Crucial Factors Regulating Site Interactions in Resin Supports Determined by Single Bead IR

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Interactions between resin-bond reactive groups were determined by measuring the single bead IR signals sensitive to their association and dissociation. Our results strongly indicate that site separation and site interaction always occur and that they are in a dynamic equilibrium in resins. The highly dynamic nature of the site interaction was demonstrated by the lack of linker-length influence on site interaction. An increased competition for nearby sites or a reduced availability of the nearby sites all suppressed site interaction, indicating the importance of the availability of sites. Our results indicated that the less bulky microenvironment, the more reactive functional group, and the more available nearby sites are factors which favor site interaction.

Introduction

We have witnessed an overwhelming progress in the field of combinatorial chemistry[1] recently. Most combinatorial libraries made up to the present day have been assembled on solid-supports. However, due to the lack of analytical methods for solid-phase organic synthesis (SPOS) and the basic understanding of the resin properties and the reaction mechanism, SPOS has been practiced largely by "trial and error". In order for SPOS to become a fundamental methodology, some basic resin properties and principles of resin-supported reactions need to be elucidated.

In an ideal picture of a resin support, reactive groups (tentatively A) are bound to an insoluble polymer, and their free motion is restricted due to the relative rigidity of the polymeric lattice. Intermolecular reactions between A molecules are minimized, and the situation is approaching infinite dilution while the "concentration" of A is still relatively high. In such an ideal situation, undesirable bimolecular reaction between A molecules is supressed. Molecule A, especially when it is highly reactive in dimerization, will exclusively react with a soluble reagent B or undergo a desired intramolecular cyclization reaction. A clear view of how a solid-phase reaction can be modulated in such a detail is extremely valuable for combinatorial chemistry.

Previous studies on >2% DVB–polystyrene resins have complicated our knowledge by observing both site separation [2] and site interaction[3] effects. Taking advantage of the site separation effect, monofunctionalization of diols and dialdehydes was achieved on solid-supports.[4]

On the other hand, by purposefully attaching two different kinds of reactants onto resin, their condensation product was formed by taking advantage of site interaction effect.[5] To understand the fundamental properties of solid-supports and steer SPOS into the desired results, we carried out a series of experiments and now report our findings here. In this work, we have studied the currently most commonly used resins based on 1% DVB–polystyrene that have not been studied in previous reports. The relationships between reactive sites depend on the competitive interplay of a number of factors. We have examined the effects of steric environment, the linker length, and the reactivity of the reactive group, as well as the availability of the nearby sites on site interactions. In the past, we have already demonstrated[6] that single bead IR is valuable in obtaining a broad range of information on solid-phase reactions such as the TLC type yes-or-no answer, the determination of the percentage of conversion in a reaction, and the selection of the optimal reaction conditions. In this work, we furthered the application of single bead IR to reveal the nature and

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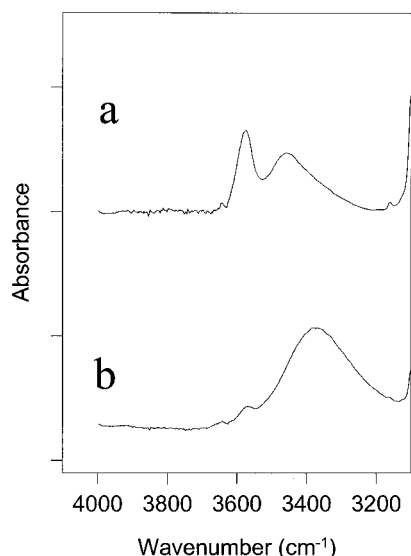(6) (a) Yan, B.; Kumaravel, G.; Anjaria, H.; Wu, A.; Petter, R.; Jewell, C. F., Jr.; Wareing, J. R. *J. Org. Chem.* **1995**, *60*, 5736–5738. (b) Yan, B.; Kumaravel, G. *Tetrahedron* **1996**, *52*, 843–848. (c) Yan, B.; Fell, J. B.; Kumaravel, G. . *J. Org. Chem.* **1996**, *61*, 7467. (d) Yan, B.; Gstach, H. *Tetrahedron Lett.* **1996**, *37*, 8325. (e) Yan, B.; Sun, Q.; Wareing, J. R.; Jewell, C. F. *J. Org. Chem.* **1996**, *61*, 8765.
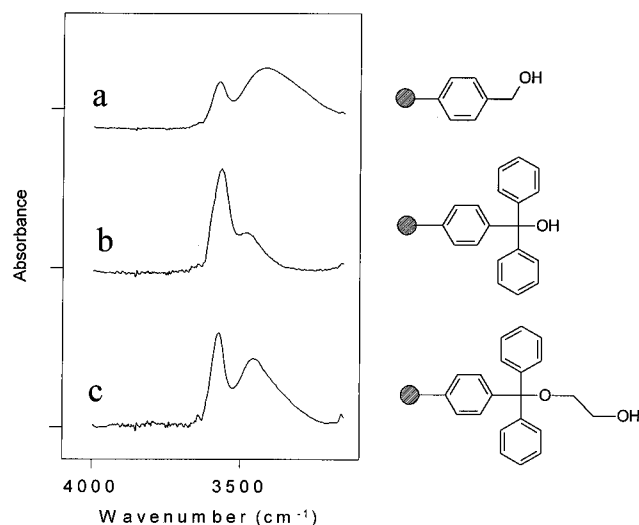
Figure 1. IR spectra taken from a single flattened bead for (a) Wang resin and (b) Wang resin treated with DMSO for 2 min and vacuum-dried for 5 min. All spectra were taken using the transmission mode at room temperature. The unbonded hydroxyl stretch at 3580 cm^{-1} is shifted to 3420 cm^{-1} after the treatment with hydrogen bond accepting molecule DMSO.

the degree of interactions between neighboring reactive groups within a single bead.

Results and Discussion

In previously published reports[7] polymer-bound alcohols were suggested to exist as partly free from and partly participating in mutual hydrogen-bonding interactions. We confirmed this by observing that the hydroxyl group band is split into two bands: a sharp band at ~3580 cm^{-1} and a broad band at ~3420 cm^{-1} for *p*-(benzyloxy)benzyl alcohol resin (Wang resin) (Figure 1a). This split was observed for untreated Wang resin from the commercial bottles. This was not changed after heating and freeze-drying.[6e] Although this splitting has been noted for a long time, it has not proven whether the sharp band is from free hydroxyl groups. Furthermore, it is unclear if the broad band is due to hydroxyl groups mutual interaction or due to hydrogen bonding with water molecules in the air. To confirm that the 3580 cm^{-1} sharp band is a result of the existence of free hydroxyl groups in Wang resin, we treated the resin with a hydrogen bonding accepting molecule DMSO briefly and dried for 5 min under vacuum. The single bead IR shows a considerable conversion from the sharp band to the broad band at lower frequency (Figure 1b). This conversion demonstrated the existence of a portion of free hydroxyl groups which is in a dynamic equilibrium with hydrogen-bonded hydroxyl groups in Wang resin. This has proven that the site separation does exist in a significant portion in Wang resin.

The question remaining is whether the broad band at 3420 cm^{-1} is from the hydroxyl mutual interaction or from the hydrogen bond between hydroxyl groups and residual water molecules in the air. We took single bead IR spectra of hydroxyl resins with variable bulky groups

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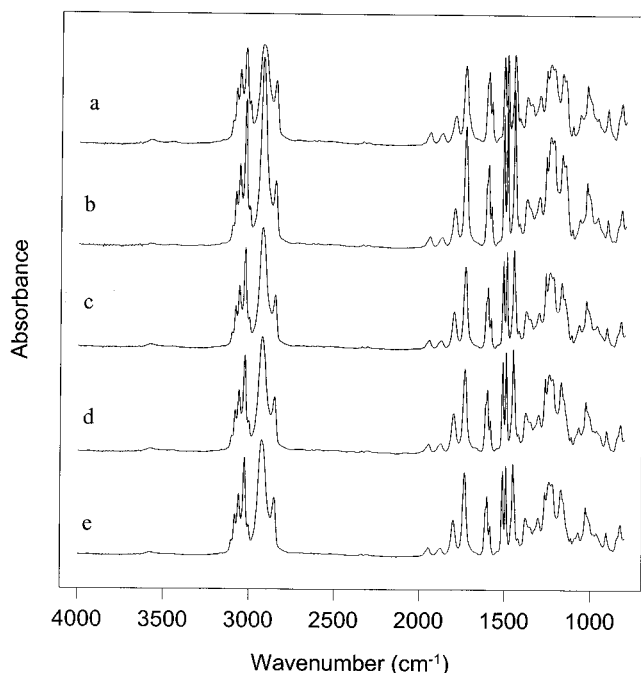

Figure 2. IR spectra taken from a single flattened bead for resins shown on the right. (a) Wang resin; (b) tritylhydroxyl resin; (c) ethylene glycol trityl resin. The intensity of the unbonded hydroxyl band at 3580 cm^{-1} increases as the microenvironment of the hydroxyl group becomes more bulky.

Scheme 1
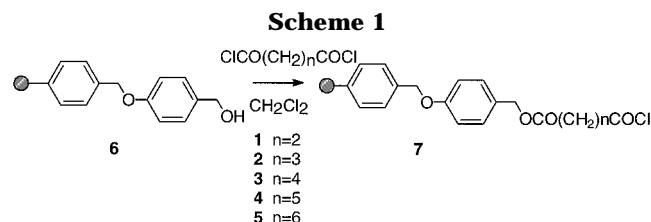
around the hydroxyl group. The increased steric hindrance will inhibit hydrogen bonding between neighboring hydroxyl groups, but will not affect hydrogen bonding with water molecules if any. Among this group of resin-bound molecules, hydroxymethyl resin (Figure 2a) has the smallest sharp peak at 3580 cm^{-1} and the largest broad band at 3420 cm^{-1} indicating that it has the greatest amount of hydrogen-bonded hydroxyl groups. The trityl-hydroxyl resin (Figure 2b) has the largest peak at 3580 cm^{-1} and the smallest peak at 3420 cm^{-1} indicating the presence of the largest portion of free hydroxyl groups. The addition of an ethylene glycol chain partially reversed the isolation status of the trityl alcohol and produced an increase in the hydrogen-bonded hydroxyl population (Figure 2c). The correlation between the increased steric hindrance around the hydroxyl groups and the increasing amount of free hydroxyl groups demonstrates that the origin of the broad band at 3420 cm^{-1} is the association between the neighboring hydroxyl groups rather than from the association with free water molecules.

Although above results show the interaction between the neighboring molecules, we still need to address the dynamic nature of interactions between these groups. In a rigid polymeric lattice, the length of linkers would regulate the mutual interactions between reactive groups. On the other hand, this linker-length dependence will not be seen in flexible and dynamic polymer backbones. We carried out a reaction (Scheme 1) to examine the extent of site−site interactions when the reagents vary the length of the linker (*n* in the scheme). In this reaction, the diacid chloride reacts with Wang resin to form an esterified acid chloride. If site interaction is
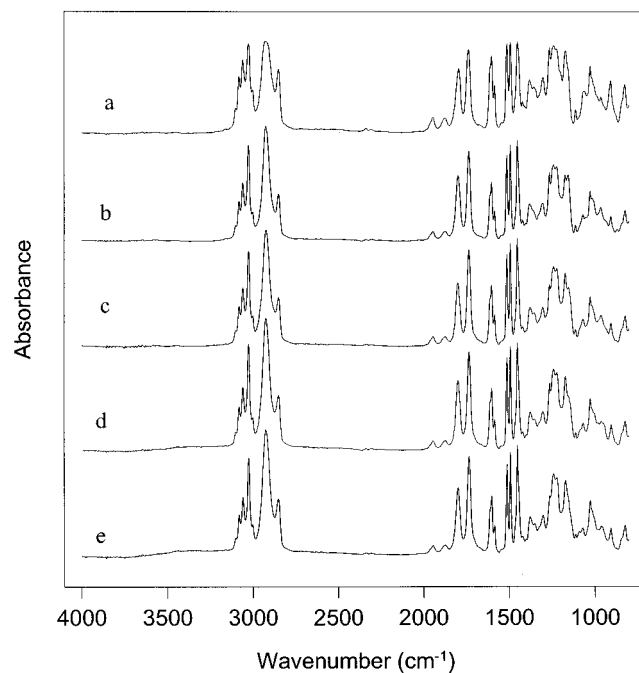
Figure 3. IR spectra taken from a single flattened bead for Wang resin that underwent the reaction in Scheme 1 for 20 min. Spectra a–e are for a 2-fold excess of compounds **1–5** as reagents in the reaction.
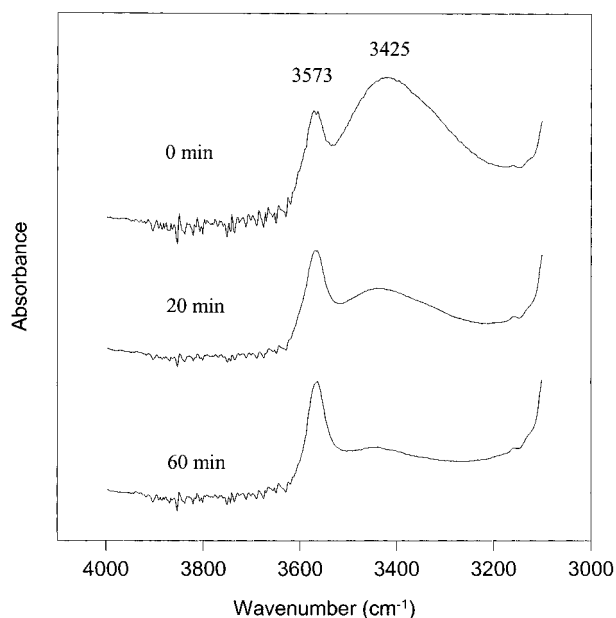

Figure 4. IR spectra taken from a single flattened bead for Wang resin that underwent the reaction in Scheme 1 for 20 min. Spectra a–e are for a 10-fold excess of compounds **1–5** as reagents in the reaction.

**Table 1. Linker Length Effect on Area Ratio Ester$_{1728}$/Acid Chloride$_{1795}$**

	area ratio (1728/1795)	
n	2-fold excess	10-fold excess
2	2.8	1.2
3	2.7	1.2
4	2.3	1.3
5	2.1	1.3
6	2.4	1.3

significant, the remaining acid chloride group, being highly reactive, will instantly react with the nearby hydroxyl group to form a diester species. Since the acid chloride carbonyl group and the ester carbonyl group show distinct IR frequencies and their relative molar absorptivity can be easily measured, the acid chloride/ester ratio (thereby the mono- and bilinked products) on the bead can be determined.

To quantitatively determine the mono- vs bilinked reaction product, we have first determined the ratio of molar absorptivities of ester bond and the acid chloride bond. We recorded an IR spectrum of a 1:1 molar ratio mixture of a diester diethyl pimelate and a diacid chloride pimeloyl chloride. The molar absorptivity of the ester bond was determined to be 1.23 times higher compared with that of the acid chloride based on the comparison of peak areas of the ester band at 1728 cm^{-1} and the acid chloride band at 1795 cm^{-1}. Figure 3 shows the IR spectra of the starting material Wang resin **6** and the reaction product **7** after reacting with 2-fold excess of compounds **1–5** for 20 min reaction. Time courses of all reaction showed that these reaction were completed in 10 min as monitored by single bead IR. Our results showed that the length of the linker had no effect on the site interaction in this case. We also examined the outcome when the reagent is in various amounts of excess. Figure 4 shows the spectra of products after a 20 min reaction using 10 fold excess compounds **1–5**. Again, no linker-length dependence was observed. These results strongly suggest the highly dynamic nature of the polymer backbone structure and, thereby, the site–site interaction.

When a 2-fold reagents was used (Figure 3), the areas of the ester bands are more than twice the areas of the acid chloride bands (Table 1), suggesting a noticeable fraction of double-linked product resulting from site interactions. This result indicates that, for this more active reactant, site interaction occurred when there are available nearby reactive sites. When 10-fold reagents were used (Figure 4), the ratio of areas for the ester and the acid chloride bands (Table 1) is the same as the ratio of their molar absorptivity, indicating that only single-linked acid chloride is formed and no site interaction occurred. In this reaction, the large excess of diacid chloride molecules rapidly occupy most of sites, and the hanging acid chloride group, though it is highly reactive, experiences difficulty in finding nearby reactive hydroxyl groups. To confirm that the band at 1795 cm^{-1} is from the hanging acid chloride carbonyl group, the selected products of the reaction in Scheme 1 were treated with 10-fold excess octanol in THF. The acid chloride carbonyl band at 1795 cm^{-1} is shifted to an ester carbonyl band at 1710 cm^{-1} (not shown). At a 2-fold excess, there is only a slightly more reactivity for short linker length (n = 2, 3) compounds (Table 1). In general, the effect of linker length is marginal. This result suggests that compounds with a longer linker and a short linker have similar probability in finding a nearby site. This is true only when the polymer backbones undergo dynamic fluctuations.

The above results demonstrated the influence of the availability of nearby-sites on site interaction through reagent competition. In the following example (Figure 5), the similar conclusion was reached by an alternative route: the control of the nearby-site availability. In this

Figure 5. IR spectra taken from a single flattened bead for resin-bound compound **8** that underwent the reaction in Scheme 2 for 20 and 60 min (approximately 40 and 60% conversion based on IR).
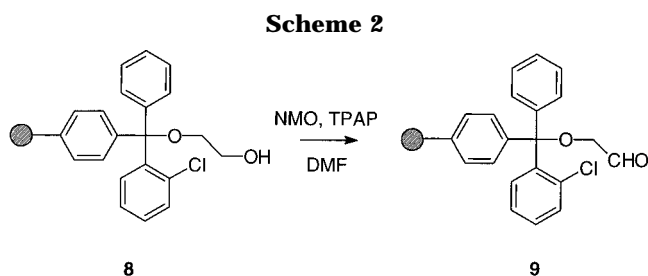
Scheme 2

reaction, resin-linked compound **8** was oxidized to **9** (Scheme 2). At 0 min during the reaction, the population of non-hydrogen-bonded hydroxyl groups is relatively smaller compared to that of hydrogen-bonded groups as seen in IR bands at 3573 (nonbonded) and 3425 cm^{-1} (bonded). As the reaction progresses, the nonbonded population is becoming relatively larger. This is because the previously bonded hydroxyl groups became free as some of its nearby neighbors were oxidized to aldehyde groups.

In summary, a high degree of site separation exists in regular 1% DVB cross-linked polystyrene resins. However, due to the dynamic nature of the polymer networks, the site interaction always occurs. This site interaction has been unambiguously demonstrated by the influence of the steric hindrance on mutual interactions of alcohols (Figure 2). Since the linker length of the reactive group shows little influence on the interaction (Figure 4 and 5), our data suggest that the polymeric lattice and the site interaction are highly dynamic. The site interaction will be favored by the reactivity of the functional group and the availability of the nearby reactive sites.

Experimental Section

Materials. Wang resin (*p*-benzyloxybenzyl alcohol resin) was purchased from Midwest Bio-Tech (Fishers, IN), and hydroxymethyl polystyrene resins from NovaBiochem (San Diego, CA). Trityl alcohol resin was prepared from trityl chloride (NovaBiochem) by heating with a 1:1 water/THF mixture for 1 h. All resins are based on 1% cross-linked divinylbenzene−styrene copolymer. They are 100−200 mesh with a loading of 0.6−1.2 mmol/g. One drop of resin suspension was taken from the reaction vessel at specified times. The resins were filtered and washed four times with DMF (0.5 mL each time), THF (four times), and then dichloromethane (four times). The sample was not vacuum dried. All other 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. General procedure for IR measurement is as in Yan et al.[6a,b] Flattened bead was used throughout experiments. IR spectra were not baseline corrected. All determinations of relative molar absorptivities are based on IR spectra recorded on solid compound (KBr pellet) or resin samples.

Reaction between Wang Resin and a Series of Diacid Chlorides. Wang resin (100 mg, 1.00 mmol/g) was added to each of six different vessels, washed with 4 mL of dichloromethane for 15 min, and then drained. Five different acid chlorides (0.2 or 1 mmol) in 2 mL of dry dichloromethane were added to each vessel. The reactions then were vigorously stirred by an orbital shaker. One drop of resin suspension was taken out of the reaction mixtures at various times, and washed with dichloromethane (six times). The reactions were monitored by single-bead IR until they were completed after 20 min.

Oxidation of Ethyleneglycol 2-Chlorotrityl Resin. As shown in Scheme 2, ethylene glycol 2-chlorotrityl resin (300 mg, 1.0 mmol/g) was washed with 8 mL of DMF and drained. A solution of *N*-methylmorpholine *N*-oxide (NMO) (215 mg, 1.83 mmol) in 8 mL of dry DMF was added to the resin, and then tetrapropylammonium perruthenate (TPAP) (12.9 mg, 0.037 mmol) was added to the resin suspension. The reaction was monitored by single bead IR at various times. A drop of suspension was taken out, washed with DMF (four times).

Supporting Information Available: IR spectra of model compounds used to determine the relative molar absorptivities for ester and acid chloride; IR spectra confirming the band at 1795 cm^{-1} is from the hanging acid chloride carbonyl group by mixing resin with octanol, thus converting the acid chloride group into an ester group (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.