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Solvent effects in the liquid phase Beckmann rearrangement of 4-hydroxyacetophenone oxime over H-Beta catalyst

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Abstract

N-acetyl-*para*-aminophenol (APAP) or acetaminophen was first synthesized via the environmentally benign liquid phase Beckmann rearrangement of 4-hydroxyacetophenone oxime over zeolite H-Beta. The reaction represents a typical case of active solvent participation. The results of co-adsorption of substrate and solvent suggest that the facility of protonation of oxime is mainly dependent upon the competitive adsorption between substrate and solvent. On the other hand, a solvent having a higher dielectric constant or more polar nature is preferred in the subsequent 1,2-*H*-shift and rearrangement steps. Consequently, the choice of a suitable solvent balancing between the two competitive aspects is the most important factor enhancing the performance of the reaction.

Keywords: Beckmann rearrangement; Acetaminophen; Zeolite Beta; Adsorption; Solvent effect

1. Introduction

N-acetyl-*para*-aminophenol (APAP) or acetaminophen, being one of the most widely used over-the-counter analgesics, has been an important commodity since its first synthesis by Morse in 1878. Conventionally, large-scale preparation of acetaminophen mainly employs the acetylation of *p*-aminophenol with acetic anhydride. Although this procedure is very convenient from a chemical point of view, its inherent problems such as difficulty of mono-acylating the amino group, oligomerization of the hydroxy aromatic amine, and color body formation may lead to the requirement of additional treatments.

The mid-eighties witnessed a new entrant to the field using a process starting from phenol, but with innovative technology via 4-hydroxyacetophenone, followed by the Beckmann rearrangement of the corresponding 4-hydroxyacetophenone oxime (to be designated hereafter as 4-HAP oxime) to acetaminophen [1]. However, the use of fuming sulfuric acid, the large amount of salt formed during the subsequent neutralization, and the corresponding problem of corrosion also make this process environmentally questionable. Furthermore, since acetaminophen is a pharmaceutical for human consumption, the product has to be as pure as possible, and, thus, trace impurities from corrosion products are not allowed.

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In order to overcome these problems, a zeolite seems to be an excellent candidate to take over the catalytic job, since the use of a zeolite as the catalyst will be very promising not only from an economical point of view but also from an ecological viewpoint. In fact, there have been a large number of works on the vapor- or liquid-phase Beckmann rearrangement of ketoximes such as cyclohexanone oxime, acetophenone oxime, and cyclododecanone oxime over zeolites [2–9]. In the case of 4-HAP oxime, however, the degradable and polar nature of 4-HAP oxime may cause some problems, when the reaction is conducted over a zeolite-based catalyst. The former makes the gas-phase reaction unrealizable, therefore the reaction has to be carried out in liquid phase. Concerning the liquid-phase reaction, solvent candidates are restricted to polar ones due to the polar nature of 4-HAP oxime. The polar solvent, which is prone to compete with the substrate for the active sites, however, may decrease the amount of adsorbed substrate, thus reducing the intrinsic reaction rate.

In this context, it is aimed here to investigate the influence of the solvent on the Beckmann rearrangement of 4-HAP oxime over zeolite H-Beta. All the polar solvents used in this study were chosen because they can form a homogeneous phase with the polar substrate 4-HAP oxime. To our knowledge, this is the first report for the preparation of acetaminophen via the environmentally benign method.

2. Experimental

The zeolite H-beta sample (Si/Al = 11) was taken from commercial batch provided by P.Q. Industries (CP814E-22). Before being used as a catalyst, the material was ion exchanged twice and calcined to obtain the catalytically active hydrogen form. For this, 10 g of the Beta zeolite and 100 g of 1 N ammonium nitrate solution were thoroughly mixed in a flask at 80°C for 48 h. Afterwards, the catalyst was recovered by filtration, washed with deionized water and dried at 110°C for 4 h. Finally, the material was calcined under air at 550°C for 12 h with a heating rate of 2°C/min.

4-HAP oxime was prepared from the corresponding ketone by reacting it with hydroxylamine sulfate in a mixture of water and ammonium hydroxide at 90°C according to the method reported in the literature [1]. After removal of the solvent under a reduced pressure, 4-HAP oxime was obtained as white crystals in a nearly quantitative yield. Its identity was confirmed by FT-IR and proton NMR spectroscopy.

The Beckmann rearrangement of 4-HAP oxime was carried out in the liquid phase at 70°C under nitrogen in a 50-ml three-necked, round-bottomed flask reactor immersed in a thermostated bath and equipped with a reflux condenser and a magnetic stirrer. For the case when acetone or methanol was used, the reaction temperature was maintained at the reflux temperature. A typical reaction run was as follows: 0.1 g catalyst, pre-calcined in air at 500°C, was suspended in a solution of 0.15 g (1 mmol) of 4-HAP oxime in 20 ml solvent, which was allowed to equilibrate to the set temperature. The reaction mixture was heated to reaction temperature and stirred under nitrogen for 5 h. After completion of the reaction, the reaction mixture was filtered and diluted with methanol. The reaction products were analyzed using an HPLC equipped with a Symmetry C_{18} (Waters) column and with a UV detector operating at 254 nm.

Adsorption studies were performed at 70°C in the same vessel as used for the reaction except for a calcium chloride guard tube for protection against humidity. A total of 0.25 mmol 4-HAP oxime, 68 mmol solvent to be tested, and 8.2 mmol *m*-xylene as an internal standard were added to 30 ml 1,3,5-tri-isopropylbenzene, a bulky solvent incapable of adsorption on the zeolite. After 0.1 g of activated catalyst was added to the solution, samples were taken periodically and analyzed by HPLC in the case of the substrate or the relatively less polar

solvents and by GC in the case of the polar solvents.

3. Results and discussion

During the reaction, the only compound observed, besides the starting material, was the corresponding amide regardless of the solvent used. There were no other products, such as *N*-methyl-*p*-hydroxybenzamide (MHBA) or *p*-aminophenol, which may be formed as a result of syn-migration of the methyl substituent or by hydrolysis of acetaminophen, respectively [10]. Concerning the Beckmann rearrangement, it is well known that the group that migrates is generally the one anti to the leaving group [11–13]. The predominant anti-migration of phenyl group results in the high selectivity of acetaminophen. The absence of the syn-migration product, MHBA, should be pointed out, because MHBA can be removed only partially from the desired product by conventional purification techniques such as aqueous recrystallization [10]. Presumably, the syn-migration of 4-HAP oxime may be suppressed inside the pores. A blank experiment was also carried out under the same reaction conditions. No substrate transformation was observed in the absence of catalyst.

As shown in Table 1, the attribute of a solvent definitely determines the performance of the reaction; the reaction did not proceed in the polar protic media, but in the presence of polar aprotic solvent, the reaction progressed to a considerable conversion. It is also interesting that in view of Snyder's eluotropic series (ε^o) [14], a polarity scale, which is established by rating solvents in the order of their strength of adsorption on an adsorbent material such as silica or alumina, makes it possible to find a close relation between the catalytic performance and the adsorption characteristics. Obviously, the stronger the solvent–adsorption sites interactions, the stronger the competition between reactant and solvent for adsorption sites.

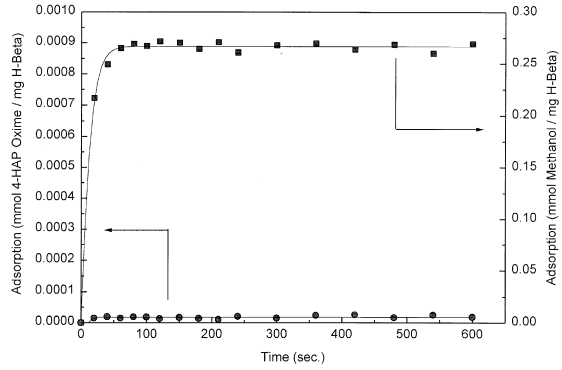


Fig. 1. Competitive adsorption of 4-HAP oxime and methanol on H-Beta.

To elucidate the adsorption site competition between solvent and substrate, we carried out a co-adsorption of the substrate and the solvent on zeolite H-Beta from the non-adsorbing medium 1,3,5-triisopropylbenzene. The results show that the site competition between solvent and sub-

Table 1
Solvent screening

Solvent	ε^o (Al_2O_3)[a]	Dielectric constant[b]	Conversion (%)	Selectivity (%)
Water	Large	80.1	–	–
Methanol	0.95	33.0	–	–
Ethanol	0.88	25.3	–	–
2-Propanol	0.82	20.18	–	–
Acetonitrile	0.65	36.64	68.5	> 98
DMSO	0.62	47.24	80.2	> 98
Acetone	0.56	21.01	95.8	> 98
MEK	0.51	18.56	83.3	> 98

[a] Solvent strength parameter in Snyder's eluotropic series, for silica a good approximation is ε^o(silica) = 0.77ε^o(alumina).
[b] Values at 293.2 K.

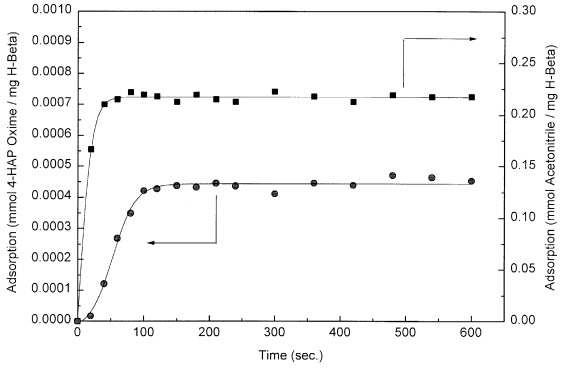


Fig. 2. Competitive adsorption of 4-HAP oxime and acetonitrile on H-Beta.

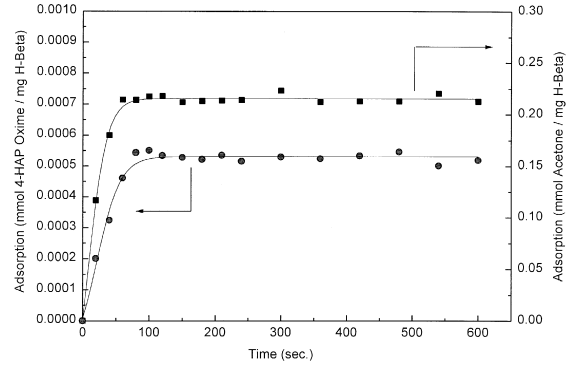


Fig. 4. Competitive adsorption of 4-HAP oxime and acetone on H-Beta.

strate is undoubtedly one of the major factors affecting the performance of the catalytic reaction. In Fig. 1, the co-adsorption of 4-HAP oxime and methanol is presented. It appears that the predominant adsorption of methanol renders the active center inaccessible to substrate and consequently brings about the low concentration of the substrate on the catalytic surface. This indicates that the affinity of zeolite H-Beta towards methanol is much higher than that towards the substrate, therefore, the reaction may not occur at all. Other polar protic solvents exhibit the same tendency as methanol (not shown here).

On the other hand, in the case of polar aprotic solvents, as shown in Figs. 2–5, the amount of adsorbed substrate on the catalyst was substantial, though that of solvent was still larger. It seems that the adsorption of solvent and substrate in polar aprotic solvent is much more in balance than in the previous system. Accordingly, the reaction may readily proceed in polar aprotic media in which the chance of the substrate to access the active sites will significantly increase in contrast to a polar protic solvent such as methanol. It should be stressed, however, that the difference in reactivity cannot be totally ascribed to the unbalanced adsorption equilibrium between solvent and substrate. Considering the adsorption equilibria alone, it may be intuitively expected that the conversion of 4-HAP oxime will be higher in MEK than that in acetonitrile, dimethyl sulfoxide (DMSO), or acetone, since the amount of substrate adsorbed on the catalyst was larger in MEK than in other solvents. However, the fact that a maximum

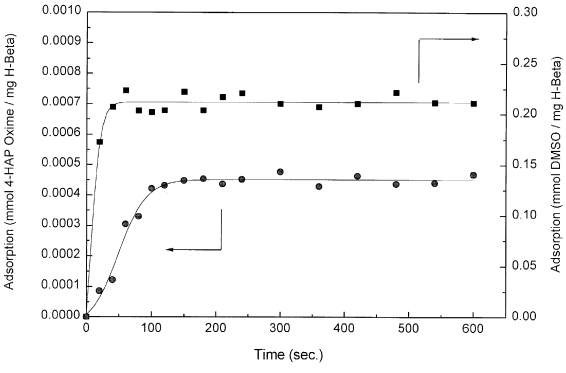


Fig. 3. Competitive adsorption of 4-HAP oxime and DMSO on H-Beta.

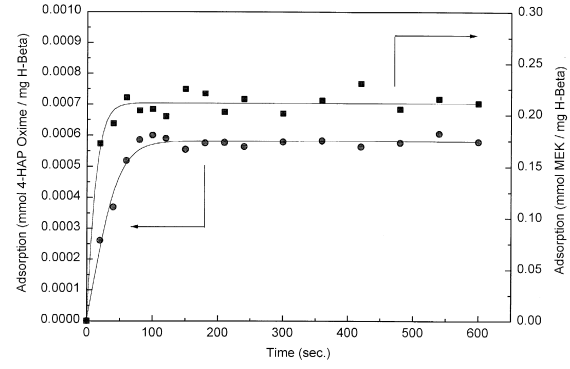


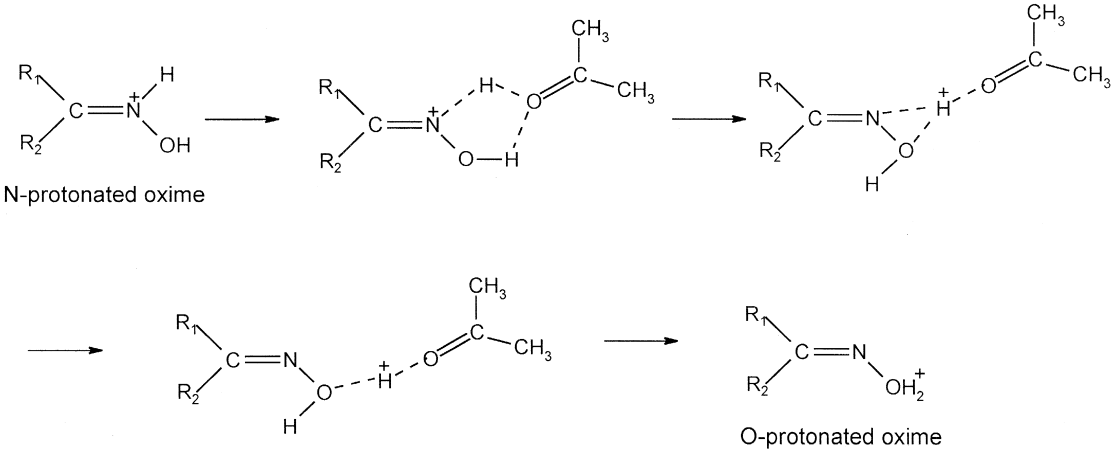
Fig. 5. Competitive adsorption of 4-HAP oxime and MEK on H-Beta.

conversion can be attained in the reaction with acetone suggests that another factor affecting the performance of the reaction may exist.

As far as the Beckmann rearrangement mechanism is concerned, it is generally assumed that the reaction involves an initial protonation at the oxygen of an oxime giving an oxonium cation (or *O*-protonated oxime), followed by the migration of an alkyl group plus the departure of a water molecule giving a nitrilium cation. The latter ion is, in turn, hydrolyzed ultimately yielding an amide [11,12,15,16]. Although there are some reports attempting to measure the rate constant and the associated activation energies of the Beckmann rearrangement [17–20], the rate-determining step has not been identified experimentally yet, and the mechanistic aspects of the reaction are yet to be understood. For the purpose of interpretation, the migration plus elimination step, characterized by the migration from C to N of the substituent having an anti-conformation relative to the departing hydroxyl group, has often been assumed to be rate-determining, even though there has been neither kinetic nor spectroscopic supporting evidence.

Recently, Nguyen et al. [21,22] calculated the energy barriers for individual steps and proposed that the most energetically favorable path is as follows: protonation of oxime → *N*-protonated oxime → *O*-protonated oxime → nitrilium cation → amide. It is of particular interest that the 1,2-*H*-shift connecting both *N*-, *O*-protonated isomers has a high activation energy than the following rearrangement and thus constitutes the rate-determining step. They also suggested that the 1,2-*H*-shift represents a typical case of active solvent participation [23].

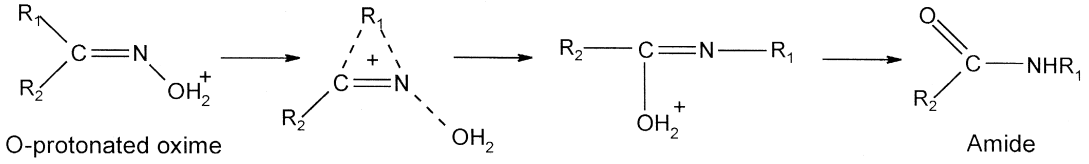
In the presence of a polar solvent, there exists a quite strong five-membered ring complex formed via a direct interaction between the solvent molecule and the *N*-protonated oxime. This complex plays a crucial role permitting a preassociation mechanism in which the reactants are oriented in an optimal manner creating the most favorable spatial conditions for a proton transfer in a rapid and subsequent step. Such a direct action of a solvent molecule to the transition structure is clearly beneficial and reduces the energy barrier dramatically [23]. This implies that the 1,2-*H*-shift, the most energy-demanding step, can be accelerated by involvement of the solvent in the transition state. Thus, the action of a solvent may be regarded as that of a catalyst from energetic point of view.



It should be noticed that the proton affinity of a solvent is an important feature determining the stability of the transition structure. The larger the proton affinity of a solvent, the more stable

the five-membered ring complex. This indicates that the 1,2-*H*-shift, migration of the hydrogen to the solvent molecule at the transition state, is accelerated by a solvent having large proton affinity and thus reduces the energy barrier of the transition state, leading to an increase in the reaction rate. Since the order of proton affinity is closely related to the dielectric constant of a solvent, it is evident that a solvent having a larger dielectric constant or proton affinity promotes the 1,2-*H*-shift.

An environment of polar molecules also facilitates the subsequent rearrangement step. In the transformation of *O*-protonated oxime, the withdrawal of electrons from the nitrogen by OH_2^+ group creates in the $N(\delta^+)-O(\delta^-)$ bond a dipole with its positive end on the nitrogen atom. Because of the configuration of the *O*-protonated oxime, the field of this dipole is so oriented as to include the electrons of the bond R_1-C on the far side of the nitrogen atom within its influence, but hardly those of the bond R_2-C on the near side [12,19,24]. When the molecule already in this state of stress acquires sufficient energy, rearrangement takes place, the group R_1 becoming anchored to the nitrogen atom and OH_2^+ migrating in compensation for the central carbon atom. This emphasizes the importance of the strong electron attraction of the OH_2^+ group, which determines the ease of the rearrangement. As the dielectric constant of a solvent becomes larger, the OH_2^+ group exerts stronger attraction for electrons. The more powerful this attraction, the more facile the change.



In line with these results, one may now speculate that both the strength of adsorption and the dielectric constant of a solvent possibly play central roles in determining the performance of the reaction. While a reactant more readily accesses the active sites in MEK than that in other polar aprotic solvents, the relatively lower dielectric constant of MEK may counterbalance the advantage (see Table 1). This means that the 1,2-*H*-shift of the *N*-protonated oxime may be more difficult in the case of MEK presumably because of the lower ability of MEK to stabilize the transition structure or to reduce the energy barrier of the transition state in comparison with other solvents, which have a larger proton affinity. Moreover, MEK is also less efficient in assisting the migration of OH_2^+ group from nitrogen to carbon atom, and, hence, the promotion of the rearrangement rate by the solvent is smaller.

In contrast to MEK, DMSO can be regarded as the most favorable reaction medium to accelerate not only the 1,2-*H*-shift, but also the subsequent rearrangement among the polar aprotic solvents used. The relatively strong adsorption of DMSO, however, may hinder a reactant from accessing the active sites and suppress the reaction. In this regard, a comparison between acetonitrile and DMSO is of particular interest because the adsorption power of acetonitrile is as good as that of DMSO, but its dielectric constant is lower than that of DMSO as shown in Table 1. The lower catalytic performance of the reaction in acetonitrile suggests that acetonitrile is less efficient than DMSO to promote the 1,2-*H*-shift due to its relatively lower dielectric constant in comparison with DMSO.

When acetone was used as the solvent, the reaction proceeded at its boiling point, which is lower than 70°C and, yet, the conversion turned

out to be higher than those with other polar aprotic solvents at 70°C. This indicates that the two important competitive effects may be in balance in the case of acetone. Acetone is placed in the middle among the representative polar aprotic solvents for both the adsorption power and the dielectric constant. Apparently, the appropriate balancing between the two competitive factors in acetone gives rise to the best performance of the reaction.

In the case of polar protic solvent such as methanol, however, the superiority to polar aprotic solvents in lowering the activation energy and in assisting the migration of OH_2^+ group is no longer meaningful, since the adsorption of a substrate on the active sites is a prerequisite in a heterogeneous reaction. On the basis of these results, it is clear that the facility of protonation of oxime through the adsorption of substrate on the active site depends on the competitive adsorption between substrate and solvent. On the other hand, a solvent having a higher dielectric constant or a more polar nature is preferred in the following two energy-demanding steps in which a solvent may accelerate the reaction by stabilizing transition structure and by promoting the migration of OH_2^+ group, respectively. This leads to the conclusion that the selection of a suitable solvent balancing both the adsorption and the dielectric constant aspects is the most important factor in the liquid-phase Beckmann rearrangement of 4-HAP oxime over zeolite H-Beta.

4. Conclusion

Acetaminophen was first synthesized by an environmentally benign synthetic method; i.e., the liquid-phase Beckmann rearrangement of 4-HAP oxime over zeolite H-Beta. It is revealed that the performance of the reaction is strongly dependent upon the nature of the solvent. Experimental results of co-adsorption of substrate and solvent show that there exists a close relation between the catalytic performance and the adsorption characteristics. Clearly, the stronger the solvent–adsorption sites interaction, the less the chance of the substrate to access the active sites. This suggests that the facility of protonation of oxime is primarily dependent upon the competitive adsorption between substrate and solvent. On the other hand, a solvent having higher dielectric constant or more polar nature is preferred in the following 1,2-*H*-shift and rearrangement steps in which the solvent may accelerate the transformations by stabilizing the transition structure and by promoting the migration of OH_2^+ group, respectively. Therefore, the choice of a suitable solvent balancing between the two competitive factors is the most important factor determining the performance of the reaction.

Acknowledgements

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