 1 | 0 | 300 |