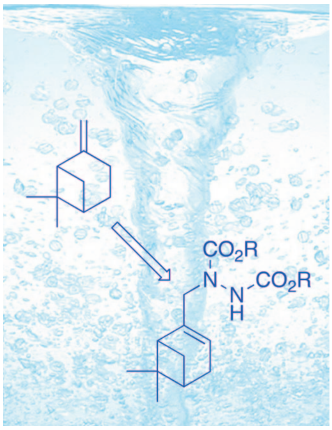
Hydrophobicity and Mixing Effects on Select Heterogeneous, Water-Accelerated Synthetic Reactions

Michael C. Pirrung,* Koushik Das Sarma,[†] and Jianmei Wang

Department of Chemistry, University of California, Riverside, CA 92521-0403

michael.pirrung@ucr.edu

Received May 27, 2008



The influence of aqueous reaction media on organic reactions is a topic of long-standing interest, particularly as it affects the rate or selectivity of synthetic reactions. Sometimes such reactions appear homogeneous, typically in dilute solution, whereas others are obviously heterogeneous, typically in concentrated solution that is more characteristic of a preparative synthetic reaction. The latter situation has been termed “on water.” Here, it is demonstrated that the rates of heterogeneous ene reactions, Passerini reactions, and Ugi reactions in pure water and in aqueous solutions are dependent on the mixing method and reactant polarity, consistent with the involvement of hydrophobic interactions in their acceleration.

Introduction

The effects of aqueous solvent on the rates of reactions of organic compounds is a topic of recent research.[1] Cycloaddition reactions, primarily of quadricyclane with azo compounds,[1b] have been examined as well as ene reactions of alkenes like pinene with azo compounds,[2] with a key feature being the insolubility of the reactants in water. Several publications have exploited these findings[3] and offered speculations[4] on the basis for the rate acceleration of such reactions.

The origin of this field can be traced at least as far back as Lubineau, who stated in 1986: “a reaction under kinetic control between two non-polar molecules for which $\Delta V^\ddagger$ is negative must be accelerated in water *as it is under pressure*”.[5] The $\Delta V^\ddagger$ term (volume of activation) in this paradigm is a quantity less recognized or used than others affecting reaction rates, such as $\Delta G^\ddagger$. The volume of activation is simply the volume of the transition state minus the volume of the reactant(s).[6] The molar volume of reactants is easily obtained from the ratio of molecular mass (M_r) to density (ρ). The molar volume of the transition state is more obscure, but in general highly ordered transition states are more compact than reactants. The $\Delta V^\ddagger$ can be determined by the pressure dependence of the reaction rate, and it contributes to the $\Delta S^\ddagger$ term of $\Delta G^\ddagger$. The acceleration of reactions by pressure was first recognized in the 1930s, and

---

[†] Department of Chemistry, Duke University, Durham, NC; Current address: Advinus Therapeutics Pvt. Ltd., International BioTech Park, Hinjewadi, Pune - 411057, India.

(1) (a) Dickerson, T. J.; Lovell, T.; Meijler, M. M.; Noodleman, L.; Janda, K. D. *J. Org. Chem.* **2004**, *69*, 6603–9. (b) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–9. (c) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492–502.

(2) (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–37. (b) Rouhi, A. M. *Chem. Eng. News* **2004**, *82* (7), 63–65. (c) Narayan, S.; Fokin, V. V.; Sharpless, K. B. *Abstr. Pap. Am. Chem. Soc.* **2004**, *228*, U126-U126 554-ORGN. (d) Narayan, S.; Fokin, V. V.; Sharpless, K. B. *Abstr. Pap. Am. Chem. Soc.* **2005**, *230*, U3087-U3088 140-ORGN. (e) Narayan, S.; Fokin, V. V.; Sharpless, K. B. In *Organic Reactions in Water: Principles, Strategies and Applications*; Lindström, U. M., Ed.; Blackwell Pub.: Ames, IA, 2007; pp 350−364.

10.1021/jo801134r CCC: $40.75 © 2008 American Chemical Society
Published on Web 10/28/2008

many reactions with significant pressure acceleration are known.[7] Bimolecular reactions that give single molecule products often fall into this category, as do those with highly ordered transition states. Application of external pressure lowers the $\Delta G^{\ddagger}$ for reactions with a large negative $\Delta V^{\ddagger}$, accelerating them. This occurs because the energy of the more compact transition state is lowered by pressure more than that of the ground state. A variety of cycloaddition and other pericyclic reactions, such as the Claisen rearrangement, have significant negative $\Delta V^{\ddagger}$ and also exhibit pressure acceleration.[8] While its relationship to pressure acceleration is one view of the acceleration of reactions in aqueous media, there are others.

A large body of work, coming initially from Breslow,[9] concerns the acceleration of the Diels−Alder reaction in aqueous media. This reaction is pertinent here because of its acceleration under pressure and therefore its relation to Lubineau's hypothesis. Interestingly, a very early report by Diels and Alder of the reaction of furan and maleic anhydride was performed in water.[10] Breslow describes the reaction mixtures as suspensions when aqueous Diels−Alder reactions of cyclopentadiene are performed at 0.45 M,[11] which he called the formal concentration because of the presence of two phases. Narayan et al.[1b] conduct their reactions at higher formal concentrations (up to 4.5 M!). Much mechanistic work discussed in the literature following was performed at low concentrations that are not useful preparatively, some as low as 0.1 mM.

Acceleration of Diels−Alder reactions of nonpolar reactants in water compared to organic solvents has been attributed to many factors, including the hydrophobic effect,[12] enforced hydrophobic interactions in the transition state,[13] enhanced hydrogen bonding in the transition state,[14] and the high cohesive energy density (ced) of water (550.2 cal•mL^{-1} at 25 °C).[15] While hydrogen bonding and the hydrophobic effect are familiar to many chemists, cohesive energy density is not. Cohesive energy density (also called cohesive pressure) is the energy of the interaction among molecules of a liquid. It is the intermolecular force that gives liquids their cohesion, and is expressed in eq 1, which is simply the molar energy of vaporization divided by the molar volume. The ced values for many pure liquids have been determined and are available from tabulations.[16] The ced of water is one of the highest known, and when expressed in units of pressure is ca. 23 kbar.

$$\text{c.e.d.} = \frac{\Delta H_{\text{vap}} - RT}{M_{\text{r}}/\rho} \tag{1}$$

The cohesive pressure concept enables consideration of the energetics of the hydrophobic effect, though there are opposing contemporary views on this matter.[17] As the ced is inversely related to molar volume, water has one of the largest ceds because of its small molar volume (18 cm^3/mol), the smallest of any liquid commonly used as a reaction solvent. When water-immiscible organic compounds are dissolved in water, a void is created and the capsule of water molecules formed around the hydrophobic compound can be described as a clathrate. The energetic cost of displacing/releasing water to form this void within bulk water relates to the ced. The cohesive energy density has proved useful to understand solvent effects on both solvolysis reactions and the Claisen rearrangement, particularly those involving aqueous solvent and the hydrophobic effect.[18] The ced of the solvent is even correlated with the rates of some Diels−Alder reactions.[19]

The phenomena underlying the acceleration of organic reactions "on water" has been considered by Marcus.[1c] He notes the unique environment of water molecules located directly at an organic-aqueous phase boundary and the special availability of 'dangling' hydrogen bonds, that is, hydrogen bonding capacity that is unfulfilled by other water molecules, unlike the situation in bulk water. He distinguishes clathrates, where water encapsulates an organic droplet, from the situation at an organic/water emulsion interface, and proposes that hydrogen bonding of dangling water to organic molecules/intermediates at such an interface exerts a rate-accelerating effect on biradical formation in the cycloaddition of quadricyclane to dimethyl azodicarboxylate.[1b] However, it seems that nonaqueous, hydrogen-bonding solvents could also exert this effect, begging the question of what makes water unique as a solvent for this reaction. This idea is reminiscent of Jorgensen's explanation for aqueous acceleration of quinone Diels−Alder reactions, enhanced hydrogen bonding in the transition state.[13] While hydrogen bonding to water may be involved in promoting cycloadditions of some reactants, other reactants whose hydrogen bonding capacity is nil (diphenylacetylene) also experience rate accelerations in water,[4b] showing that hydrogen bonding cannot account for all of these effects. Marcus discounts the value of concentrating the reactants into an organic droplet by hydrophobic interactions, reasoning that the concentration inside a clathrate must be similar to that of neat reactants (wherein the reaction is slower). This view does not take into account the vastly different polarities of aqueous media and the neat organic reactants, an effect Breslow believes is important.[10] This theory also does not consider the known pressure acceleration of quadricyclane-azo compound cycloadditions.[20] In sum, there are many perspectives on the factors that influence the rates of

---

(3) (a) Cho, S. H.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1897–1900. (b) González-Cruz, D.; Tejedor, D.; de Armas, P.; Moralesa, E. Q.; García-Tellado, F. *Chem. Commun.* **2006**, 2798–2800. (c) Suzuki, I.; Suzumura, Y.; Takeda, K. *Tetrahedron Lett.* **2006**, *47*, 7861–7864. (d) Bose, A. K.; Manhas, M. S.; Pednekar, S.; Ganguly, S. N.; Dand, H.; He, W.; Mandadi, A. *Tetrahedron Lett.* **2005**, *46*, 1901–1903. (e) Yadav, J. S.; Reddy, B. V. S.; Sridhar, P.; Reddy, J. S. S.; Nagaiah, K.; Lingaiah, N.; Saiprasad, P. S. *Eur. J. Org. Chem.* **2004**, 552–557. (f) Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587–590.

(4) (a) Carril, M.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2006**, *8*, 1467–1470. (b) Butler, R. N.; Coyne, A. G.; Moloney, E. M. *Tetrahedron Lett.* **2007**, *48*, 3501–3503.

(5) Lubineau, A. *J. Org. Chem.* **1986**, *51*, 2142–2144.

(6) Drljaca, A.; Hubbard, C. D.; van Eldik, R.; Asano, T.; Basilevsky, M. V.; le Noble, W. J. *Chem. Rev.* **1998**, *98*, 2167–2289.

(7) (a) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1–26. (b) Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999–1027. (c) Isaacs, N. S. *Tetrahedron* **1991**, *47*, 8463–97. (d) Jenner, G. *Tetrahedron* **1997**, *53*, 2669–95. (e) Klärner, F.-G.; Wurche, F. *J. Prakt. Chem.* **2000**, *342*, 609–36.

(8) Matsumoto, K.; Uchida, T.; Acheson, R. M. *Heterocycles* **1981**, *16*, 11367–87.

(9) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164.

(10) (a) Diels, O.; Alder, K. *Ann. Chem.* **1931**, *490*, 243–7. (b) Otto, S.; Engberts, J. B. F. N. *Pure Appl. Chem.* **2000**, *72*, 1365–1372.

(11) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901–4.

(12) (a) Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809–20. (b) Lindström, U. M.; Andersson, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 548–51.

(13) Blokzijl, W.; Engberts, J. B. F. N. *Angew. Chem., Int. Ed.* **1993**, *32*, 1545–79.

(14) Chandrasekhar, J.; Shariffskul, S.; Jorgensen, W. L. *J. Phys. Chem. B* **2002**, *106*, 8078–85.

(15) (a) Lubineau, A.; Augé, J. *Top. Curr. Chem.* **1999**, *206*, 2. (b) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 742. (c) Lubineau, A. *Tetrahedron* **1988**, *44*, 6065.

(16) Dack, M. R. *J. Chem. Soc. Rev.* **1975**, *4*, 211.

(17) (a) Lazaridis, T. *Acc. Chem. Res.* **2001**, *34*, 931–7. (b) Graziano, G. *J. Chem. Phys.* **2004**, *121*, 1878–82.

(18) (a) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219–225. (b) Gajewski, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 10877–83.

(19) Gajewski, J. J. *J. Org. Chem.* **1992**, *57*, 5500.

reactions of nonpolar compounds in aqueous media, but no unified theory has been developed that accounts for all observations and has been accepted as valid.

Many reactions of organic compounds in aqueous media are heterogeneous. Chemists typically avoid heterogeneous reactions if possible because they can be difficult to scale up. One basis of this problem may be a rate-limiting mass-transport step between phases, rather than a chemical step as in a homogeneous reaction. In such circumstances, the efficiency of mixing can strongly influence the rate of reactant movement across the phase boundary and therefore the reaction rate. The inability to ensure efficient mixing on all reaction scales translates to scalability issues. One natural response to this concern is to use organic cosolvents in an attempt to render the reaction mixture homogeneous. Because the unique properties of water (such as its high surface tension and high cohesive pressure) may contribute significantly to the rate acceleration, creating homogeneous reaction media using organic cosolvents that lack these traits may compromise the potential benefits of water on reaction rate.

Work in our laboratory concerning the acceleration of reactions in water has focused on multicomponent reactions such as the Ugi and Passerini reactions,[21] a class also known to be pressure-accelerated. The reactions described are far faster in water than in organic solvents that are more polar than water (formamide) or are less polar but offer similar hydrogen bonding capability (methanol). These two solvents have c.e.d.s much smaller than water. These reactions are heterogeneous at the beginning and become more so as they proceed because the products are typically much less soluble in aqueous media than the reactants. A follow-on study examined the scope of the water-accelerated Passerini reaction, and found that reactants that include alcohols and tertiary basic nitrogen gave poor results.[22] As will be described following, such polar functionality likely decreases the hydrophobicity of the reactants and therefore hydrophobic interactions and cohesive pressure effects that we propose play an important role in rate acceleration.

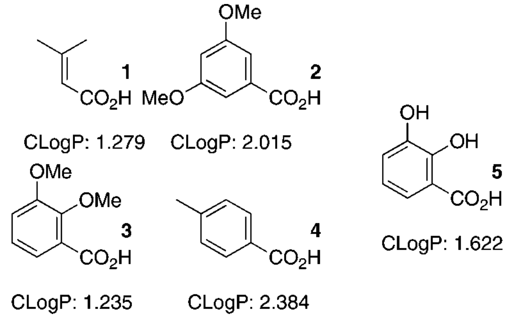
The foregoing alludes to possible effects of reactant hydrophobicity on rate acceleration for organic reactions conducted in water. While in some ways obvious, this factor has not been given much past consideration.[23] The hydrophobicity of an organic compound may be viewed from many perspectives, but one useful convention is the log of the octanol/water partition coefficient, or log P. It is widely used in physicochemical studies, tabulated for many organic compounds, and easily calculated for compounds for which it has not been measured (using chemical drawing programs, inter alia). For example, the water-miscible acetone has a calculated log P (Clog P) of −0.2, and more hydrophobic molecules have positive log Ps. To keep this representative value for polarity/hydrophobicity in mind, the Clog Ps are provided for all reactants in this paper. In unpublished work, we examined in water solution several reactions of acetone and nitromethane that are known to be pressure-accelerated[24] and observed *no* reaction. We hypothesize that polar reactants that are miscible with water, as these are, will not experience unique reaction environments (such as clathrates) or the hydrophobic/ cohesive pressure effect. That reactions of such compounds would not benefit from rate acceleration in water is consistent with Lubineau's hypothesis, which specifies its application to nonpolar compounds. That these reactions are homogeneous is a hindrance rather than a help.

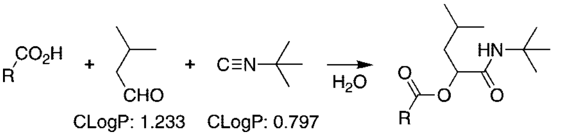
We aimed here to further study the rates of some organic reactions in water to better understand the effects of hydrophobic interactions and mixing on rates.

Results

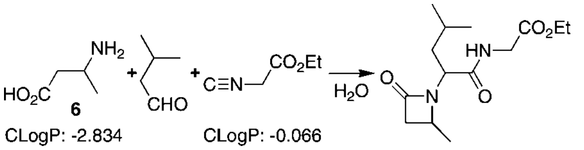
While the effects of mixing on organic reactions such as heterogeneous hydrogenations can be investigated through variables such as stirring rate, we aimed to discover an optimum mixing method for multicomponent reactions in water that would offer significant rate acceleration over earlier work. An initial qualitative study of the effect of the mixing method on Passerini reactions in water (eq 2) was performed using carboxylic acids **1**−**5** (Chart 1), *tert*-butylisonitrile, and isovaleraldehyde. Isolated yields following the reaction times given in Table 1 were determined for reactions performed under magnetic stirring, wrist-action shaking, or in a laboratory ultrasonic cleaning bath. Some reactions were also performed without agitation. Yields were determined based on mass recovered and comparison of starting material and product peak areas by HPLC. All of these reactions were performed on a 0.1−0.3 mmol scale at a concentration of 0.1 M. This concentration is comparable to that used in almost all of Breslow's work; reaction mixtures were visibly heterogeneous at their initiation. Because we have previously demonstrated that

CHART 1





(2)



(3)

---

(20) (a) Papadopoulos, M.; Jost, R.; Jenner, G. *J. Chem. Soc. Chem. Commun.* **1983**, 221–222. (b) Papadopoulos, M.; Jenner, G. *Nouv. J. Chim.* **1983**, *7*, 463–464. (c) Jenner, G. *Bull. Soc. Chim. Fr.* **1984**, 275–284. (d) Papadopoulos, M.; Jenner, G. *Nouv. J. Chim.* **1984**, *8*, 729–732. (e) Jenner, G. *New J. Chem.* **1991**, *15*, 897–899. (f) Pirrung, M. C. *Chem.−Eur. J.* **2006**, *12*, 1312.

[21] (a) Pirrung, M. C.; Sarma, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 444. (b) Pirrung, M. C.; Das Sarma, K. *Synlett* **2004**, 1425–1427. (c) Pirrung, M. C.; Sarma, K. D. *Tetrahedron* **2005**, *61*, 11456.

[22] Extance, A. R.; Benzies, D. W. M.; Morrish, J. J. *QSAR Comb. Sci.* **2006**, *25*, 484–490.

[23] Otto, S.; Engberts, J. B. F. N. *Org. Biomol. Chem.* **2003**, *1*, 2809–20.

[24] (a) Musumi, Y.; Bulman, R.; Matsumoto, K. *Heterocycles* **2002**, *56*, 599. (b) Sekiguchi, Y.; Sasaoka, A.; Shimomoto, A.; Fujioka, S.; Kotsuki, H. *Synlett* **2003**, 1655. (c) Sera, A.; Takagi, K.; Katayama, H.; Yamada, H.; Matsumoto, K. *J. Org. Chem.* **1988**, *53*, 1157.

TABLE 1. Effect of Mixing Method on the Product Yield for Reactions 2 and 3[a]

acid	Clog P	time (min)	stirring	shaking	ultrasound	still
1	1.279	30	NP	41	100	<5
2	2.015	30	10	NP	32	NP
3	1.235	60	35	32	55	10−20
4	2.384	30	52	54	65	variable
5	1.622	15	10	NP	52	NP
6	−2.834	360	47	83	NP	NP

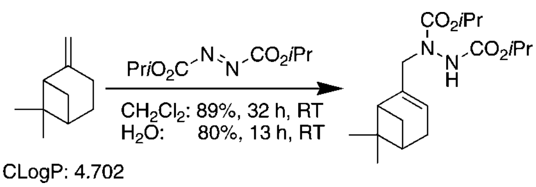
[a] NP - not performed.

Passerini reactions in water can show an inverse temperature dependence and the water in the ultrasonic bath warms over time, ice was added periodically to maintain the bath temperature at ambient, like the reactions performed with the other mixing methods.

The Passerini reaction of acid **1** in water gives the product in quantitative yield after 30 min under ultrasonication. We earlier reported[18] that this reaction gives the product in 95% yield in 200 min; that trial was performed using wrist-action shaking. As a control for ultrasound-specific effects, this reaction was also performed for 30 min in CH_2Cl_2 with ultrasonic irradiation, and the product was obtained in only 15% yield. Passerini reaction of **1** in water without mixing gives less than 5% conversion to product. Ultrasonication also proved to be the superior method of mixing in promoting Passerini reactions of acids **2**−**5**. Reactions without mixing were either very slow or variable in their rates. The variance of the rate of Passerini reactions in water with mixing method is consistent with heterogeneous reaction media. A similar investigation of the Ugi reaction of acid **6** to create a β-lactam (eq 3) was performed. It also shows a dependence of rate on the mixing method, with wrist-action shaking being superior to conventional magnetic stirring.

Ultrasound can exert profound effects on organic reactions.[25] While many explanations have been offered for these observations, ultrasonication commonly speeds reactions with heterogeneous character, which can be attributed at least partially to an increase in the rate of transfer between phases. Ultrasound is regarded by some as the most efficient method of mixing. There is also specific precedent for the acceleration of reactions of organic compounds in water by ultrasonication,[26] which may also be attributed to enhanced phase transfer. The ultrasonication literature makes clear that common laboratory ultrasonic cleaning baths can be poor sources of ultrasound for enhancing chemical reactions. The observation of an ultrasound effect on reaction 2 using such a source is thus encouraging. Superior ultrasound effects are often observed using power ultrasound from a sonic horn. We therefore aimed to investigate reaction 2 using power ultrasound. Because of our interest in high-throughput synthesis using multicomponent reactions in water,[18a] we sought an ultrasound source that could irradiate multiple, small volumes. A 96-well format sonicator is available for resuspension of compounds in chemical libraries following storage in frozen DMSO.[27] It uses a metal plate bearing multiple metal pins to transmit sonic energy into each well of a 96-well plate, permitting parallel sonication. When the Passerini reaction of **1** was performed using this instrument, the ultrasound effects were dramatic. A single 10 s pulse of ultrasound gave 40% conversion to product, and six 10 s ultrasound pulses gave 60% conversion. There was no background reaction without ultrasound. Because of the heating that is intrinsic to ultrasonication, cooling of these reactions and short pulses of sonic irradiation were essential, as we have previously shown that this reaction exhibits an inverse temperature dependence (i.e., it is slower at higher temperature).

While the foregoing results support a strong effect of mixing method on the rate of these multicomponent reactions in water, we aimed to gain more quantitative data on the effect of mixing on aqueous organic reactions. To obtain high-quality reaction progress data on a heterogeneous process is tedious and laborious (vide infra), but precise rate constants would be needed to discern small rate differences dependent on the mixing method. Because the Passerini reaction has a third-order rate law,[28] it was less desirable for initial studies, so we instead sought a water-accelerated reaction with a second-order rate law. We chose the ene reaction of azo compounds with β-pinene, which was known in organic solvents[29] and had been reported by Narayan et al.[2d,e] to be water-accelerated (concentration not specified). Our initial study showed a modest rate increase of about 3-fold in water for the reaction between β-pinene and DIAD (eq 4), similar to the initial report of Narayan et al. A study reported later[2e] using DEAD as the azo compound gave the ene reaction product in 82% yield in water in 3 h, while the same reaction neat gave the product in 90% yield but in 36 h.



(4)

The dependence of the rate of the reaction in eq 1 on mixing method, the medium, and reactant hydrophobicity were next investigated. It was followed by internal standard gas chromatography, evaluating the amount of β-pinene remaining. Replicate reactions were set up in the same number as the number of time points and all were treated identically. The initial reactant concentration was 0.25 M. These reactions were performed at ambient without special efforts to control temperature, as the inability to monitor the reaction continuously was viewed as a far larger contribution to the variation in observed reaction progress than temperature fluctuations. There is no assurance that the effectiveness of each mixing method is equal to the others, but the intensity of each method was maintained across all experiments. These reactions are clearly heterogeneous at their initiation, with organic liquid droplets on or under the aqueous phase. At each time point, one replicate was extracted with organic solvent to ensure that no reactants or products were depleted or enriched by differential solubility in the medium. The inverse of reactant concentration was plotted vs time, and data were linear for more than 3 half-lives (Figure 1). The mixing methods used included magnetic stirring, wrist-action

---

[25] Cravotto, G.; Cintas, P. *Chem. Soc. Rev.* **2006**, *35*, 180–196.

[26] (a) Varma, R. S.; Naicker, K. P.; Kumar, D. *J. Mol. Cat. A Chem.* **1999**, *149*, 153. (b) Cravotto, G.; Demetri, A.; Nano, G. M.; Palmisano, G.; Penoni, A.; Tagliapietra, S. *Eur. J. Org. Chem.* **2003**, 4438. (c) Cravotto, G.; Palmisano, G.; Tollari, S.; Nano, G. M.; Penoni, A. *Ultrason. Sonochem.* **2005**, *12*, 91. (d) Li, J.-T.; Zhang, X.-H.; Lin, Z.-P. *Beilstein J. Org. Chem.* **2007**, *3*, 13.

[27] Oldenburg, K.; Pooler, D.; Scudder, K.; Lipinski, C.; Kelly, M. *Comb. Chem. High Throughput Screen.* **2005**, *8*, 499–512.

[28] Baker, R. H.; Stanonis, D. *J. Am. Chem. Soc.* **1951**, *73*, 699.

[29] Jenner, G.; Salem, R. B. *J. Chem. Soc., Perkin Trans. II* **1989**, 1671.

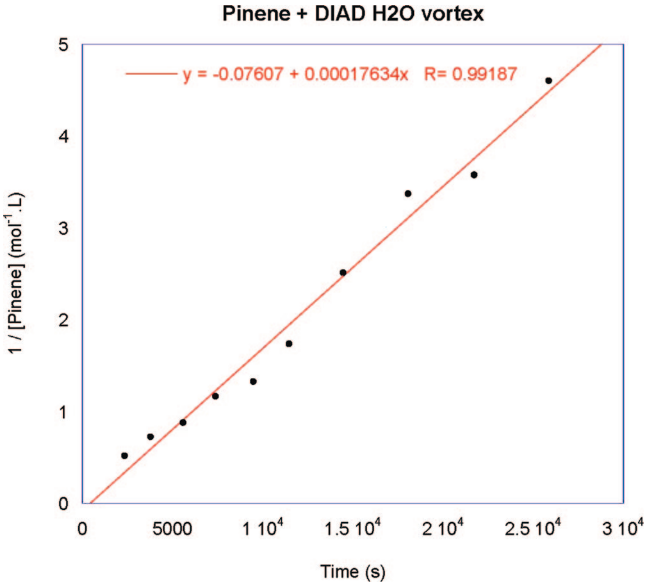


FIGURE 1. Kinetic plot for the ene reaction of β-pinene and **7** in water with vortexing.

TABLE 2. Effect of Mixing Method and Solvent on the Rate of Reaction 4

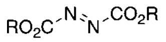
solvent	mixing method	rate constant × 10^5 ($L \cdot mol^{-1} \cdot s^{-1}$)	SD
CH_2Cl_2	stir	2.8	0.3
H_2O	stir	8.3	0.8
H_2O	shake	9.4	0.9
H_2O	vortex	17.6	1.8
H_2O	still	6.7	0.7
1 M aq LiCl	shake	8.1	0.8
2 M aq glucose	shake	9.1	0.9
1:9 $CH_3OH:H_2O$	shake	13.7	1.4

shaking, vortexing, and no mixing. The effect of water-soluble solutes was also examined. The results are summarized in Table 2.

The rate constants measured in water and in methylene chloride with stirring were consistent with the preliminary study. The rate in water increased as this reaction was shaken or vortexed. Interestingly, little decrement in rate was noted for reactions that were not mixed at all. Some agitation must have occurred through handling essential to the experimental procedure, however. The effect of solutes on this reaction was examined because of extensive earlier studies of the effect of salting-in or salting-out agents on the hydrophobic effect and reactions affected by it.[8] For this reaction, there was no significant effect of solutes. One of the faster reactions studied included low proportions of an organic cosolvent. Overall, the rate differences are modest, but their variation with mixing method is as expected for the heterogeneous medium observed.

Considering the implication discussed earlier that the ability of aqueous solvents to affect organic reaction rates should be related to reactant hydrophobicity, we examined the dependence of the rate of this ene reaction on the Clog P of the azo compound. Rate constants were determined in triplicate. Four available azo compounds **7**−**10** were studied using vortexing, the most efficient mixing method found above, for these reactions in water (Chart 2). Their rates in CH_2Cl_2 were also determined to discern the solvent effect. The log Ps of each azo reactant were also calculated, and all data are given in Table 3.

CHART 2



7: R=*i*Pr
8: R=*t*Bu
9: R=Bn
10: R=CH_2CCl_3

TABLE 3. Effect of azo Reactant on the Rate of the ene Reaction with Pinene

R	Clog P	H_2O[a]	CH_2Cl_2[a]	$k(H_2O)/k(CH_2Cl_2)$	SD
i-Propyl	2.33	18	2.8	6.4	0.6
tert-Butyl	2.76	1.1	0.38	2.9	0.3
Benzyl	4.48	16	21	0.76	0.08
Trichloroethyl	4.47	83	1700	0.05	0.005

[a] Rate constant × 10^5 ($L \cdot mol^{-1} \cdot s^{-1}$) average, $n = 3$.

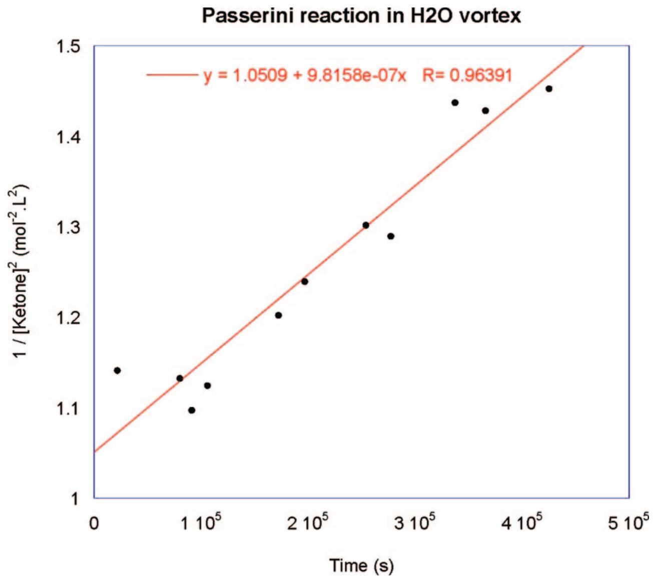


FIGURE 2. Kinetic plot for a single run of the Passerini reaction in eq 3.

Within each solvent series, the intrinsic reactivity of these azo compounds can be discerned. The azo compound **10** with the electron-withdrawing trichloroethyl ester is most reactive, and the azo compound **8** with the bulky *tert*-butyl ester is least reactive. For azo reactants **7** and **8** of intermediate hydrophobicity, reactions were modestly faster in water. For azo reactants **9** and **10** of high hydrophobicity, reactions were faster in the organic solvent.

While the foregoing studies were instructive, the rate acceleration by the solvent water was small by comparison to some of the more interesting reactions that have been earlier studied. We therefore undertook a kinetics study of a Passerini reaction that experiences a substantial rate acceleration in water. Following some initial scouting, reaction 5 was chosen because it does not proceed at all in methanol, analysis of the ketone reactant by internal standard gas chromatography is reliable, and the reaction in water has a reasonable rate. The same protocols as described for reaction 4 were observed. Reaction progress data were plotted according to the integrated form of the third-order rate equation. Plots of the inverse of the square of the reactant concentration vs time were linear (Figure 2). Rate constants were determined in triplicate.

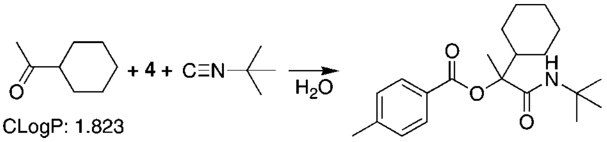
The rate of reaction 5 varies with the mixing method as expected for this heterogeneous medium (Table 4). Surprisingly,

TABLE 4. Effect of Mixing Method and Solvent on the Rate of Reaction 5

conditions	rate constant[a]	SD
H_2O, stir	15	1.5
H_2O, vortex	8.8	1.8
H_2O, shake	7.4	0.89
2.5 M aq LiCl, shake	12	1.5

[a] Rate constant × 10^7 ($L^2 \cdot mol^{-2} \cdot s^{-1}$), average, $n = 3$.

magnetic stirring proved to be the most effective method of mixing for this reaction. The addition of LiCl with shaking caused nearly a doubling of the reaction rate, clearly a significant effect, but smaller than some observed earlier.[18]



(5)

Discussion

The observations reported here that mixing affects the rates of several organic reactions in water were certainly foreshadowed in the work of Breslow. His original work on the Diels−Alder reaction in water noted an increase of reaction rate with vigorous stirring,[8] certainly an expectation in a heterogeneous reaction.

For reactions best accelerated by ultrasonication, it is tempting to consider that the extreme conditions of temperature and pressure associated with the formation and collapse of bubbles in solution, the so-called sonochemical hot spot,[30] plays a role. However, the effects of this spectroscopically determined hot spot do not appear to be available to accelerate most solution-phase reactions; if they were, ultrasonication could be much more broadly used to promote reactions. Ultrasonication is undoubtedly a very effective method to facilitate phase transfer in heterogeneous organic reactions, and most of the circumstances in which significant rate/efficiency effects of ultrasonication have been demonstrated involve some aspect of heterogeneity. While ultrasonication of water can generate hydroxyl radical, it is difficult to see how this could affect the reactions studied here. The hot spot also seems to be comparable in organic and aqueous media,[30] so the differential effects of ultrasound on these reactions in different solvents cannot be explained by variations in the effects of ultrasound.

One potentially puzzling aspect of our results is the acceleration in water of the β-lactam-forming Ugi reaction. The amino acid reactant is surely fully soluble in water, and therefore it is not expected to form a clathrate. However, the initial step in the Ugi reaction is condensation of the amino acid with the aldehyde to form imine **11**, and its hydrophobicity is similar to reactants in other water-accelerated reactions. It is also interesting that the Ugi reaction is successful in water even though this initial imine-forming reaction produces a molecule of water, and the 55 M concentration of water as solvent creates as disfavorable an equilibrium as can be imagined. This fact requires that imine formation make no contribution to the rate limitation of the Ugi reaction in water. Indeed, knowing the rate-determining step is key to considering the acceleration of these reactions. For the Passerini reaction, addition of the carboxylic acid to the nitrilium ion to form an imidate, or its rearrangment to give the product, are thought to be rate-determining.[25] For the Ugi reaction, the rate-determining step is unknown; a rate law has not been reported. While it is also possible that the rate-determining step for the reaction might change with solvent, we have observed no evidence of such behavior.

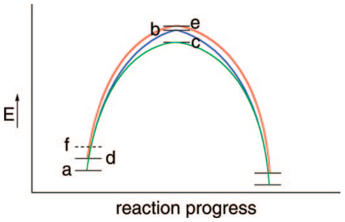
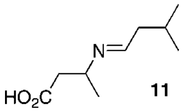


FIGURE 3. Proposed reaction progress plot for an idealized organic reaction with a large negative $\Delta V^{\ddagger}$ in organic solvent (blue), in organic solvent under pressure (green), or in water (red). External static pressure lowers the transition state energy from **b** to **c**. In water, the ground-state energy is raised to **d**, but the transition state **e** is not raised as much owing to the favorable effect of cohesive pressure. Salting-out solutes (like LiCl) raise the ground-state energy from **d** to **f**.



11

CLogP: 1.31

One hypothesis stimulated by the results in Table 3 is that reactants that are too nonpolar and therefore totally insoluble will react poorly when water is used as solvent because they are in the wrong phase. Likewise, the ability of 10% (v/v) methanol to provide a rate enhancement in reaction 4 compared to pure water could be explained by its ability to increase the mixing of the reactants. While one might expect 10% methanol to reduce the ced of the solution, just as it reduces its surface tension (observed when volatile alcohols or ketones are used to rinse water droplets from glassware), the effect of organic cosolvents on the ced itself is unknown. Small amounts of organic cosolvents can significantly change the course of solvolysis reactions, which might be partly attributed to changes in the c.e.d.

The observation that reaction 5 is fastest when stirred rather than mixed by other methods, when aggregated with our other observations, suggests that the most effective mixing method for organic reactions in water may need to be determined empirically for each reaction in question. While this is less convenient than knowing in advance that the best outcome should be obtained with a specific method, awareness of this phenomenon at least permits the chemist to undertake appropriate studies to ensure that optimum reaction procedures are reached. It was perplexing, however, that some reactions of pinene with azodicarboxylates were not slowed without mixing. Formation of clathrates is less likely in the absence of agitation, so such reactions might be good candidates for explanation by the ‘surface waters’ hypothesis.

Understanding of all of the effects that may impinge on organic reactions that are accelerated in water compared to organic solvents is certainly incomplete. We propose here a simplified reaction coordinate diagram given in Figure 3 for several different reaction conditions. Ground state reactants in

---

(30) (a) Suslick, K. S.; Hammerton, D. A.; Cline, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 5641–5642. (b) Didenko, Y. T.; McNamara, W. B., III.; Suslick, K. S. *J. Am. Chem. Soc.* **1999**, *121*, 5817–5818.

organic solvent are state **a**, and under normal conditions the reaction proceeds via the blue pathway through transition state **b**, which has a smaller volume than the reactants. If this reaction is pressurized, the relative energy of the transition state is reduced to state **c** and the reaction is accelerated, proceeding through the green pathway. If this reaction is performed in aqueous solution, the energy of the ground-state reactants is now **d** [ground-state destabilization in water is well-known for *tert*-butyl chloride solvolysis,[16] for example], and the reaction proceeds through transition state **e** via the red pathway. For this reaction to be accelerated, the increase of the transition state energy owing to the performance of the reaction in water must be *less than* the increase in the ground-state energy. This phenomenon has been demonstrated for a limited set of Diels–Alder reactions.[31] Reactions that should meet this requirement include those with large negative $\Delta V^{\ddagger}$s, forming the basis of Lubineau's rule. When the water also contains a "salting-out" solute, the energy of the ground-state reactants in water is increased, just as saturating the aqueous phase of a solvent-partitioning extraction with salt sends water-soluble organics to the organic phase. The energy of ground-state reactants is then state **f** and, *provided that the transition state for the reaction is not also salted out*, this raising of the ground-state energy should lower $\Delta G^{\ddagger}$ and further speed the reaction.

One question posed in recent discussions of organic reactions in water is whether a 'concentrated organic phase' might be involved, and whether in such instances the reaction is properly identified as occurring in water.[32] If a clathrate, which is intrinsic to the hydrophobic effect, is identified as such a phase, then any reaction that owes its effectiveness in water to the hydrophobic effect does involve a concentrated organic phase. Reactions that are accelerated in water, are fully homogeneous, and do not involve clathrates must exploit phenomena other than the hydrophobic effect. Many organic reactions have been reported in "aqueous" reaction media,[33] which could mean as little as 10% water in an organic solvent. While such solvents clearly offer far fewer concerns about reaction heterogeneity, the hydrophobic effect or cohesive pressure should play *no* role in the effectiveness of such reactions.

Many reactions in water studied here that have reactants with Clog Ps in the range of 1–2 exhibit the larger rate accelerations. We suggest that among reactions that fit Lubineau's criterion of a large negative $\Delta V^{\ddagger}$, those with reactants of about this polarity will prove the best candidates for acceleration in water. This measurement of hydrophobicity refines Lubineau's rule for rate acceleration, which only specified nonpolar compounds generally. Earlier correlations of rate acceleration in aqueous media with hydrophobicity have shown definite effects, but used the free energy of transfer of a compound from organic solvent to water to represent hydrophobicity.[31] While rigorous, the free energy of transfer is not nearly so available or intuitive as Clog P as a measure of the hydrophobicity of reactants that would commonly be used in synthetic reactions. As mentioned earlier, since water-miscible organic compounds do not experience the hydrophobic effect, reactions of compounds that are too polar should not benefit from aqueous acceleration. Likewise, compounds that are too nonpolar may be unable to achieve adequate concentrations to react in aqueous media and their reactions should be poor candidates for aqueous acceleration. However, ene reactions of pinene (Clog P 4.70) with azo compounds of the appropriate polarity are accelerated in water, whereas reactions with very nonpolar azo compounds are not. One reactant of the correct Clog P may be enough. Even for reactions with a large negative $\Delta V^{\ddagger}$, a parabolic dependence of aqueous reaction rate is expected as reactant polarity varies from polar and water-miscible to nonpolar and water-immiscible. However, water-soluble reactants or intermediates that are not involved in the rate-determining step may still permit the observation of aqueous reaction acceleration, as for the Ugi reaction studied in this work.

It is worthwhile to emphasize the reaction conditions under which the unique characteristics of water can accelerate organic reactions through the hydrophobic effect. Pure water or water including salting-out solutes should work best. A balance must be struck in the addition of organic cosolvents, because even though reaction homogeneity may be improved, the hydrophobic/cohesive pressure effect could be compromised. While there is no direct evidence concerning the ced of organic/water solvent mixtures, they have significantly lower surface tension than water and are therefore expected to have reduced hydrophobic effects. Dramatic, nonlinear effects of organic cosolvents on the rates of some dipolar cycloaddition reactions in aqueous media provide strong support for this caution.[34] Similar effects are known for Diels–Alder reactions when alcoholic cosolvents reach critical proportions at a mole fraction of ca. 0.3.[35] Reactions conducted at high temperatures are not likely to benefit from hydrophobic/cohesive pressure acceleration, simply because it is an entropic phenomenon and is less favorable toward $\Delta G^{\ddagger}$ at higher temperature. The ced also diminishes with temperature. We and others have observed inverse temperature dependence for reactions in water promoted by solvophobic interactions.[30a] To gain the benefit of hydrophobic/cohesive pressure effects, reactants should *not* be water-miscible, and therefore reactions will *all* be heterogeneous, if not at the macroscopic level, at the microscopic, and mixing effects on reaction efficiency are to be expected.

This topic is clearly one that is drawing a great deal of attention, and controversy. As stated by one reviewer: "Whether such reactions occur at the water-organic interface or in droplets or in clathrate 'cages' is not clear (and all of these can, in principle, be operational)." This work does not present a definitive view on the subject but aims to provide further data to inform the development of a better understanding of these phenomena.

Experimental Section

Well Plate Ultrasonication of the Passerini Reaction of 1. This reaction has been previously described in water with mixing by shaking.[18a] Ultrasonication was performed on a 0.05 mmol scale at 0.10 M. A suspension of the acid and aldehyde in water was introduced into each well of a deep-well 96-well plate and frozen at −80 °C overnight. The *tert*-butyl isocyanide was then added and the plate was again kept at −80 °C for 4 h before transfer to the SonicMan well plate sonicator. Blank reactions were not sonicated. A flat plate bearing metal pins was inserted into the 96-well plate,

---

(31) Meijer, A.; Otto, S.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8989–8994.

(32) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100–8102.

(33) (a) Kobayashi, S. *Adv. Synth. Catal.* **2002**, *344*, 219. (b) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095–3165.

(34) (a) Butler, R. N.; Cunningham, W. J.; Coyne, A. G.; Burke, L. A. *J. Am. Chem. Soc.* **2004**, *126*, 11923–9. (b) Gholami, M. R.; Yangjeh, A. H. *J. Phys. Org. Chem.* **2000**, *13*, 468–472.

(35) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, *113*, 4241–4246.

which was cooled to ca. 5 °C before sonication. Sonication of these plates was performed on the SonicMan in two ways, one at full power for 10 s and one at full power in six 10 s pulses. In each case, four pins were removed to give negative control wells which experienced the same temperature fluctuations but not sonication. The increase in temperature with each pulse was 6−9 °C. Cooling time between pulses was up to 25 min. No more than two ten-second bursts were performed without a cool-down period of 30−45 min in an ice bath to remove the heat produced by the sonication.

Kinetic Studies of ene Reactions. β-Pinene (39 μL, 0.25 mmol) and a disubstituted azodicarboxylate (0.28 mmol) were added to a glass vial (15 × 45 mm). Solvent (CH_2Cl_2 or H_2O) (1 mL) was added. 1-Nitro-2-propyl benzene (30 μL) was added as the internal standard. The reaction in CH_2Cl_2 was mixed by magnetic stirring. Reactions in H_2O were mixed by magnetic stirring, shaking, or vortexing, and also conducted still, without mixing. Reaction progress was monitored by GC under standard-1 or standard-2 conditions. Dibenzyl azodicarboxylate (**9**) and bis(2,2,2-trichloroethyl) azodicarboxylate (**10**) did not show GC peaks under either temperature program. The concentration of β-pinene was calculated by comparison of GC peak areas with the internal standard. These data were used for determination of rate constants using KaleidaGraph (version 3.5) software to fit the linear equation by least-squares.

Diisopropyl 1-((6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-hydrazine-1,2-dicarboxylate (15). β-Pinene (39 μL, 0.25 mmol) and **7** (53 μL, 0.28 mmol) were added to a glass vial (15 × 45 mm). Solvent (CH_2Cl_2 or H_2O) (1.0 mL) was then added. The reaction mixture was mixed by different mixing methods at room temperature for 7−24 h. Reactions were monitored by GC under standard-1 conditions. For reaction in CH_2Cl_2: The reaction mixture was concentrated in vacuo and the product was purified by flash chromatography (ethyl acetate/hexanes 1:5) to give the product as a colorless liquid (75 mg, 89%). For reaction in H_2O: The reaction mixture was extracted with CH_2Cl_2 (1 mL × 2). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the product was purified by flash chromatography (ethyl acetate/hexanes 1:5) to give the product as a colorless liquid (67 mg, 80%). R_f = 0.34 (ethyl acetate/hexanes 1:5). ^{1}H NMR ($CDCl_3$): δ 5.40 (s, 1H), 4.95 (m, 2H), 4.10 (brs, 2H), 2.38 (m, 1H), 2.26 (d, J = 9.3 Hz, 2H), 2.10 (m, 2H), 1.21−1.28 (m, 15H), 1.15 (d, J = 8.7 Hz, 1H), 0.84 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 156.1, 155.6, 143.1, 120.9, 120.2, 69.9, 69.5, 54.4, 43.5, 40.7, 38.0, 31.4, 31.1, 26.1, 22.0, 21.9, 21.0. IR (neat): 3298, 2982, 2917, 1698, 1468, 1406, 1385, 1375, 1261, 1218, 1180, 1106, 1037, 918, 764, 731 cm^{-1}. HRMS (ESI): calcd for $C_{18}H_{31}N_2O_4$ [M + H]$^+$ 339.2283, found 339.2280.

Ditert-butyl 1-((6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)hydrazine-1,2-dicarboxylate (16). This compound was prepared as in the previous procedure starting with di-*tert*-butyl azodicarboxylate (**8**). Colorless liquid (62 mg, 68%). R_f = 0.49 (ethyl acetate/hexanes 1:5). ^{1}H NMR ($CDCl_3$): δ 5.38 (brs, 1H), 3.96 (brs, 2H), 2.37−2.41 (m, 1H), 2.26 (d, J = 9.9 Hz, 2H), 2.10 (m, 2H), 1.46 (s, 18H), 1.26 (s, 3H), 1.15 (d, J = 8.7 Hz, 1H), 0.84 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 155.7 (2C), 143.7, 120.8, 81.2 (2C), 54.1, 43.8, 40.9, 38.2, 31.6, 31.4, 28.3 (2C), 26.3, 21.2. IR (neat): 3321, 2979, 2916, 2834, 1705, 1478, 1456, 1392, 1366, 1345, 1253, 1153, 1049, 1021, 910, 861, 780, 761, 733 cm^{-1}. HRMS (ESI): calcd for $C_{20}H_{34}N_2O_4Na$ [M + Na]$^+$ 389.2416, found 389.2403.

Dibenzyl 1-((6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)hydrazine-1,2-dicarboxylate (17). This compound was prepared as in the previous procedure starting with dibenzyl azodicarboxylate (**9**). Colorless liquid (97 mg, 89%). R_f = 0.32 (ethyl acetate/hexanes 1:5). ^{1}H NMR ($CDCl_3$) δ 5.37 (brs, 1H), 5.15 (brs, 4H), 4.07 (brs, 2H), 2.33 (m, 1H), 2.22 (d, J = 8.1 Hz, 2H), 2.07 (m, 2H), 1.23 (s, 3H), 1.09 (d, J = 8.7 Hz, 1H), 0.79 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 156.5, 155.9, 142.8, 136.0, 135.8, 128.7, 128.6, 128.4, 128.3, 128.0 (2C), 121.8, 121.2, 68.2, 67.7, 55.1, 54.4, 43.7, 40.8, 38.2, 31.6, 31.3, 26.2, 21.2. IR (neat): 3293, 3033, 2916, 2832, 1709, 1498, 1455, 1408, 1341, 1305, 1261, 1207, 1120, 1046, 1029, 1002, 910, 887, 734, 695 cm^{-1}. HRMS (ESI): calcd for $C_{26}H_{30}N_2O_4Na$ [M + Na]$^+$ 457.2103, found 457.2094.

Bis(2,2,2-trichloroethyl) 1-((6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)hydrazine-1,2-dicarboxylate (18). This compound was prepared as in the previous procedure starting with bis(2,2,2-trichloroethyl) azodicarboxylate (**10**). Colorless liquid (129 mg, 100%). R_f = 0.52 (ethyl acetate/hexanes 1:5). ^{1}H NMR ($CDCl_3$): δ 5.49 (brs, 1H), 4.78 (m, 4H), 4.14 (m, 2H), 2.37−2.45 (m, 1H), 2.28 (m, 2H), 2.13 (m, 2H), 1.28 (s, 3H), 1.17 (d, J = 9 Hz, 1H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 154.9, 154.5, 153.9, 153.4, 142.0, 122.7, 122.2, 94.9, 75.9, 75.7, 75.1, 55.4, 54.7, 43.6, 40.8, 38.3, 31.6, 31.4, 26.2, 21.2. IR (neat): 3298, 2919, 2833, 1725, 1494, 1439, 1408, 1306, 1254, 1198, 1136, 1105, 1047, 972, 908, 862, 807, 719 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{21}Cl_6N_2O_4$ [M + H]$^+$ 514.9632, found 514.9609.

Kinetic Studies of Passerini Reactions. Cyclohexyl methyl ketone (28 μL, 0.20 mmol), *p*-toluic acid (27 mg, 0.20 mmol), and *tert*-butyl isocyanide (23 μL, 0.20 mmol) were added to a glass vial (15 × 45 mm). Solvent (H_2O, 1 mL) was added. 1,4-Dimethoxy benzene (40 μL of a 5 M solution in $CHCl_3$, 0.20 mmol) was added as the internal standard. Reactions in H_2O were mixed by magnetic stirring, shaking and vortexing. The reaction in 2.5 M aq. LiCl solution was mixed by shaking. Reaction progress was monitored by GC under standard-1 conditions. The concentration of cyclohexyl methyl ketone was calculated by comparison of GC peak areas with the internal standard. These data were used for determination of the rate constant using KaleidaGraph (version 3.5) software to fit the linear equation by least-squares.

4-Methyl-benzoic Acid 1-Tert-butylcarbamoyl-1-cyclohexyl-ethyl Ester (19). Cyclohexyl methyl ketone (28 μL, 0.20 mmol), *p*-toluic acid (27 mg, 0.20 mmol), and *tert*-butyl isocyanide (23 μL, 0.20 mmol) were placed in a glass vial (15 × 45 mm). Solvent (H_2O, 1 mL) was added and the reaction mixture was mixed by shaking at room temperature for 4−6 d. The reaction mixture was extracted with CH_2Cl_2 (1 mL × 2). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the product was purified by flash chromatography (ethyl acetate/hexanes 1:5) to give the product as a white solid (17 mg, 25%). R_f = 0.40 (ethyl acetate/hexanes 1:5). ^{1}H NMR ($CDCl_3$): δ 7.88 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 7.6 Hz, 2H), 5.66 (s, 1H), 2.40 (s, 3H), 1.70−1.95 (m, 6H), 1.65 (s, 3H), 1.32 (s, 9H), 1.10−1.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 170.8, 164.8, 143.8, 129.5, 129.1, 128.0, 86.5, 46.3, 28.6, 27.4, 27.0, 26.5, 26.4, 26.4. IR (neat): 3402, 2932, 2853, 1701, 1648, 1609, 1517, 1456, 1365, 1285, 1219, 1177, 1101, 1074, 1016, 834, 762, 696 cm^{-1}. HRMS (ESI), calcd for $C_{21}H_{32}NO_3$ [M + H]$^+$ 346.2382, found 346.2382. mp: 124 °C.

Acknowledgment. We are grateful to Kevin Oldenburg and Kurt M. Scudder for providing access to their SonicMan well plate sonicator and for performing irradiations.

Supporting Information Available: General experimental conditions, characterization of **12−14** and the Passerini products of the acids in Chart 1, and ^{1}H NMR spectra for **12−19**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801134R