Effects of Solvent Polarity on the Reaction of Aldehydes and Ketones with a Hydrazide-Bound Scavenger Resin

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* Supporting Information

ABSTRACT: Polymer-supported reagents have been extensively studied and used in various applications, such as condensation reactions and multiple component reactions. This paper examines the reactions between a solid-functionalized resin, named Amb15-Iso, and aldehydes and ketones that have been solubilized in different solvents. The reactions between these molecules and a hydrazide (isoniazid) in both neutral and acidic media were also studied. The results showed that the solvent polarity influenced the kinetics of the reaction and the yields of carbonyl compounds that were captured by the resin, particularly, for less-reactive molecules. The reactions using the resin were faster than those using free isoniazid in solution, likely because the acidic sites remaining in the resin can catalyze the reaction, increasing the rate of capture. A high dependence on the presence of acidic compounds and the rate of the reaction was observed, in which trifluoroacetic acid was used to catalyze the reaction between the tested molecules and isoniazid in solution. The differential reactivities of the examined ketones and aldehydes in these condensation reactions demonstrate that the resin can provide selective criteria, preferentially scavenging aldehydes from solution. While benzaldehyde reacted quite quickly with the resin, acetophenone barely had any reaction and remained in solution.

1. INTRODUCTION

Solid-phase reactions using polymer-supported reagents have revolutionized various areas of organic chemistry because of their easy recovery at the end of a chemical process.1 For example, polymer reagents have been used in industry, especially in the pharmaceutical industry, as catalytic and stoichiometric reagents in the synthesis of nucleotides and peptides.2−4 In these cases, the polymers were directly involved in the reaction. Other class of polymer reagents are for the scavenging of substances in solutions, in which it is used after the reaction occurred for the removal of impurities and byproducts.5−7 Over the past years, polymer-supported reagents containing hydrazine or semicarbazide groups have been extensively studied and used in various applications to scavenge carbonyl compounds from solutions.8−14 To investigate the possibility of a novel and low-cost resin for the scavenging of substances in solutions, in which it is used after the reaction occurred for the removal of impurities and byproducts.5−7

Acetone and isobutyaldehyde were used as models to study the capture of molecules by the resin. Preparations of the Amb15-Iso resin in batch and continuous processes were also compared, showing that the use of Amb15-Iso resin packed into a column is advantageous for extracting carbonyl compounds from solution.16 The reaction between the Amb15-Iso resin and carbonyl-containing compounds involves a condensation reaction between the aldehyde/ketone and the hydrazide group of isoniazid, which is bound to the sulfonyl group within the resin. Scheme 1 shows the reaction between the ketone/aldehyde and the Amb15-Iso resin.

Condensation reactions between aldehydes and ketones and nitrogen nucleophiles involve addition and elimination steps that proceed through tetrahedral intermediates.19 These steps can be either acid-catalyzed or base-catalyzed.17 The rates of these reactions are determined by the energy and reactivity of the tetrahedral intermediates.18 For primary amines, C=N bond formation ultimately occurs. These reactions are

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reversible, and the position of the overall equilibrium depends on the nitrogen substituents and the structures of the carbonyl compounds.\textsuperscript{17,18}

This type of reaction may also occur with hydrazines and semicarbazides, forming hydrazones and semicarbazones (special types of imines), as shown in Scheme 2.\textsuperscript{20} Isoniazid, the molecule used for this type of reaction in the Amb15-Iso, is a semicarbazide.

Although these reactions are well-understood in homogeneous media, how the kinetics and thermodynamics of these systems change when these reactions occur within the confined spaces of a polymeric matrix, such as the Amb15-Iso resin, must still be evaluated. Evaluating the effects of different solvents can provide information regarding the application on these types of resins for the removal of aldehydes and ketones in different media.

Therefore, the present work aims to study the reactivity of different aldehydes and ketones with the Amb15-Iso resin, in a batch process, using different solvents, and to compare these reactivities to those with free isoniazid in solution. It should be noted that the Amb15-Iso is a model resin for the scavenging of aldehydes and ketones, and previous results and characterizations have already been published elsewhere. The aim of the work is solely in studying the reactivity of the molecules with the isoniazid present in the resin, and the evaluation on how the media (different solvents) may affect the reaction within the confined spaces of a polymeric matrix. For this study, a real-time technique was used: attenuated total reflectance–Fourier transform infrared (ATR–FTIR). Using this technique, it is possible to continuously measure the infrared spectrum of a medium over time, for the evaluation of changes in the vibrational absorption bands and the calculation of concentration trends for the present species.\textsuperscript{21–25}

2. EXPERIMENTAL SECTION

2.1. Apparatus. All reactions were performed in a 100 mL reactor controlled by an EasyMax Workstation (Mettler Toledo). The temperature of the reaction was maintained at 25 °C, regulated with a Pt100 temperature sensor and a Peltier system jacket. The medium was stirred at 120 rpm using a magnetic stirrer.

An infrared equipment, ReactIR 45m (Mettler Toledo), was used to monitor the reactions in real time. It was equipped with a DS Micro Flow Cell, with a diamond crystal as the internal reflection element (IRE), and a mercury cadmium telluride detector, using Happ Genzel apodization. The spectra were acquired in the range of 4000–650 cm\(^{-1}\), with a resolution of 8 cm\(^{-1}\), in intervals of 15 s between each spectrum (an average of 25 scans). The analysis was performed on-line, where the reaction medium was sampled from the reactor using a ProMinent Beta pump, passed through the IR flow cell, and then returned to the reactor.

2.2. Procedure. The resin (Amb15-Iso) was synthetized according to the procedure previously described by our group.\textsuperscript{15} For the batch system, 40 mL of the solvent (water) and 2 g of isoniazid were added to the reaction vessel. The system was maintained at a constant temperature of 40 °C, at a stirring speed of 150 rpm. After the solubilization of isoniazid, 5.0 g of Amberlyst-15 resin was added to the medium. After completion of the reaction (60 min), the resin was drained by vacuum filtration and washed with water and methanol. Thereafter, the resin was dried at 60 °C for 12 h, and stored in a desiccator to be used in the following experiments.

The performed reactions were divided into three categories: (A) reactions between the aldehyde/ketone and the Amb15-Iso resin; (B) reactions between the aldehyde/ketone and the free isoniazid in solution; and (C) reactions between the aldehyde/ketone and free isoniazid in solution catalyzed by
trifluoroacetic acid. For all of the reactions, the reagents were mixed with 40 mL of different solvents at a temperature of 25 °C and at a stirring rate of 120 rpm; all reactions were monitored by ATR−FTIR until no signal variation was observed for the carbonyl band. The following carbonyl compounds were studied: cyclohexanone, cyclohexancarboxaldehyde, α-ionone, and cinnamaldehyde. The following solvents were studied: dichloromethane, hexane, acetonitrile, and ethanol.

For reactions of type A, 100 μL of the aldehyde or ketone was added to the solvent, prior to the addition of 5.0 g of the dry Amb15-Iso resin; this type of reaction was also studied using a mixture of an aldehyde (1 mmol, benzaldehyde) and a ketone (1 mmol, acetonophenone), added prior to the addition of 5.0 g of the dry Amb15-Iso resin. For reactions of type B, 1 mmol of the aldehyde or ketone was added, prior to the addition of 1 mmol of isoniazid. Finally, for reactions of type C, 1 mmol of aldehyde or ketone was added with 0.1 mmol of trifluoroacetic acid, prior to the addition of 1 mmol of isoniazid.

3. RESULTS AND DISCUSSION

3.1. Capture of Aldehydes/Ketones by the Amb15-Iso Resin. To evaluate the reactions, ATR−FTIR spectroscopy was used to monitor the signal of the carbonyl absorption band of the aldehydes and ketones. The infrared signals were generated by the contact between the samples and the IRE of the equipment (in this case, the ATR diamond crystal). Therefore, this type of equipment can only be used to measure the signals of liquids, gases, and very small solids. Because the Amb15-Iso resin is much larger than the ATR probe tip, it was not possible to measure the carbonyl absorption bands from the compounds present in the solid phase of the resin. However, it was possible to measure the signal of the species present in the liquid phase of the medium; the concentrations of these species correlated with their signals, as defined by the Lambert−Beer law. The analysis was performed in real time and continued until the stabilization of the carbonyl absorption band signal occurred. Figure 1 shows the 3D graph of part of the infrared spectra monitored over time for the cinnamaldehyde captured by the Amb15-Iso resin.

Figure 1 shows that following the addition of cinnamaldehyde, an absorption band appears in a wavenumber of 1682 cm⁻¹, related to the C=O stretch band (point A). This band has a lower energy compared to the usual absorption of aldehydes because of the unsaturation next to the carbonyl. As soon as the Amb15-Iso resin was added to the solution (point B), a decrease in this absorption intensity was observed, indicating a decrease in the cinnamaldehyde concentration in solution, suggesting that the molecules were leaving the liquid phase toward the interior of the resin. At the same time, an absorption band appears in a wavenumber of 1645 cm⁻¹ because of the O−H bending band of the water produced in the reaction (Scheme 1). Because the intensity of the carbonyl band is related to the concentration of the ketone or aldehyde in solution, its variation after the addition of the resin is also related to the number of molecules that have reacted with the resin. Monitoring this intensity over time provides information regarding how fast this reaction occurs and enables the calculation of how much of the aldehydes or ketones have been incorporated into the resin.

Figure 2a shows the carbonyl band intensity and the O−H bending band intensity of water over time for the cinnamaldehyde reaction. As in Figure 1, point A represents the addition of the aldehyde to the solution, and its intensity increases until it stabilizes at a maximum value. Up until point B, no reaction occurs, thus the experimental time is not representative of the process. The beginning of the reaction coincides with the addition of the resin, at point B, when the aldehyde band decreases and the water band begins to increase. Therefore, point B marks the real initial time, t(0), which can be defined as a new zero point.

The carbonyl band intensity can be directly related to variations in the aldehyde concentration by normalizing the

Figure 1. Time-dependent 3D ATR−FTIR graph of the cinnamaldehyde captured by the reaction with Amb15-Iso resin (pure solvent spectrum subtracted), showing the decreasing carbonyl band (I) and the increasing water band (II) as the reaction occurs. Point A represents the addition of the aldehyde to the solution, while point B represents the addition of the resin to the solution.

Figure 2. (a) Monitoring cinnamaldehyde and water band intensities during the reaction; (b) reaction conversion calculated from the cinnamaldehyde signal, using eq 2.
This normalized concentration, $c(t)$, is related to the IR signal at the beginning of the reaction, $I(0)$, as shown in eq 1

$$c(t) = \frac{I(t)}{I(0)}$$  

(1)

where $I(t)$ is the intensity of the carbonyl band at time $t$. This normalization of the infrared signal shows how much of the aldehyde/ketone has reacted with the Amb15-Iso resin. The time-dependent reaction conversion can then be calculated by eq 2

$$\text{conv}(t) = \left[1 - c(t)\right] \times 100 = \left[1 - \frac{I(t)}{I(0)}\right] \times 100$$  

(2)

This conversion is shown in Figure 2b and allows the comparison of the different systems containing ketones and aldehydes. For the rest of this work, all of the ATR–FTIR will be represented as reaction conversions.

To verify the effects of the different solvents on the rate of hydrazone formation, a set of reactions were performed using the Amb15-Iso resin and different aldehydes and ketones: cyclohexanone, cyclohexanecarboxaldehyde, $\alpha$-ionone, and cinnamaldehyde. The first and the latter two aldehydes/ketones are structurally comparable, which allows the best understanding of the differences among the reactions between the carbonyl compounds in terms of different organic functions. A comparison among the four compounds demonstrates the effect of $\alpha, \beta$-unsaturation, which decreases the reactivity of the compounds. The reactions were performed in dichloromethane, hexane, methanol, and acetonitrile. To illustrate, the results for the reactions containing cyclohexanone are presented in Figure 3. An exponential curve was fitted to all data and is shown along with the graphs to more directly visualize the concentration changes over the experimental time. Results for the reactions with cyclohexanecarboxaldehyde, $\alpha$-ionone, and cinnamaldehyde are presented in the Supporting Information, while a summary of the results obtained in different solvents is shown in Table 1.

For cyclohexanone, the reaction occurred in all of the solvents, and the ATR–FTIR signal stopped varying at almost the same time for all systems, meaning that the capture occurred for all four solvents with the same equilibrium time (approximately 10 min). If the reaction in hexane is excluded, the amount of cyclohexanone removed from solution increased in more polar solvents: 23% in dichloromethane, 44% in acetonitrile, and 79% in ethanol. This behavior is in agreement with the results presented in an earlier paper. However, if hexane is included in the discussion, the correlation with solvent polarity disappears, which may be explained by the water solubility of the different solvents. While water is miscible with ethanol and acetonitrile, it has a low solubility in dichloromethane and an even lower solubility in hexane. The water solubility in hexane is so low that, even though hexane is a worst solvent in terms of polarity, it induces the displacement of the reaction equilibrium because of the separation of water from the medium, leading to a higher conversion rate (51%).

The same study was performed with cyclohexanecarboxaldehyde, an aldehyde that is structurally equivalent to cyclohexanone. Similar to cyclohexanone, a conversion was observed for its reaction with the resin, but the amounts of captured molecules were higher than those observed for cyclohexanone. This may be due to the fact that aldehydes are generally much more reactive than ketones. Moreover, in the systems using ethanol and hexane, the resin captured all of the carbonyl compounds after 30 min, whereas in acetonitrile and dichloromethane only approximately 84 and 93% were captured, respectively. These results show that when the molecules are more reactive, the polarity of the solvent does not have as large an effect on the reaction conversion compared with molecules that are less reactive.

To further examine the effects of molecule reactivity on the system, carbonyl compounds with $\alpha, \beta$-unsaturation were tested, as this type of unsaturation should decrease the reactivity for both types of molecules. The Amb15-Iso resin captured $\alpha$-ionone more efficiently in more polar solvents: 81% of the initial ketone was captured when the reaction was conducted in ethanol (Figure 3b). However, the equilibrium time took longer than for the other solvents, approximately 130 min. In acetonitrile, the equilibrium time was the same as that in ethanol, but the amount captured was lower (approximately 52%). The equilibrium times for the systems using hexane and dichloromethane as solvents were the same (approximately 15 min). However, a different result was found for the capture of $\alpha$-ionone in hexane (60%) than for dichloromethane (13%), even though hexane is less polar than dichloromethane. In this case, the reaction was more efficient in the polar solvent.

### Table 1. Results of the Reaction between Amb15-Iso Resin and Different Aldehyde and Ketones in Different Solvents

| compound            | hexane    | dichloromethane | ethanol   | acetonitrile |
|---------------------|-----------|-----------------|-----------|--------------|
| cinnamaldehyde      | 95/19     | 98/30           | 81/80     | 96/33        |
| cyclohexanecarboxaldehyde | 100/16   | 94/18           | 100/2     | 81/19        |
| $\alpha$-ionone     | 60/15     | 13/15           | 87/135    | 52/130       |
| cyclohexanone       | 51/9      | 23/8            | 79/5      | 44/6         |

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Lastly, cinnamaldehyde, as an aldehyde, is expected to be more reactive than α-ionone. Hence, the influence of the solvent polarity on the amount of cinnamaldehyde captured was less pronounced than for α-ionone. For systems in which acetonitrile, dichloromethane and hexane were used as solvents, the resin was more efficient, capturing more than 90% of the substrate (cinnamaldehyde), whereas in ethanol the percentage captured was approximately 81%, showing a different effect on the solvent polarity. For the capture of cinnamaldehyde, equilibrium was reached in ethanol after approximately 80 min, whereas in acetonitrile, dichloromethane and hexane equilibrium was reached after approximately 20–30 min.

The reaction behavior with the resin varied between the aldehydes and ketones studied. For aldehydes, the presence of an α,β-unsaturation led to different effects of the solvent polarity because it decreases the molecules’ reactivity. In this case, when the molecule is more reactive (cyclohexanecarboxyaldehyde), the solvent polarity does not appear to influence either the kinetics of the reaction or the reaction conversion. With a less-reactive functional group (cinnamaldehyde), the solvent polarity tends to influence more the kinetics of the reaction, in which the more polar solvent led to a slower reaction, as in the case of the reaction using ethanol. For ketones, whose molecules are even less reactive, the solvent polarity influences even more the kinetics and the equilibrium. In these cases, the same behavior is seen for the kinetics, in which more polar solvents led to slower reactions. As for the equilibrium, the solvent polarity tends to increase the amount of ketones captured, in which the conversion decreased from ethanol > acetonitrile > dichloromethane. However, for hexane, the less polar solvent, this behavior changes because of the water solubility, which changes the direction of the equilibrium, increasing once again the amount of molecules captured. These results correlate with those reported by Ciaccia and Di Stefano in their study on the imine formation mechanisms. They proposed that the nature of a solvent exerts a relevant influence on the rate of the reaction during the formation of imines. It should be noted, however, that the different behavior between the reaction time and the reaction conversion is because of the fact that the two phenomena are not correlated: one is kinetic and the other is thermodynamic. How fast the reaction goes relates to its activation energy, and that may vary depending on the solvents’ properties, such as the polarity. The interaction and stabilization of intermediates may change the overall activation energy, leading to faster kinetics. As for the number of reacted molecules, it depends exclusively on the thermodynamics of the system, specifically the equilibrium constant. That may also change depending on the solvents’ properties.

To further understand the system, an analysis was performed to evaluate the reactivity of a mixture containing a ketone and an aldehyde with the Amb15-Iso resin. Solutions containing benzaldehyde and acetalophenone, in ethanol and hexane, were studied using ATR–FTIR, and the results are shown in Figure 4.

For both solvents, there was a clear preference for the benzaldehyde reaction, due to their higher reactivity. In ethanol, acetalophenone barely reacted with the Amb15-Iso resin, whereas in hexane, only approximately 10% of acetalophenone reacted with the resin. Here, a kinetic effect was the main driving force for the consumption of isoniazid with benzaldehyde because benzaldehyde is much more reactive than acetalophenone. The same effect was not observed when using a nonpolar solvent, such as hexane, as shown in Figure 4b.

3.2. Comparison between the Reaction with the Free and the Bonded Isoniazid. To better understand the reactions of the carbonyl compounds with the resin, the reactions were also conducted in solution, with a free hydrazine group that was not bound to the resin matrix. The reactions were performed using the four previously studied carbonyl compounds and isoniazid, in acetonitrile and ethanol. Figure 5a,b show a comparison between the reaction of cyclohexanone with Amb15-Iso resin and the reaction of cyclohexanone with the free isoniazid, both in acetonitrile and ethanol. Table 2 summarizes the results for the four molecules, while the graphs for the other reactions are presented as Supporting Information.

When the results were compared, the equilibrium was obtained more quickly for the isoniazid bound to the resin than for the free isoniazid in solution. For the cyclohexanone reaction in both ethanol and acetonitrile, equilibrium was not achieved for more than 2 h with the free isoniazid, whereas equilibrium was achieved in approximately 10 min with the Amb15-Iso resin. The kinetic aspects of these results were observed for all of the molecules and for both solvents. However, the ketones did not react completely with the resin. For cyclohexanone, approximately 46% reacted with the resin in acetonitrile and 81% reacted in ethanol; in contrast, the ketones reacted completely with the free isoniazid. This behavior may be because of the fact that the Amb15-Iso resin is formed by the reaction between the acid sites of the Amberlyst-15 resin and the pyridine ring of the isoniazid. The
saturation that was achieved for the isoniazid in the resin was 2 mEq/g resin.15 However, the capacity of the acidic sites in the commercial Amberlyst-15 is 4.7 mEq/g. The smaller saturation concentration of isoniazid with respect to the concentration of acidic sites in the resin indicates that there are still free acid sites left in the resin, as shown in Scheme 3.

This excess acid in the Amb15-Iso resin may be acting as a catalyst for the reaction between the carbonyl compounds and the hydrazide group, making the reactions with the resin faster than those with the free isoniazid in solution, as demonstrated by the above experiments.

To verify the presence of free acidic groups in the Amb15-Iso resin, the pH of an aqueous medium containing pure Amberlyst-15 was compared with the pH of an aqueous solution containing the same weight of the Amb15-Iso resin, and results are presented in Figure 6. After the addition of Amberlyst-15, the pH of the solution dropped from 6.05 to 3.14. The same procedure using Amb15-Iso resin decreased the pH from 6.07 to 4.29. Because suspension of the Amb15-Iso resin in water was acidic, this indicates that free acidic groups are still present in the Amb15-Iso resin.

As the formation of imines, hydrazones, and semicarbazones can be acid-catalyzed,18,19 the acidic sites of the Amb15-Iso resin may catalyze the reactions with aldehydes or ketones, increasing the rates of the reactions with the Amb15-Iso resin relative to those with free isoniazid in solution. The Amb15-Iso resin works not only as a nucleophilic agent for capturing aldehydes and ketones but also as a catalyst. To demonstrate the influence of the pH on the kinetics of the condensation of the substrate with free isoniazid in solution, the reactions of

Table 2. Results of the Reactions between Amb15-Iso Resin and the Different Aldehyde and Ketones and the Reactions between Free Isoniazid and the Different Aldehydes and Ketones, in Both Ethanol and Acetonitrile

| compound                        | conversion (%) | equilibrium time (min) |
|---------------------------------|---------------|------------------------|
|                                 | ethanol       | acetonitrile           | ethanol       | acetonitrile           |
| cinnamaldehyde                  | 79/80         | 96/35                  | 63/160        | 32/>350               |
| cyclohexanecarboxaldehyde       | 100/20        | 84/18                  | 100/10        | 100/350               |
| α-ionone                        | 81/100        | 52/130                 | 51/330        | 3/110                 |
| cyclohexanone                   | 81/5          | 46/12                  | 100/140       | 100/350               |

Scheme 3. Reaction of the Amberlyst-15 Resin with Isoniazid during the Synthesis of the Amb15-Iso Resin
Cinnamaldehyde and α-ionone with the free isoniazid were examined with and without the addition of trifluoroacetic acid as the catalyst. The experiments containing the acid catalyst showed a faster kinetics for both the ketone and the aldehyde. This suggests the likely catalytic behavior of free acids in the Amb15-Iso resin during the condensation reactions (Figure 7).

4. CONCLUSIONS

In summary, the effect of solvent polarity was evaluated on the reaction between ketones/aldehydes and the Amb15-Iso resin, and the results showed that the solvent polarity influenced the yields, especially for less reactive molecules. When the ketones/aldehydes presented α,β-unsaturation profiles, the solvent polarity exerted strong influence on the yields of the reactions, without influencing the rates of the reactions. In these cases, polar solvents tended to result in higher yields. An exception was observed when using hexane as a solvent because of its reduced water solubility, which changed the equilibrium of the reactions toward the products, leading to higher yields. Moreover, aldehydes were more reactive with the resin than ketones, and the scavenging of a mixture between the two showed the resin to be selective toward extracting the aldehyde. Finally, the comparisons between the reaction of the ketones/aldehydes with the resin and the reaction with free isoniazid showed that the latter has slower kinetics because of the fact that the resin contains acidic sites that catalyze the condensation reactions.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b01874.

Reactivity comparison of the reaction between Amb15-Iso and all the molecules in different solvents; reactivity comparison of the reaction between the molecules and the Amb15-Iso and the free isoniazid; and GC−MS data for the reaction between the free isoniazid and the molecules (PDF)

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Notes
The authors declare no competing financial interest.

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