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Rate Enhancement in Ethanolic Aqueous Buffer. The Diels-Alder Reaction

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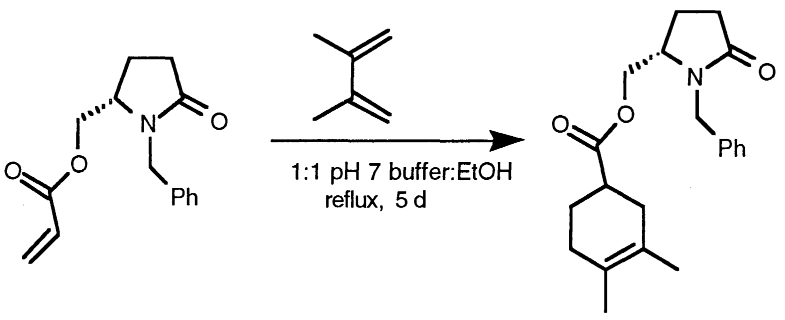
We have observed a 2.5-3-fold increase in the rate of Diels-Alder reactions when done in aqueous ethanol, where the aqueous solution was prepared with a pH 7 buffer. This is a simple, inexpensive and convenient method for modest acceleration of the Diels-Alder reaction, in addition to the rate increase normally observed in aqueous media.

Rate enhancement in the Diels-Alder reaction in aqueous media is well-known. Breslow showed that the thermal reaction of dienes and alkenes generally considered to be 'insoluble' was greatly accelerated in aqueous media.1) Berson showed a clear relationship between the *endo/exo* product ratio and solvent polarity in the Diels-Alder reaction of cyclopentadiene and acrylates.2) Greico applied this idea to synthetic problems, often using water soluble dienes and dienophiles.3) Hopff and Rautenstrauch4) established that Diels-Alder reactions were accelerated in aqueous solutions of detergents as early as 1939. More recently, Liotta showed that substrates that were totally insoluble in water gave little or no acceleration in aqueous Diels-Alder reactions.5) In these cases, ethylene glycol provided significant rate acceleration for the Diels-Alder reaction.5) When non-polar compounds are suspended in water their relative insolubility causes them to associate, diminishing the water-hydrocarbon interfacial area. Any additive which increases the hydrophobic effect will increase the rate.1) Both lithium chloride (LiCl) and guanidinium chloride have been shown to increase the rate of Diels-Alder reactions.1,2)

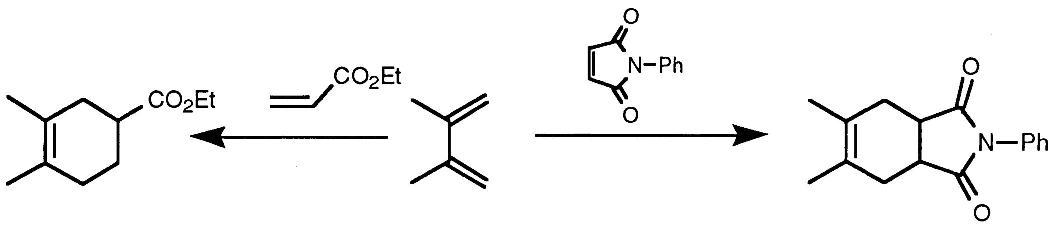
Rate acceleration in these reactions is generally observed when non-polar compounds are suspended in water or aqueous media. The relative insolubility of the alkene and/or diene in aqueous media causes these molecules to associate, diminishing the water-hydrocarbon interfacial area (a hydrophobic effect).6) This association is greater in water than in methanol and brings the reactive partners into close proximity, increasing the rate of reaction. Any additive which increases this hydrophobic effect (such as β-cyclodextrin [cycloheptaamylose]) will increase the rate of reaction.1) As mentioned, lithium chloride (LiCl) increases the hydrophobic effect by salting out nonpolar material. This phenomenon can be related to formation of a micelle in which the reaction occurs. As stated by Liotta: an aqueous environment creates a medium where the "reactants orient them-selves within a micelle, thereby increasing their effective molarity and, consequently, the rate".5)

In a synthetic project, we attempted to prepare a 'designer' chiral auxiliary based on pyroglutamate. When this auxiliary was attached to acrylic acid (ester **1**), and reacted with 2,3-dimethyl-1,3-butadiene, cycloadduct **2** was isolated in 78% yield. The idea was to change the groups on the lactam nitrogen and examine any changes in diastereoselectivity during the cycloaddition. This reaction was very sluggish in boiling toluene and even addition of $ZnCl_2$ required refluxing conditions for cycloaddition to occur at a reasonable rate (3-5 days). We turned to an aqueous ethanol medium in an attempt to accelerate the reaction in accord with our previous success in accelerating such reactions.7) We found only a modest acceleration of the rate (about 1.3 fold increase), however. We then added $ZnCl_2$ to the aqueous medium with the hope that some rate enhancement would occur via the usual coordination of the Lewis acid to the carbonyl of the dienophile. In this case, we anticipated reversible binding of $ZnCl_2$ in the aqueous medium. The reaction was about 1.5 times faster when $ZnCl_2$ was added but still required refluxing conditions (for about 50 hours) to obtain reasonable yields of the cycloadduct. As part of this study we examined the rate of reaction in a controlled experiment in which a pH 7 buffer was used to make up the solvent rather than water (a solution of 50% ethanol and 50% aqueous buffer was used). The rationale for this experiment was to examine the role of acid catalysis in the $ZnCl_2$ reaction. We found a larger increase in rate of reaction when the reactants were refluxed in this solvent. When the control experiment was run, without $ZnCl_2$ but with aqueous buffer in ethanol, we were surprised to find the Diels-Alder reaction was <u>faster</u> in the buffered medium <u>without</u> $ZnCl_2$. We therefore turned our attention to this phenomenon for possible application to other Diels-Alder reactions.



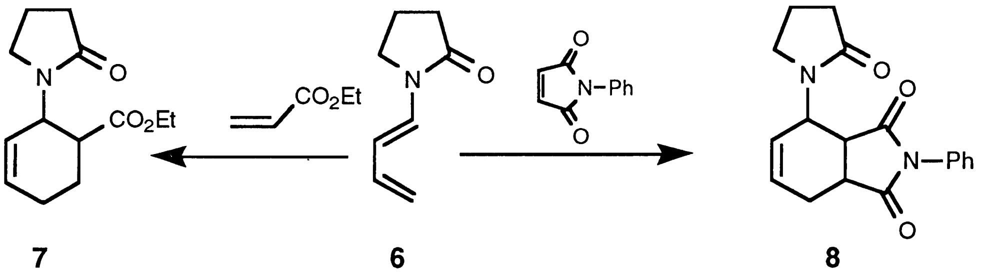
1 **2**

Our initial experiments reacted 1,2-dimethyl-1,3-butadiene (**3**) with ethyl acrylate (to give **4**) and with N-phenyl-maleimide (to give **5**). When compared with the unbuffered reaction, ethyl acrylate reacted with 2,3-dimethyl-1,3-butadiene (**3**) in the buffered medium to give cycloadduct **4** about 3.5 times faster. Similar reaction of **3** with N-phenylmaleimide gave cycloadduct **5** about two times faster in the buffered medium. We also reacted dienyl lactam **6** (prepared by our previously reported procedure)7) with ethyl acrylate (to give **7**) and with N-phenylmalimide (to give **8**). In this case, diene **6** reacted with ethyl acrylate to give **7** about 3.3 times faster in the buffered medium and N-phenylmaleimide gave **8** about 3.5 times faster in the buffer. This rate data is shown in Table 1.



4 **3** **5**

A comparison of buffered and unbuffered reactions shows approximately a 3.5 fold increase in the rate of the Diels-Alder reaction in the buffer, with the exception of the conversion of **3** to **5**, which was only twice as fast. This is consistent with the 3.4 fold increase we observed in the conversion of **1** to **2**. The measured rate enhancement is remarkably uniform for the three dienes examined and the various alkenes (**1** → **2**, **3** → **4** or **5** and **6** → **7** or **8**). The dienophiles are all electron deficient and we have not, as yet, examined the reaction with a wider range of alkenes or dienes. The uniformity of the rate enhancement with several alkene/diene combinations, however, suggests that the effect may be applicable to a wide range of Diels-Alder reactions.



7 **6** **8**

It is not yet clear why the pH 7 buffer gives this rate acceleration effect. Further work is obviously required to establish the basis for this phenomenon, including the range of buffers, if any, that may promote the reaction. The micelle effect invoked in other aqueous Diels-Alder reactions may explain our results. Breslow's analysis that an additive which increases association and hydrophobic effects will increase the rate and the buffer may increase the rate of reaction by this 'salting out' process.1) Another possibility is a secondary reaction between the sodium or potassium phosphate and the diene or dienophile that catalyzes the reaction. We found that the pure acidic salt used in this buffer (KH_2PO_4) gave about the same rate of acceleration for the conversion of 3 to 4 as we observed with the buffer. The pure basic salt found in this buffer (Na_2HPO_4), however, gave no additional rate enhancement over that observed with aqueous ethanol. This suggests a proton transfer from the slightly acidic KH_2PO_4 to the dienophile, generating a protonated dienophile. Such as intermediate is analogous to that formed by Lewis acids by coordination to the oxygen of electron deficient dienophiles. This lowers the LUMO of the alkene sufficiently to accelerate the reaction rate.8) The modest rate enhancement observed with the pH 7 buffer may simply reflect a small lowering of the LUMO energy due to protonation of the ester. Further experiments are required to determine if protonation is responsible for the rate enhancement or if it is the usual effect noted by adding salts such as LiCl or guanidinium salts.1,2) This communication simply presents an interesting addition to the growing field of aqueous Diels-Alder chemistry. The ability to enhance the rate of a Diels-Alder reaction beyond the usual rate enhancement occurring in aqueous media in a facile and convenient manner is an important discovery. The possible applications to process development are obvious if this phenomenon occurs with large-scale Diels-Alder reactions, and this will be explored.

Table 1. Rate Enhancement in pH 7 Buffer/Ethanol Solution

Diene	Alkene	Reaction conditions[a]	$k \times 10^{-4}/M^{-1}\ min^{-1}$
3	Ethyl acrylate	A, 35 h	11.9
		B, 20 h	42.1
3	N-Phenyl maleimide	A, 50 h	17.1
		B, 25 h	33.0
6	Ethyl acrylate	A, 85 h	9.4
		B, 35 h	31.1
6	N-Phenyl maleimide	A, 100 h	5.8
		B, 35 h	20.1

a) A =- 1:1 aq. EtOH; B = 1:1 pH 7 buffer:EtOH. All reactions were carried out at reflux.

In conclusion, we have demonstrated that rate enhancement is possible in buffered aqueous ethanol, in addition to the rate enhancement usually observed in aqueous media.

The pH 7 buffer was a commercial mixture of Na_2HPO_4 and KH_2PO_4, available in a 'capsule'.9) This capsule (about 1.0 g) was mixed with one liter of water and a 1:1 mixture (by volume) was used for the reactions in the 'buffered' medium (pH 7.2). The control reaction was done in a 1:1 aqueous ethanol mixture. The temperature, solution volumes and concentrations were identical in all runs, for all dienes and dienophiles. Typically, 100 mmol of alkene and 100 mmol of diene were reacted in a mixture of 100 mL of aqueous buffer and 100 mL of ethanol. This reaction mixture was refluxed for the time indicated in Table 1. Standard aliquots (10 mL) were analyzed on a reverse phase (C_{18}) HPLC column using aqueous acetonitrile as the mobile phase with concentrations determined relative to the internal standard. A standard amount of cyclohexene was added to the reaction of **3** and ethyl acrylate but 2-pyrrolidinone was used as an internal standard in all other cases (the rate of reaction with and without 2-pyrrolidinone was identical). Plots of ln concentration of the alkene vs. time (in minutes) provided linear pots with a correlation of >0.97 over three half-lives.

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9) Marketed as pHydroin Buffer (7.2 ±0.05 at 25 °C) by Micro Essential Laboratories, Brooklyn 10, New York.

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