

Report

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Kinetic Comparison of Amide Formation on Various Cross-Linked Polystyrene Resins

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Solid-phase organic synthesis (SPOS) is widely used to construct small molecule combinatorial libraries for drug discovery.¹ Advantages of SPOS over solution synthesis include the ease of product isolation and the ability to drive reactions to completion by the use of excess reagents. However, not all solution chemistry can be directly transferred to solid supports, and the conversion from solution chemistry to solid phase can be a slow, trial-and-error process, due in part to the lack of kinetic and mechanistic information for reactions on solid supports. Quantitative studies of solid-phase reactions can provide reaction rate and conversion data, as well as valuable information about reaction mechanisms. Recently, the kinetic effects of polystyrene (PS)- and TentaGel-based resins have been reported for several solid-phase organic reactions using single-bead IR and fluorescence methods.^{2–4} Here, we report a kinetic comparison of amide formation on various cross-linked polystyrene resins, using the attachment of Knorr linker as the model reaction (Scheme 1).

Figure 1 depicts reaction time courses of two independent amide formation experiments on 100–200 mesh aminomethyl PS resin using 0.2 M Knorr/0.4 M *N,N*-diisopropylethylamine (DIEA)/0.2 M benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) in either dichloromethane (DCM) or dimethylformamide (DMF) at 25 °C. The amount of the reactive intermediates formed by the carboxylic acid and PyBOP^{5,6} is present in approximately 20 times molar excess over the amino groups on the resins. Therefore, the reaction can be treated as a pseudo-first-order reaction and be expressed as

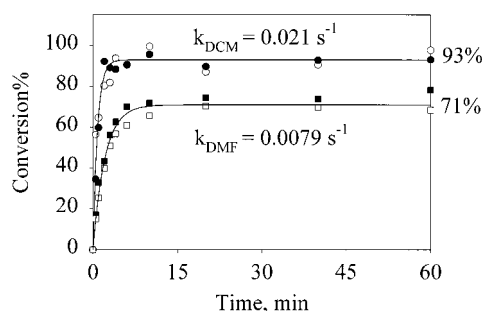
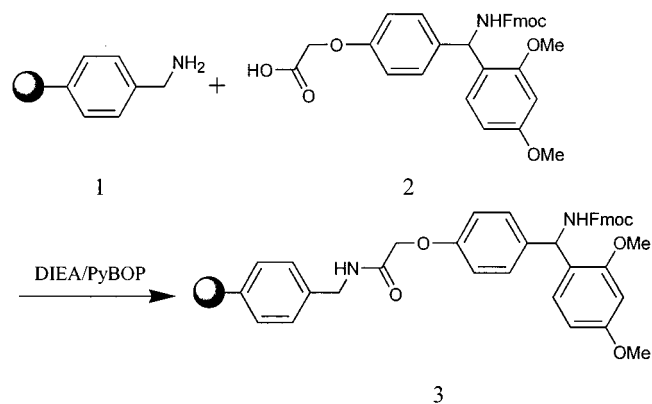


Figure 1. Time courses of Knorr attachment onto 100–200 mesh aminomethyl polystyrene resin (0.5 mmol) in DCM (circles) and DMF (squares). Experimental conditions: 0.2 M Knorr, 0.4 M DIEA, 0.2 M PyBOP, 50 mL of DCM or DMF, 25 °C. Lines are the fitting of eq 1 with an observed rate constant of $2.1 \times 10^{-2} \text{ s}^{-1}$ and a reaction conversion of 93% in DCM, or with an observed rate constant of $7.9 \times 10^{-3} \text{ s}^{-1}$ and a reaction conversion of 71% in DMF.

Scheme 1



$$y = a_0(1 - e^{-k_{\text{obs}}t}) \quad (1)$$

where k_{obs} is the observed reaction rate constant, a_0 is the amide formation conversion percentage when the reaction is completed, and y is the measured Knorr resin product percentage at each time point by Fmoc analysis.⁷ Then, the reaction half-life ($t_{1/2}$) can be calculated with eq 2.

$$t_{1/2} = 0.693/k_{\text{obs}} \quad (2)$$

An observed rate constant of $2.1 \times 10^{-2} \text{ s}^{-1}$ and half-life ($t_{1/2}$) of 33 s were obtained on 100–200 mesh PS resin by

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Table 1. Kinetics of Knorr Formation Reaction on Various Resins^a

resins (size)	k_{obs} (1/s)	$t_{1/2}$ (s)	con- version (%)	loading (mmol/g) ^b
PS (100–200 mesh)	2.1×10^{-2}	33	93	1.38
PS (100–200 mesh) ^c	7.9×10^{-3}	88	71	1.38
PS (200–400 mesh)	$ca. 8 \times 10^{-2}$	ca. 9	96	0.43
PS (70–90 mesh)	3.9×10^{-3}	178	96	1.12
Champion-1 (100–200 mesh) ^d	$ca. 4 \times 10^{-1}$	ca. 2	98	0.40
ArgoGel-AM ((164 μm) ^e	$ca. 7 \times 10^{-2}$	ca. 10	94	0.44
TentaGel-AM ((130 μm) ^e	$ca. 6 \times 10^{-2}$	ca. 12	91	0.29

^a Experimental conditions: 0.2 M Knorr/0.4 M DIEA/0.2 M PyBOP in DCM at 25 °C. ^b Measured loading by Fmoc-Cl before Knorr formation (see Supporting Information for details). ^c The same experimental conditions used in previous entry but carried out in DMF instead of DCM. ^d Champion-1, a type of PEG-AMPS resin that has 60% PEG content from Biosearch Technologies.⁸ ^e Scheme 2.

fitting the duplicated data obtained using DCM (Figure 1 and Table 1). The reaction conversion is 93%, which has been corrected for the weight increase of the attached Knorr component on the aminomethyl resins (see Experimental Section for details).

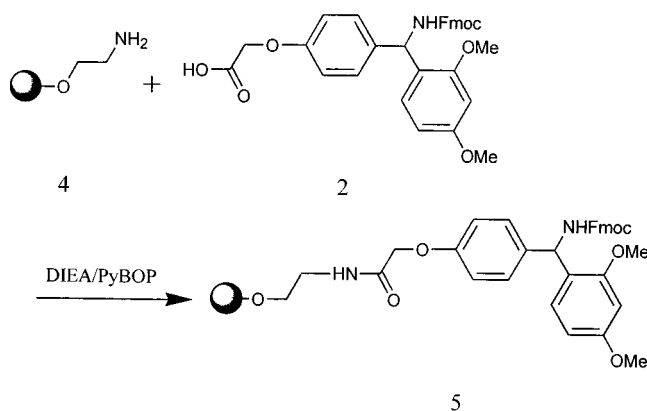
When the same reaction was performed in DMF, an observed rate constant of $7.9 \times 10^{-3} \text{ s}^{-1}$ ($t_{1/2} = 88 \text{ s}$) and a corrected reaction conversion of 71% were fitted with eq 1 (Figure 1 and Table 1). The slower reaction rate and lower conversion could be at least partially explained by the lower swelling of PS resin in DMF as compared to that in DCM.

Table 1 also lists the kinetic constants for the same reaction using 200–400 and 70–90 mesh PS resins in DCM. The observed rate constants are $ca. 8 \times 10^{-2} \text{ s}^{-1}$ and $3.9 \times 10^{-3} \text{ s}^{-1}$, respectively. The results indicate that the amide formation is faster on smaller (larger mesh) resins.

Also, we carried out the same kinetic study on 100–200 mesh poly(ethylene glycol) (PEG)-AMPS Champion-1 resin consisting of ~60% PEG and ~40% PS content. The reaction is very fast in DCM, with an observed rate constant of $ca. 0.4 \text{ s}^{-1}$ (Table 1). The faster reaction rate on this PEG resin indicates that the PEG moiety plays an important and favorable role in the amide formation. Recently, excellent swelling properties and fast acylation characteristics of this resin have been reported.⁸

To further establish the effect of the PEG moiety in resins, two additional PEG-containing resins, namely ArgoGel-AM (~70% PEG-containing) and TentaGel-AM (70–80% PEG-containing), were also studied under the identical conditions in DCM (Scheme 2). The observed rate constants are $ca. 6 \times 10^{-2} \text{ s}^{-1}$ and $ca. 7 \times 10^{-2} \text{ s}^{-1}$ for TentaGel and ArgoGel, respectively (Table 1). Unique properties of the solution-like PEG long chains, such as favorable PEG-induced local environmental changes in solvation, dielectric properties, and hydrogen bonding, are possible explanations for the faster kinetics;⁹ however, this effect is highly reaction-dependent.^{3,4}

In summary, a kinetic comparison of amide formation on a variety of solid supports has been performed. Results indicate that amide formation is faster on smaller size (larger mesh) and PEG-containing resins, largely due to the resin size and the solution-like reaction environment.

Scheme 2

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Supporting Information Available. Experimental Section. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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