Effects of Polymer Supports on the Kinetics of Solid-Phase Organic Reactions: A Comparison of Polystyrene- and TentaGel-Based Resins

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A quantitative comparison of kinetics of seven solid-phase organic reactions on two commonly used resin supports, polystyrene (PS)- and Tentagel (TG)-based resins, is presented. The data we obtained contradict the popular presumption that reactions proceed more rapidly on "solution-like" TG resins. Our results are discussed in terms of a hypothesis in which the resin bead is viewed as another "solvent phase". The effect of polymer backbones on the reaction kinetics is similar to the effect of solvent on a solution reaction rate. There is no single polymer support that favors all reactions. Depending on the nature of a chosen reaction, TG- or PS-based resins can be a better choice for solid-phase organic synthesis.

Introduction

Both solid-phase[1] and liquid-phase[2] synthetic methods are used for combinatorial chemistry.[3] To date, the majority of small molecule combinatorial libraries have been assembled by solid-phase organic synthesis (SPOS).[1] One advantage of SPOS is the complete removal of purification procedures, therefore making it particularly useful for multistep-automated synthesis. To realize this advantage, the reactions should go to completion in each step, preferably at a high rate. It is important to consider the efficiency and kinetics of the intended reaction on the resin support when selecting a resin for library synthesis. A better understanding of the effect on reaction kinetics by the currently used solid supports would aid in their applications in SPOS and combinatorial chemistry.

In SPOS, molecules are built up on the end of a spacer group, which serves to attach the reactant molecule to the resin bead. Resin is uniformly functionalized. The amount of reactive groups on the bead surface and in the bead interior can be easily estimated by volume calculations. If the "depth" of the surface is defined as 0.1 μm, the total amount of reactive sites on the surface is about 0.6% of the total reactive sites for a bead with a diameter of 100 μm. Therefore, more than 99% of these reactive sites are in the interior of the resin bead. The stereotypical view of a resin bead is a rigid, nonsolution-like matrix in which organic reagents have to overcome a steric barrier in order to diffuse into the resin bead. Although the resins are usually heavily solvated (swollen resin beads contain 80% solvent by weight), reactions are undoubtedly affected by the proximity of the attached reactant to the spacer and the polymer matrix. In this paper, we examine the effect of a solvated polymer support on reaction kinetics.

Although synthesis using polystyrene-based (PS) resins[4] has been considered superior to solution-synthesis techniques, it has always been classified as a support that retards reaction kinetics. A synthesis using soluble poly(ethylene glycol) (PEG) polymers was sought in order to maintain the advantages of both solution synthesis and solid-phase synthesis. An alternative approach was the development of TentaGel (TG) resin, which was designed to combine useful features from both insoluble PS support and the soluble PEG support.[5]

PS resin is highly hydrophobic, being made up of mainly 1% divinylbenzene (DVB) cross-linked polystyrene. For PS resin, the spacer separating the reactant and the resin matrix is usually short. Due to the short spacer length, reactions on PS resin tend to be affected by the hydrophobic PS matrix, which may disfavor reactions involving polar and charged species. The architecture of TG resin is based on a very small portion of cross-linked 1% DVB−polystyrene backbone that is

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Scheme 1

extensively grafted with long PEG spacers (50−60 ethylene oxide units). The PEG content is up to 70% of the resin weight. Therefore, the properties of the PEG chains determine the mechanical, physicochemical behavior of the resin. Because the reactive sites in TG resins are located at the end of a long, flexible spacer and are therefore well separated from the PS backbone, they are less affected by hydrophobic PS matrix, although the influence of the PEG spacers remains. On the basis of previous experience with solid-phase peptide synthesis, it is generally assumed that a reaction is faster on TG resin due to its "solution-like" property. We, however, would like to raise the possibility that SPOS may follow different rules from that of peptide synthesis. The purpose of this investigation is to quantitatively compare the influence of polymer matrix on the kinetics of seven organic reactions on PS- and TG-based resins using the single-bead IR method.[6]

Results

Case 1: Catalytic Oxidation of an Alcohol to an Aldehyde with Tetra-*n*-propylammonium Perruthenate (TPAP) and *N*-Methylmorpholine *N*-Oxide (NMO). We have previously reported the kinetics of the catalytic oxidation of a PS-bound benzylic alcohol (Wang resin) to the corresponding aldehyde with a pseudo first-order rate constant of 4.6×10^{-4} 1/s.[7] In this work, we carried out the same reaction (Scheme 1) on TG resin under identical reaction conditions (i.e., molar amount of resin-bound alcohol, the reaction volume, the concentrations of reagents and catalyst). The single-bead IR spectra taken at various times over the course of the reaction are shown in Figure 1A. This figure shows the progressive disappearance of the hydroxyl stretch at 3475 cm^{-1} and the appearance of a band at 1689 cm^{-1} attributable to the aldehyde carbonyl. The integration of IR peak areas and the result from the quantitation of the absolute amount of aldehyde groups on resin by a fluorescence method[8] are plotted in Figure 1B. All data were fitted well with a pseudo-first-order rate equation.[9] The rate on TG resin ($k = 1.8 \times 10^{-3}$) is four times faster compared to that on PS resin (Table 1).

Case 2: Ester Formations. A series of reactions in Scheme 2 were carried out under identical conditions on PS and TG resins. Single-bead IR spectra for the reaction of **1** with reagent **3** are shown in Figure 2. It is worth mentioning that prior to the reaction the IR bands for the hydroxyl in TG are a single broad band but in PS a sharp band at 3580 plus a broad one at ~3420. These indicate that the hydroxyl isolation is not allowed in TG resin, but partially allowed in PS resin (only partial hydrogen bonding between hydroxyl groups occurs).[10] The

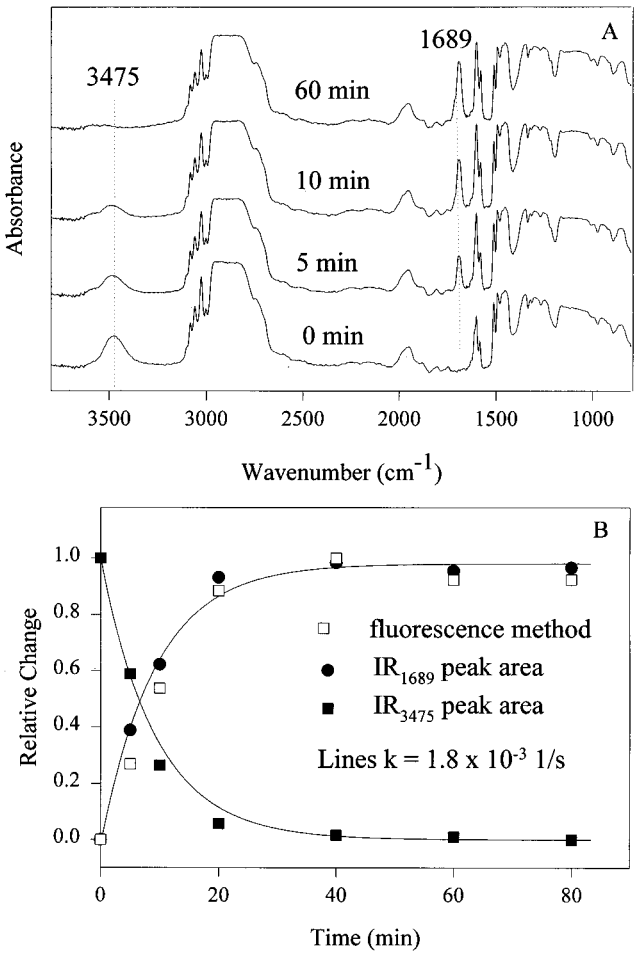


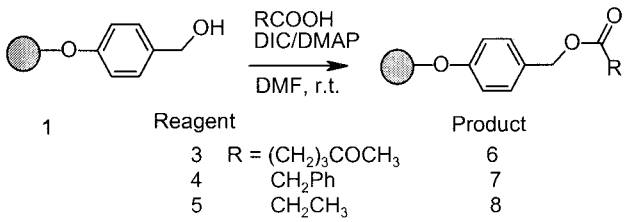
Figure 1. (A) IR spectra taken from a single bead at various times during the reaction in Scheme 1. (B) Integrations of peak areas for bands at 1689 cm^{-1} (solid circles) and 3475 cm^{-1} (solid squares) and values from determination of the absolute amount of aldehyde groups (open squares).

Table 1. Comparison of Reaction Rates on PS- and TG-Based Resins

reaction scheme	k_{PS} (1/s)	k_{TG} (1/s)	k_{TG}/k_{PS}
1	4.6×10^{-4} [a]	1.8×10^{-3}	3.9
2 (R = 3)	2.2×10^{-4}	2.3×10^{-4}	1.0
2 (R = 4)	4.8×10^{-4}	4.2×10^{-4}	0.9
2 (R = 5)	2.0×10^{-4}	2.2×10^{-4}	1.1
3 (R = H)	3.1×10^{-3}	1.8×10^{-3}	0.6
3 (R = 3)	4.1×10^{-4}	1.9×10^{-4}	0.5
4 (step 2)	1.13×10^{-4}	6.26×10^{-6}	0.055

[a] From ref 7.

Scheme 2



progressive formation of bands at 1732/1734 and 1716 cm^{-1} due to the ester and ketone carbonyl groups indicates the formation of the product. The integrations of the single-bead IR peaks areas are shown in Figure 3. A rate constant of 2.2×10^{-4} 1/s (lines) can fit data from both TG (filled symbols) and PS (open symbols) resins.

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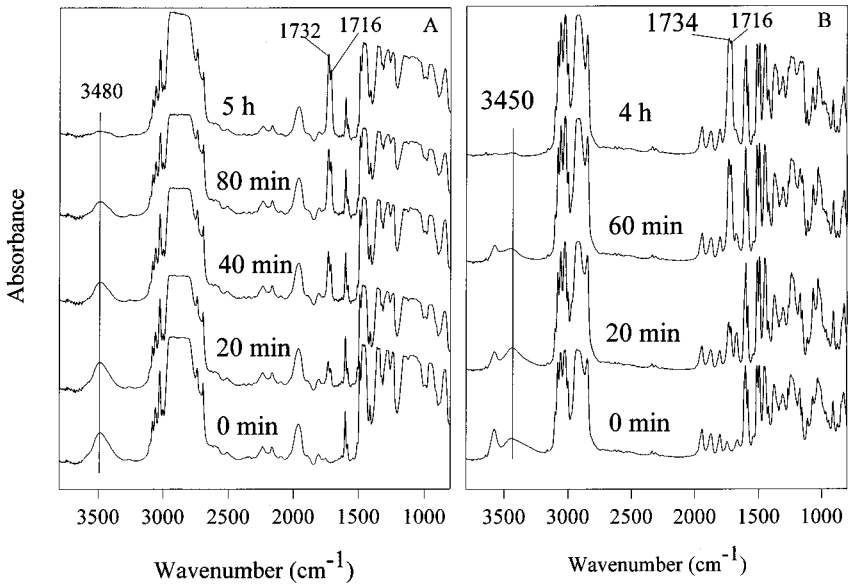


Figure 2. IR spectra taken from a single bead (A) or a single flattened bead (B) at various times during the reaction in Scheme 2 on TG- (A) or PS-based (B) resins.

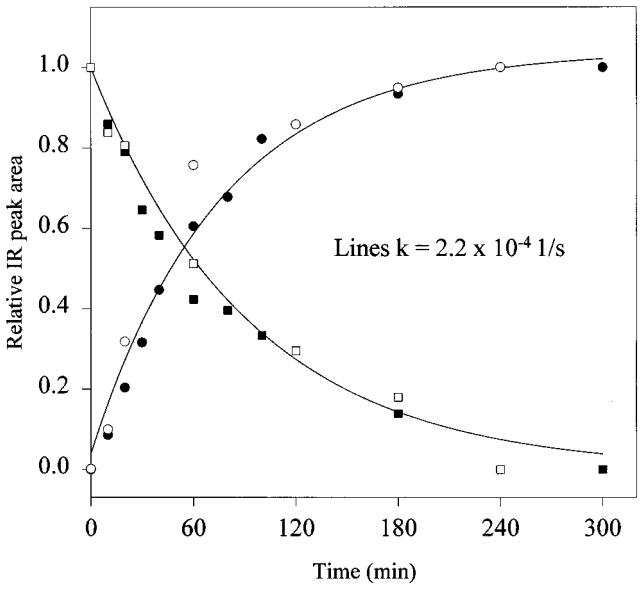
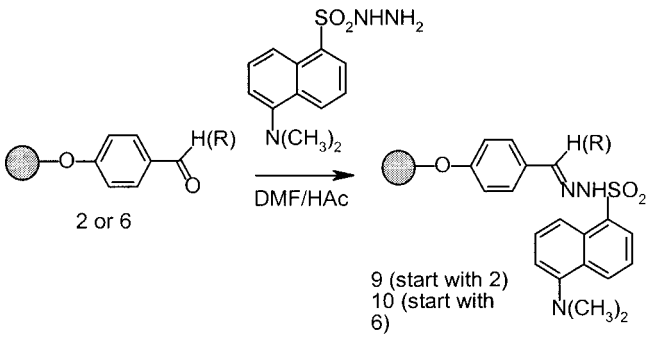


Figure 3. Integrations of peak areas for bands at 1716 and 1732/1734 cm^{-1} (circles) and 3450/3480 cm^{-1} (squares). Values from TG-based resin are shown in solid symbols and from PS-based resin in open symbols. Lines are a theoretical time course with a rate constant of 2.2×10^{-4} 1/s.

The results of similar reactions carried out with reagents **4** and **5** show that the reaction rate is approximately the same on both resins (Table 1).

Case 3: Synthesis of Dansyl Hydrazones. Both resin-bound **2** and **6** were reacted with dansylhydrazine under identical conditions on TG and PS resins (Scheme 3). Single-bead IR spectra for the transformation from **6** to **10** is shown in Figure 4. The ester carbonyl bands at 1734 remain while the ketone carbonyl band at 1716 disappears accompanying the formation of dansylhydrazone. The formation of the band for the hydrazone N−H stretch at 3230 cm^{-1} and the band for $N(CH_3)_2$ stretch on the dansyl group at ~2790 cm^{-1} on PS resin product proved the product formation. Although the product band at 2790 is not evident due to the overlaps between

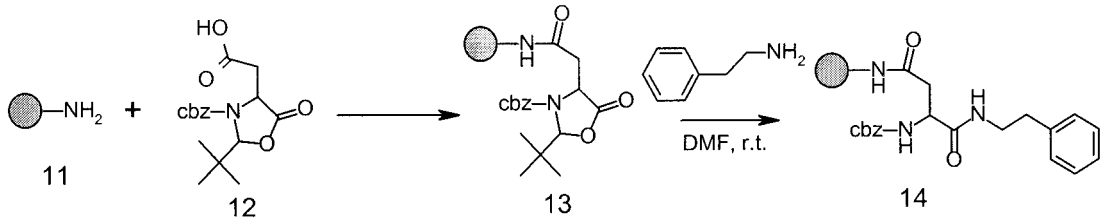
Scheme 3



the strong CH_2 band and the hydrazone signal in the TG resin, the appearance of the band at 3230 and the disappearance of the band at 1715 cm^{-1} are evident. Due to the overlap between the ester and the ketone carbonyl bands, a peak deconvolution analysis using PeakFit (Jandel Scientific, San Rafael, CA) was carried out for a clear-cut quantitation. One such analysis of the data for PS reaction at 0 and 60 min (taken from Figure 4) is shown in Figure 5. It demonstrates that overlapping bands can be resolved to aid a quantitative analysis. The areas of the resolved ketone carbonyl band after PeakFit analysis were used to obtain the time course for these reactions. The results are plotted in Figure 6. In this case, the reaction on PS resin is 2.2 times faster than that on TG resin.

Case 4: C-Terminal Modification of Aspartic Acid through a Ring-Opening Reaction. PS and TG amine resins reacted with **12** to produce **13** (Scheme 4). Since three carbonyl groups were introduced in the reaction product, the formation of **13** on both resins after 6 h was confirmed by the formation of strong bands at 1675, 1722, and 1795 cm^{-1}. The band at 1795 cm^{-1} is from the carbonyl group on the five-membered ring. The reaction kinetics of the reaction between **13** and 2-phenethylamine to form **14** was monitored. Single-bead IR spectra in this process are shown in Figure 7. The opening of the five-membered ring during the transformation of **13** to **14** (confirmed by NMR after cleavage) was indicated by the

Scheme 4



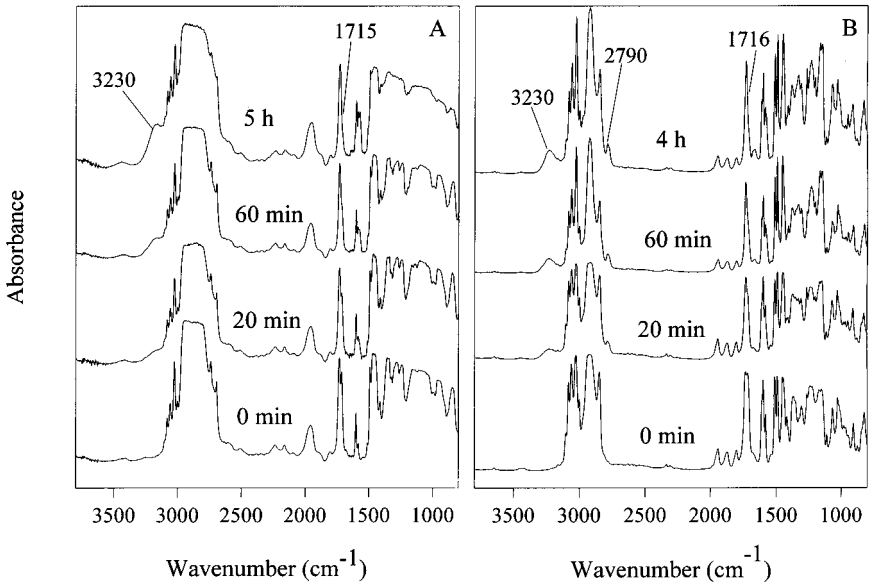


Figure 4. IR spectra taken from a single bead (A) or a single flattened bead (B) at various times during the reaction in Scheme 3 on TG- (A) or PS-based (B) resins.

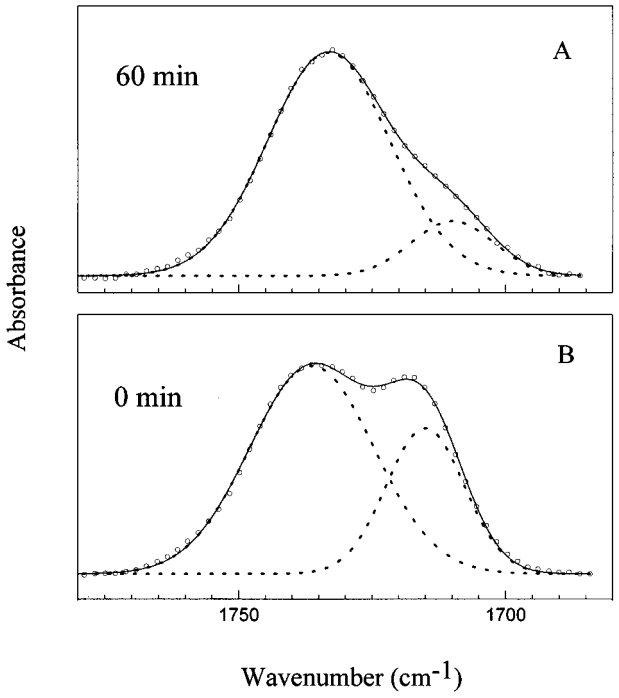


Figure 5. PeakFit analysis of overlapping IR bands. Overlapping IR bands at ~1716 cm^{-1} from Figure 4B were analyzed with the PeakFit program.

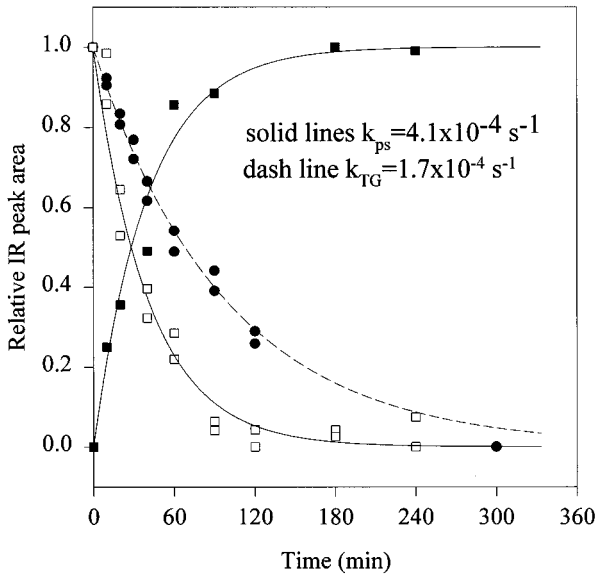


Figure 6. Integrations of peak areas for the band at 3230 cm^{-1} for PS-based resin (solid squares) and PeakFit resolved peak areas at 1715/1716 cm^{-1} (solid circles for TG-based resins and open squares for PS-based resins). Solid lines are a theoretical time course with a rate constant of 4.1×10^{-4} 1/s, and the dashed line is a theoretical time course with a rate constant of 1.7×10^{-4}.

disappearance of the IR band at 1795 cm^{-1} for both PS and TG resins. Integrations of IR peak areas of this band resulted in time courses for this conversion and are shown in Figure 8. The reaction on PS was 18 times faster than that on TG resin ($k = 1.13 \times 10^{-4}$ vs 6.26×10^{-6}, Table 1).

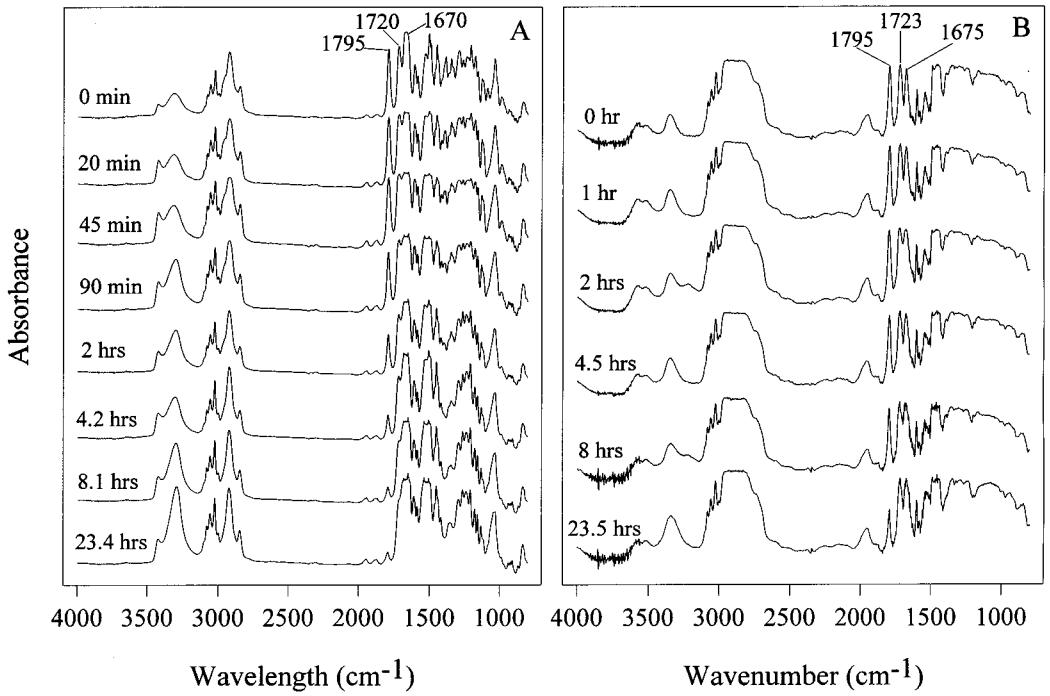


Figure 7. IR spectra taken from a single flattened bead (A) or a single bead (B) at various times during the reaction in step 2 in Scheme 4.

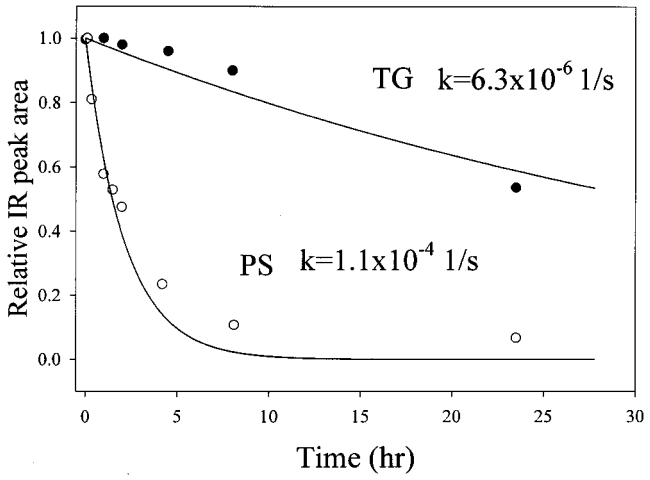


Figure 8. Integrations of peak areas for the band at 1795 cm^{-1} (see Figure 8) for both PS- (open circles) and TG-based resins (solid circles). Solid lines are theoretical time courses with rate constants of 6.26×10^{-6} 1/s (TG) and 1.13×10^{-4} 1/s (PS).

Discussion

It is generally assumed that a TG resin allows a faster reaction since it provides a more "solution-like" matrix compared with PS resins. The so-called "solution-like" matrix means that the attached reactant is floating in a mobile PEG phase in the TG resin while in the PS resin the reactant is attached on an "immobile" PS phase that does not appear to be very "solution-like". This hypothesis may explain the results on peptide synthesis and on some organic reactions involving polar reagents. As we observed, the kinetics for the oxidation of an alcohol are more rapid on TG than on PS resin. In this reaction, the catalyst TPAP is a salt and the polar resin matrix of TG may be more compatible with the catalyst. Kinetics data on reactions in Schemes 3 and 4 show that this hypothesis is not generally true. Another general assumption is that PS resin poses more steric hindrance to the penetration of reagents into the resin interior compared with TG resins. Due to the highly flexible spacers in TG resins, the matrix usually poses no steric hindrance[11] to reagents.

However, ESR[12] studies have shown that the motional rate of the pendant group in the PS resin is high in a good swelling solvent. Merrifield pointed out that this extensive chain flexibility plays an important role in the rate and extent of the reactions in solid-phase peptide synthesis.[13] In our previous kinetics studies,[7−10] we have found that, except for trityl-like spacers, the proximity of spacer to the PS backbones in general poses little steric hindrance. This may be due to the fact that a full solvation and the dynamic fluctuation of the PS matrix allow free access of reagent into the resin bead. In the four reaction types studied in this investigation, two reactions even exhibited a higher reaction rate when carried out on PS resins than that on TG resins. The steric hindrance assumption is again not generally true. Then, what determines the relative reaction rate on different resin supports?

Recently, Czarnik has summarized some key observations including ours on this subject and pointed out that solid-phase synthesis supports are like solvents.[15] The effect of polymer matrix on the reaction rate may be very similar to the effect of solvent on the rate of a solution reaction. A swollen bead is the ultimate microreactor for SPOS. Although its 80% constituents are solvent, spac-

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ers and matrix evidently pose important effects on incoming reagents and reactants depending on their molecular properties such as polarity. Early reports[14] on that phase-transfer catalysts accelerated the solid-phase reaction rate provided support for this proposal. Our experimental results established that the matrix of a swollen resin bead behaves indeed like another "solvent phase". A complete understanding how the structure of a support affects the reactivity of an attached reactant will await more investigations.

Summary

We have presented the first quantitative comparison of kinetics of seven organic reactions on two of the most commonly used resin supports: PS- and TG-based resins. The results of this study contradict the popular presumptions that TG resins always afford a faster reaction compared to PS resins. On the basis of our experimental results, we have taken the view that the solvated resin can be viewed as another "solvent phase". There is no single polymer support that favors all reactions. The choice between PS and TG resins should depend on the nature of the reaction and its requirement for polar or nonpolar medium.

Experimental Section

Materials. All PS-based resins and TG aldehyde and amino resins were purchased from NovaBiochem (San Diego, CA). Knorr resin from Advanced ChemTech. (Louisville, KY). Other TG-based resins from Rapp Polymere (Tubingen, Germany). PS-based resins are based on 1% cross-linked divinylbenzene−styrene copolymer. They have loadings between 0.54 and 0.8 mmol/g. The loadings of TG-based resins are between 0.22 and 0.27. The diameter of TentaGel beads is ~90 μm. The average diameter for polystyrene-based resin is also around 90 μm with a larger variations compared with TentaGel resins. One drop of resin suspension was taken from the reaction vessel at specified times. The resins were filtered and washed with THF (five times) and dichloromethane (five times). All reagents, if not specified, were purchased from Aldrich (Milwaukee, WI).

FTIR Microspectroscopy. All spectra were collected on a BIO-RAD, FTS-40 spectrophotometer coupled with a UMA-300 IR microscope, using a SPC-3200 data station. The microscope is equipped with a 36X Cassegrain objective and liquid nitrogen cooled mercury−cadmium−telluride (MCT) detector. The general procedure for single bead FTIR measurements was previously described.[6a] The single TG resin bead or the flattened PS bead[6b] were used throughout experiments.

Data Analysis. To correct the effect of bead sizes, IR spectra were normalized by making the intensity of a polystyrene band at 1947 cm^{-1} or a TG resin band at 1952 cm^{-1} equal. The areas under the typical bands of the starting material or the product were integrated. The values of integration were plotted against time. These data points were fitted to a pseudo-first-order rate equation by using a nonlinear regression program, SigmaPlot for windows (Jandel Scientific, San Rafael, CA), on a PC computer. For overlapping IR bands, PeakFit program (Jandel Scientific) was used to fit bands with a Gaussian function. Areas of the deconvoluted peaks were used for quantitation.

Synthesis of an Aldehyde 2 on TG Resin. In Scheme 1, TG PHB resin (22.2 mg, 0.27 mmol/g) was washed with 0.5 mL of DMF for 30 min and then drained. The resuspended resin reacted with 10 equiv of NMO and 0.2 equiv TPAP in 200 μL of DMF. The mixture was rotated on a Glas-Col Laboratory rotator with a 16 rpm speed at rt. At specified times, a drop of resins was washed with THF (five times) and dichloromethane (five times). Single-bead IR was then taken without the need of vaccum drying.

Esterifications and Synthesis of 6−8. Wang resin (11.1 mg, 0.54 mmol/g) or TG PHB resin (22.2 mg, 0.27 mmol/g) was swollen with DMF for 30 min and then reacted with 10 equiv of acid (see Scheme 2), 5 equiv of DIC, and 10 equiv of DMAP in 250 μL of DMF. The suspension was mixed with a rotator (16 rpm).

Synthesis of Hydrazone 9 and 10. Formylpolystyrene (10.3 mg, 0.58 mmol/g), TG aldehyde from catalytic oxidation (22.2 mg), or ketone resins from acetylbutyric acid esterification product (11.1 mg for PS and 22.2 mg for TG products) reacted with 2 equiv of dansylhydrazine in 0.2 mL of 33% (for aldehyde) or 15% (for ketones) HOAc/DMF solution. Reaction mixtures were mixed with a rotator (16 rpm).

Synthesis of 13 and 14. Knorr resin (0.8 mmol/g) or TG amino resin (0.25 mmol/g) was washed and reacted with protected aspartic acid as described.[16] The procedures for the ring-opening reaction with phenethylamine were as previously described.[16] IR analysis was performed as above.

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