Microwave-Induced Esterification Using Heterogeneous Acid Catalyst in a Low Dielectric Constant Medium

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Introduction

During the past decade, our knowledge of microwave-assisted organic synthesis has increased significantly.[1−4] Initial studies of several reactions revealed an enhancement of reaction rates in the presence of microwave irradiation, as compared to identical reactions heated by classical methods. Early hypotheses suggested that the rate enhancements were due to athermal effects induced by microwave radiation.[5a−e] However, subsequent investigations, in which reaction mixtures were stirred or mixed to ensure thermal homogeneity, revealed that reaction rates of microwave-irradiated and classically heated reactions were comparable.[6a−c] These studies led to the hypothesis that rate enhancement observed as a result of microwave irradition is caused by superheating of the reaction solution.[7,8]

Despite limitations, domestic microwave ovens are widely used for laboratory organic synthesis.[1] These devices are multimode applicators, which operate at a fixed maximum power level for varying periods of time (duty cycle). The resulting electric field is thus nonuniform or heterogeneous, resulting from multiple reflections inside the microwave cavity. Efforts to model the electromagnetic field inside such reactors reveals the fact that temperature measurement of an irradiated sample cannot be easily determined.[9−10] These underlying factors are a large cause of variation in reported rate enhancements. The limitations of the domestic microwave oven can be overcome by the use of a monomode applicator, capable of focusing electromagnetic waves with the use of a waveguide to achieve a homogeneous electromaginetic field.[3] However, despite the advantages, such equipment remains relatively unavailable in contemporary organic synthesis laboratories.

Concomitant with the technological advances in microwave reactors, several strategies for microwave-assisted organic synthesis are currently in use.[1−4,11] A significant body of work concerning the applications of microwave radiation to homogeneous reactions exists.[2−4] However, heterogeneous reactions, in particular those that involve the use of solid-state catalysts, are particularly advantageous in terms of ease of use, separation, and catalytic recycling.[12] Most reports of kinetic studies involving the use heterogeneous catalysts in microwave-irradiated systems, suggest that selective superheating of the catalyst may account for observations of small rate enhancements.[13−16]

To effectively study the kinetics of a heterogeneous system, absorption of microwave radiation should be limited only to the reacting species. This can be accomplished through the use of a low dielectric constant medium (i.e., hydrocarbons) as a reaction solvent.[17] Additionally, the reaction should occur entirely inside the microwave cavity to maximize irradiation of all reacting species. This constraint poses severe practical limitations, since adequate temperature and pressure control in such a system is difficult to achieve.[17] To overcome this problem, we have developed a continuous-flow reactor for heterogeneous systems, which localizes a bed of Amberlyst-15 cation-exchange resin contained in a radiolucent polyethylene tube inside the microwave cavity (Figure 1).

We have chosen the acid-catalyzed Fischer-type esterification of isopentyl alcohol and acetic acid as our model system. Esterifications are of practical interest because esters are used in the production of a wide range of products such as cosmetics, lubricants, pharmaceuticals, and plasticizers. This reaction represents a well-understood Fischer esterification that in homogeneous systems occurs by the AAC2 mechanism[18] (Scheme 1). Since the reaction is driven by the protonation of the carbonyl functionality, reacting species should be localized to the bed of acid catalyst, subject to microwave radiation. This model is also advantageous to study because all reagents

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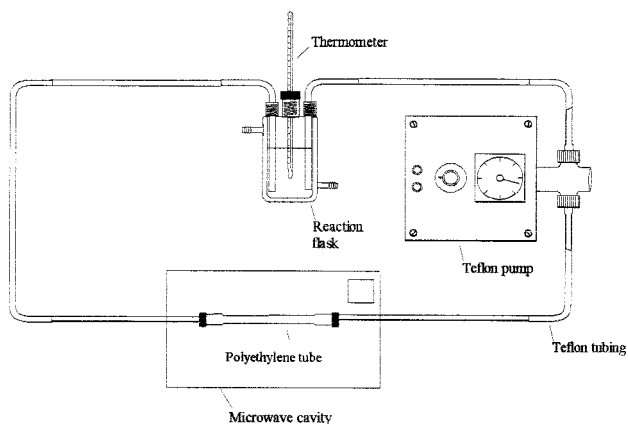
Figure 1. Continuous flow setup for esterification of isopentyl alcohol and acetic acid using microwave radiation.

Scheme 1.   Proposed Mechanism for the Acid-Catalyzed Esterification of Isopentyl Alcohol with Acetic Acid; AAC2 Mechanism Is Preferred for Reactions with Small R Groups and Little Steric Hindrance[9]
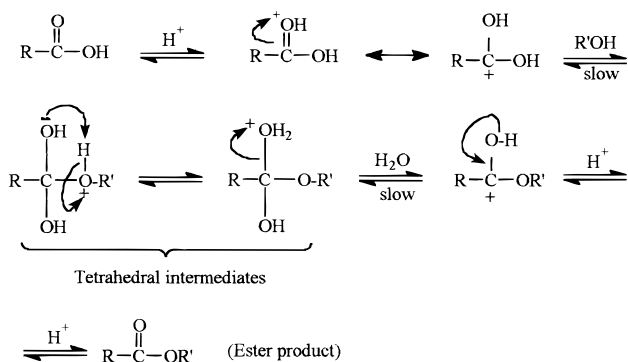
Table 1.   Control Experiment To Compare Catalytic Efficiency of Ion-Exchange Resin to Aqueous Sulfuric Acid

trial	isoamyl acetate (mg/mL)[a]
1	190.2 ± 7.8^b
2	192.2 ± 18.5^c

[a] Average of time points (10, 20, 30, 60). [b] Reactions were performed using 2.6 mL of concentrated sulfuric acid (42.5 mequiv H+). [c] Reactions were performed using 20.0 g (wet weight) of AG SOW-X8 resin (42.5 mequiv H+).

and products are soluble in hexane (low dielectric constant). The product, isoamyl acetate, is also easily assayed by gas chromatography.

Amberlyst-15 was shown previously[12] to be an effective catalyst for the Fischer-type synthesis of esters in a heterogeneous, aqueous system. In fact, to compare the Amberlyst-15 catalytic activity with that of liquid H_2SO_4, we have performed a control experiment (Table 1), which indicated similar effeciences in ester formation for both hetero- and homogeneous systems. A strictly water-free system for Fischer-type esterification is unattainable. Even the factory-dried Amberlyst-15 resin contains traces of moisture (Tables 2 and 3). In addition, the resin is highly hygroscopic and readily adsorbs water from the air upon short exposure to ambient conditions.

In studies of microwave-assisted chemical conversions it is important to concentrate on possible factors influencing reaction progress. Since 2.45 GHz microwaves are "tuned" to heat water with high efficiency, we have made

**Table 2.   Rate Constants for the Production of Isoamyl Acetate vs Catalyst Water Content**

catalyst water content[a]	rate constant[b] (k/min^{-1})
0	2.3×10^{-1}
5	1.8×10^{-1}
10	1.2×10^{-1}
20	8.2×10^{-2}

[a] Water content is reported in % (w/w). [b] Rate constants were determined using a Langmuir−Hinshelwood model.[12]

Table 3.   Catalyst Water Content Measured by TGA

calcd catalyst water content[a]	actual catalyst water content[b]
dry	1.5
5	7^c
10	9
20	18

[a] Water content is reported in % (w/w), calculated from the weight change upon addition of water to the resin. Dry resin was taken directly out of vacuum sealed package. [b] Water content measured by isothermal gravimetric analysis (TGA). [c] Sample size was only 5 mg, compared to an average of 30 mg for all other samples.
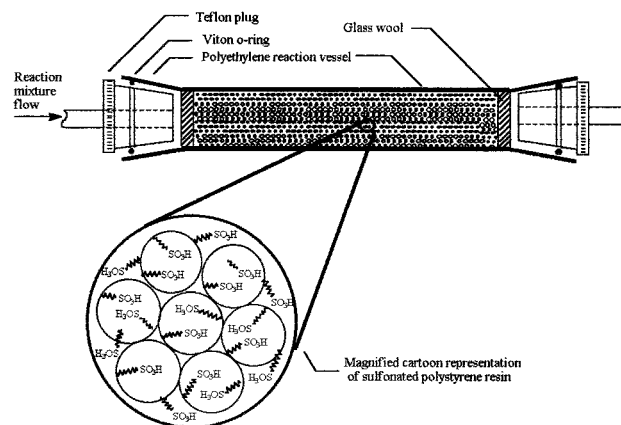
Figure 2. Enlargement of polyethylene reaction tube containing Amberlyst-15 cation-exchange resin.

a point of studying progressively hydrated catalysts. In principle, water present in the catalystic resin could facilitate superheating of the resin, leading to an increased reaction rate under microwave radiation. In addition, the presence of water could facilitate proton transfer and thus influence the reaction kinetics. To test the effect of water contained within the resin upon reaction progress, we measured rates of reactions heated by microwave radiation and classical heating, in the presence of catalytic resin loaded with varying amounts of water.

Experimental Section

General Information. The experimental setup (Figures 1 and 2) was a closed system consisting of a polyethylene reaction tube, Teflon tubing (4.5 mm i.d.), and a glass reaction vessel. Teflon and polyethylene were used inside the microwave to ensure transparency toward microwave radiation.[11] A purge valve was installed in the external reaction vessel to maintain constant ambient pressure inside the system.

All esterification reactions were run at 40 ± 3 °C in nondistilled hexane (Fischer). The total volume of the system was 120 mL, and the flow rate of the reaction mixture was held constant at 88 mL/min. Gas chromatography data was collected using a GOW-MAC (GC series 350) gas chromatograph connected to an integrator (HP 3390A).

The microwave oven used was a commercially available model (General Electric JES-0601T) operating at a maximum power level of 650 W. The oven was equipped with a digital timer and could be operated at 10 different power levels. Domestic microwave ovens operate by alternating from maximum power to zero power in timed cycles (duty cycles).[7a] The frequency of the maximum power cycle is represented by a power level number. For example, power level 2 means that the magnetron is actually on for an average of 2 s out of every 10 s, and power level 10 represents continuous radiation.

Addition of Water to Catalytic Resin. Amberlyst-15 cation-exchange resin (20.0 g, Aldrich) was spread out in a large weighing dish to maximize surface area. The dish was placed on a raised platform inside a sealable, cylindrical container partially filled with water. The catalytic resin was allowed to adsorb water from the vapor-saturated environment. The water content of the resin was verified by analyzing samples using isothermal gravimetric analysis (Dupont 951 Thermogravimetric Analyzer) (Table 3).

Esterification of Isopentyl Acetate and Acetic Acid. Hexane (93.6 mL) was pumped into the system and allowed to circulate for 2 min under ambient conditions. Isoamyl alcohol (12.0 mL, Aldrich) was added to the external flask (Figure 2) and allowed to circulate for 30 s. Glacial acetic acid (14.4 mL, Fischer) was added, and the microwave turned on. The initial power level setting was 2, but this setting was alternated between 2 and 1, to maintain a constant temperature of 40 ± 3 °C as monitored by a digital thermometer (Digi-thermo, quartz) placed in the external flask. Since multimode applicators are only capable of producing maximum power electromagnetic fields, alternating between power level settings 1 and 2 produced a "virtual power level" of $1.3-1.6$ (estimated). The reaction progress was followed by extracting 1.0 mL aliquots from the external flask every 10 min, for 1 h. Aliquots were flushed through columns containing Amberlite CG-400 anion-exchange resin ($100-200$ mesh, chromatographic grade, Mallinckrodt) to remove residual acetic acid and stop the reaction, and 1 μL samples were analyzed by gas chromatography.

Conventional heating was accomplished by submerging the reaction vessel in a constant temperature water bath maintained at 56 °C, which resulted in a solution temperature of 40 ± 1 °C as monitored in the external flask. All analytical procedures used to prepare solutions for both of the processes (thermal and microwave heating) were identical.

Gas Chromatographic Analysis. The reaction products were separated using a 20% DC200 (on chrom) column (80/100 mesh). The operating conditions for the gas chromatograph were

injector: 180 °C	approximate retention times:
detector: 160 °C	hexanes: 0.8 min.
oven: 139 °C	isoamyl acetate: 2.5 min.
flow rate: He, 50 mL/min	isopentyl alcohol: 3.5 min.

The injection size of all samples was 1 μL. The approximate retention times for the three components are shown above.

Results and Discussion

Effective rate comparison of microwave and classically heated reactions is complicated by a variety of factors. These typically include microwave absorption by polar solvents, superheating, ineffective mixing, and inaccurate temperature measurement. We used a nonpolar solvent in a heterogeneous, continuous-flow system in an attempt to minimize solvent absorption and superheating, while maximizing the microwave absorption by reacting species.

No comparable difference between reaction rates of microwave-mediated and classically heated reactions was observed (Figure 3). Although our system did not utilize a monomode reactor, the reproducibility and precision of our results from both microwave and classically heated reactions at the same temperature serve as an indication that our appartus eliminates some of the typical problems
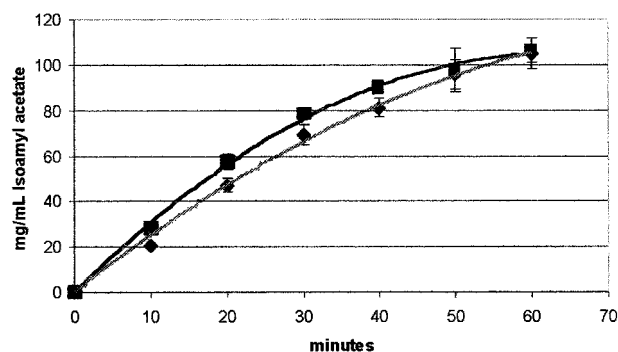
Figure 3. Comparison of conventionally heated (■) and microwave-irradiated (◆) reactions. Each point represents the average of three experiments. Error bars represent one standard deviation.

associated with multimode microwave reactors. Furthermore, this result supports the finding of several others that if the thermal effects of microwave radiation are eliminated, reaction rates are comparable to those of classically heated systems.

This result is interesting, because while our results agree with previous findings for homogeneous systems, our understanding of heterogeneous systems is less complete. One might predict that superheating of the catalyst bed could create localized thermal gradients that would influence the reaction rate but be virtually undetctable by measurement of the temperature at the outlet. This phenomenon was reported by Chemat et al. for esterification reactions performed in a continuous microwave reactor, catalyzed by $Fe_2(SO_4)_3$ adsorbed onto Montmorillonite clay, localized inside the microwave cavity.[15]

Further evidence for selective superheating of solid supports was reported by Gedye et al., who propose that solid CuCl (strongly absorbs microwave radiation) present in the addition reaction of $CCl_3CO_2CH_2CH_3$ and CCl_4 to styrene result in rapid heating of the reaction, thus accounting for the observed rate enhancement.[13]

Shibata et al. recently reported a reduction in activation energy in the microwave-assisted decomposition of sodium bicarbonate in water, attributing the result to nonthermal microwave effects.[14] However, as Gedye et al. point out, the presence of solid sodium bicarbonate suspension (20%) in solution may have resulted in selective heating of the solid, thus accounting for the apparent decrease in activation energy.[13] This critical observation is supported by a recent report that indicates that the microwave heating of nonpolar solvents can be increased by the addition of magnetic nanoparticles.[16]

Amberlyst-15 strongly absorbs microwave radiation and will readily melt if irradiated at power level 10 for more than 2 min. In addition, if the catalytic resin is omitted from the reactor system, absorption of microwave radiation is significantly reduced (data not shown), suggesting that the catalytic resin is absorbing a large amount of the microwave radiation during the reaction.

These results prompted us to test whether preloading the catalyst with small amounts of a polar solvent would facilitate selective superheating of the resin, resulting in a rate enhancement. Since microwave radiation is strongly absorbed by polar species, it follows that the presence of additional water associated with the catalytic resin could induce the formation of thermal gradients in
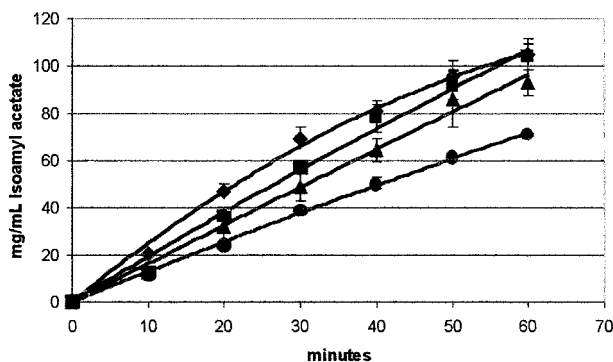
Figure 4. Comparison of varying degrees of Amberlyst-15 water content in reactions heated by microwave radiation. Diamonds (♦) represent dry resin; squares (■) represent 5% water content by mass; triangles (▲) represent 10% water by mass; and circles (●) represent 20% water content by mass. Each point represents the average of three experiments. Error bars represent one standard deviation.
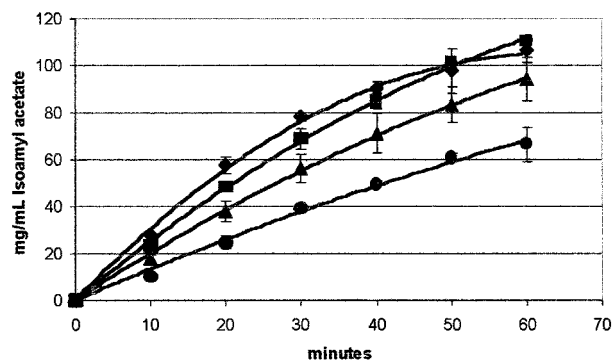
Figure 5. Comparison of varying degrees of Amberlyst-15 water content in reactions heated by conventional water bath. Diamonds (♦) represent dry resin; squares (■) represent 5% water content by mass; triangles (▲) represent 10% water by mass; and circles (●) represent 20% water content by mass. Each point represents the average of three experiments. Error bars represent one standard deviation.

the catalytic resin, leading to superheating and an increased reaction rate. Surprisingly, we observed that increasing the amount of water present within the catalytic resin significantly decreased the reaction rate, regardless of the method of energy input (Figures 4 and 5). This result indicates that the ability of water to enhance the formation of thermal gradients is not the most important factor controlling the reaction rate in this system. In fact, the data graphically represented in Figure 4 provided us with numerical values computed from the initial (linear) portions of the curves in accordance to a Langmuir–Hinschelwood model (Table 2). Obtained rate constants were on the same order as those reported by Xu et al., who used a fully aqueous system.[12]

Previous studies on the esterification of acetic acid and methanol in a heterogeneous, aqueous system suggest that such a system can be treated as homogeneous for the purpose of kinetic measurement.[12] This treatment assumes that absorption by the resin, Amberlyst-15, is weak for all components. We have empirically observed that absorption of water and other solvents by Amberlyst-15 causes the resin to swell up to several times its normal size. This is caused by solvent molecules entering the porous space within the resin. In an aqueous environ-
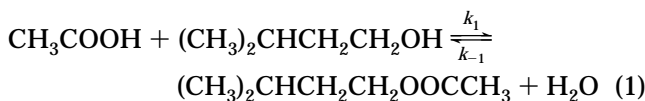
Table 4. Yield Comparisons for Isoamyl Acetate

water content (%)	homogeneous calc theoretical yield[a] (mg/mL)	heterogeneous exptl yield[b] (mg/mL)	% difference, heterogeneous vs homogeneous reactions[c]
dry	106	105	0
5	80	104	30
10	62	93	50
20	40	71	76

[a] Theoretical yield for a homogeneous system was calculated using initial concentrations of isopentyl alcohol and acetic acid and comparable equivalents of aqueous acid. The amount of water present in the resin was assumed to be added directly to the reaction solution. [b] Actual experimental yield for the heterogeneous system described in the Experimental Section. [c] The percent difference represents the variance of the experimental yields (from heterogeneous reaction) compared to the calculated theoretical yields for a homogeneous reaction.

ment, water is free to diffuse into and out of the resin, creating a quasi-homogeneous system and thus satisfying the proposed kinetic model.[12] However, in our system, the nonpolar nature of hexane could prevent water molecules present in the pores of the resin from escaping, blocking access to sulfonic acid groups. This overall lack of accessibility to the resin would cause a decrease in reaction rate. This prediction is consistent with studies of water hydration in Amberlyst-15 resin that suggest the presence of a constant amount of bulk water present in the pores of the resin.[19]

On the basis of the fact that the esterification reaction is a reversible one, as described in eqs 1 and 2, the

$$CH_3COOH + (CH_3)_2CHCH_2CH_2OH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}$$
$$(CH_3)_2CHCH_2CH_2OOCCH_3 + H_2O \quad (1)$$

$$K_{eq} = \frac{[(CH_3)_2CHCH_2CH_2OOCCH_3][H_2O]}{[CH_3COOH][(CH_3)_2CHCH_2CH_2OH]} = 6.2 \quad (2)$$

presence of extra water in hydrated catalytic resins (5%, 10%, 20% w/w) could shift the equilibrium toward the reactants. This, however, is not supported by experimental findings as compiled in Table 4. In fact, these data indicate that the more hydrated resins are more efficient in product ester formation than would be expected for an idealized homogeneous system. These results indicate the complexity of dealing with the kinetics of a heterogeneous system and suggest an interesting starting point for future studies.

Conclusions

In conclusion, we have found that our model heterogeneous esterification reaction behaves comparably under both microwave and thermal conditions. Furthermore, the presence of water in the catalytic resin caused an overall reduction in the reaction rate, independent of the type energy input. These findings provide further evidence that if the reaction mixture is thoroughly circulated, chemical reactions seem to behave similarly regardless of the source of energy that drives them. These data support our previous studies, which also indicated a lack of energy type preference for the reaction kinet-

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ics.[20] Although we had no method of testing for the selective superheating of the reaction solution or the catalytic resin, if superheating did occur, it had no effect on the reaction rate. Further study of a similar system in a monomode reactor and a more accurate method of temperature measurement within the solid-state catalyst, such as an infrared sensor/camera or thermocouple, are needed before a difinitive conclusion can be reached. These data, coupled with kinetic studies of macroreticular resins in a microwave environment, will further our understanding of heterogeneous microwave catalysis.

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