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Catalytic Activity of Proton Sponge: Application to Knoevenagel Condensation Reactions

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The catalytic activity of proton sponge 1,8-bisdimethylamino naphthalene (DMAN) ($pK_a = 12.1$), tested with Knoevenagel condensation between benzaldehyde and activated methylenic group compounds, was investigated. When the reaction is performed with ethyl acetoacetate ($pK_a = 10.3$), the proton sponge stabilizes the protonated form during the abstraction of the proton of the methylenic group. The stability of the protonated form is so high that the desorption step, the return of the proton to the condensed product, becomes the controlling step of the reaction and results in the "poisoning" of the catalyst. It is shown that, in this case, the solvent used plays a determining role in the reaction. Indeed, dimethylsulfoxide (DMSO) can stabilize the open form of the protonated amine due to its hydrogen bond acceptor characteristics. When the intermediate bond angle N-H^+-N is slightly modified from the original 180°, the rate of deprotonation strongly increases, and the reaction of ethyl acetoacetate with benzaldehyde can then be carried out. The results are discussed on the basis of quantum chemical calculations.

The effects of the nature of the solvent on the reaction rate and the mechanism of Knoevenagel condensation on the proton sponge were studied in depth by means of the reaction between ethyl cyanoacetate ($pK_a < 9$) and benzaldehyde in solvents of different polarities.

Key Words: **proton sponge**; **Knoevenagel**; **quantum chemical ab initio calculations.**

I. INTRODUCTION

The synthesis of very high surface area mesoporous materials containing a large number of silanol groups that allow the anchoring of amines has made it possible to synthesize heterogeneized base catalysts (1) in which the basicity can be modified by changing the pK_a of the anchored amine. When aliphatic amines are used, the pK_a is limited to values below 11. Aromatic amines have the advantage that they can be functionalized easily. Unfortunately, they are only slightly basic due to the strong resonance interaction between the nitrogen lone-pair and the aromatic ring. However, diamines with neighboring atoms at short distance and aromatic frames such as naphthalene, fluorene, and phenanthrene, for example, (Scheme 1), exhibit unusually high basicity constants and are referred to as proton sponges, the archetype being 1,8-bisdimethylamino naphthalene (DMAN) with $pK_a = 12.1$.

Several detailed investigations (2–4) concluded that steric strain is the main reason for the high basicity constants shown by these molecules. In the case of DMAN, for example, there is no possibility of bringing even one of the dimethyl amino groups into the plane of the rings, resulting in a very low resonance interaction between the nitrogen lone pairs and the aromatic system. The extreme steric hindrance of such systems and the destabilizing effect of the overlap of nitrogen lone pairs of the neutral diamines explain why strong N–H–N hydrogen bonds are formed upon monoprotonation leading to a considerable relaxation of the steric strain (Scheme 2).

The deviation of the naphthalene fragment from planarity is then much less in $DMANH^+$ than in neutral DMAN. The particularly tight hydrogen bond makes the removal of the proton quite difficult and slow (5) and is responsible for the fact that DMAN undergoes only monoprotonation even in the presence of an excess of strong acid.

Moreover, DMAN is a weak proton acceptor when nonionized hydrogen bonds are formed, as has been shown by infrared studies (6).

Several papers deal with DMAN and its derivatives, but they concentrate mainly on NMR (^1H, ^{13}C, ^{14}N, ^{15}N) (7–14), FT-IR (6, 12, 14, 16), XPS (15), XRD (12, 14, 16, 17), and quantum chemical ab initio (18–21) studies in order to determine the structure and properties of these interesting base molecules. Despite the interest in proton sponges as potential base catalysts and the fact that they are widely used for proton abstraction (22), no papers dealing with their application as a catalyst for the preparation of fine chemicals were found. Therefore, we studied, first, the behavior of the 1,8-bisdimethylamino naphthalene as a catalyst for a series of Knoevenagel condensation reactions to form carbon–carbon bonds. We show the dramatic change in the catalytic behavior of this proton sponge depending on the solvent used. The active role played by the solvent in

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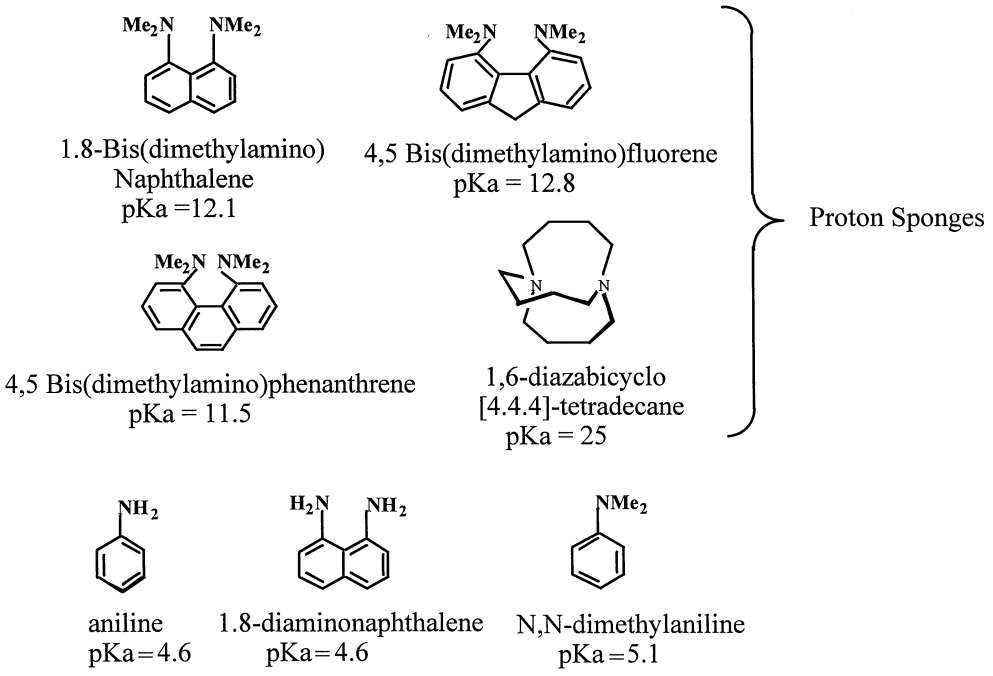


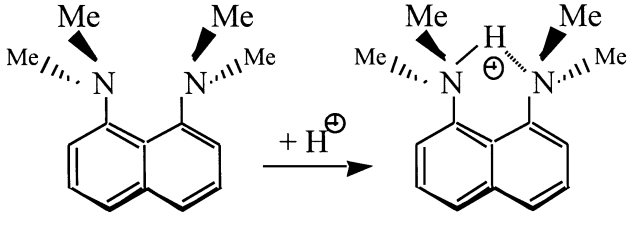
SCHEME 1

the transition state of the reaction is presented. This work shows that these homogeneous base catalysts are promising candidates for heterogeneization.

II. EXPERIMENTAL

General Procedure

Ethyl cyanoacetate (ECA), ethyl acetoacetate, and ethyl malonate were added to 1,8-bisdimethylamino naphthalene (2% with respect to the molar amount of ECA) that had been previously activated overnight under vacuum and stirred in a batch reactor under nitrogen atmosphere, with and without solvent. After temperature adjustment, benzaldehyde (BA) was added in a slightly molar (1.2/1.0) excess, over the solution containing the reactant with the activated methylenic group; the reaction was started. Samples were taken at intervals, and the reaction products were separated by gas chromatography (Fisons, GC 8000 series) using a 30-m capillary column (SPB-5: 5% diphenyl–95% dimethylpolysiloxane) and identified by mass spectroscopy.



SCHEME 2

Reactants, solvents, and DMAN were of reagent grade and purchased from Aldrich.

Quantum Chemical Calculations

Quantum chemical calculations were performed at the DFT level of theory using the B3LYP (23) functional and the 6-31G** (24) standard basis set, except for the study of the stabilisation of $DMANH^+$ by DMSO, in which the 3-21G** basis set (25) at the Hartree–Fock level of theory was used. The geometry optimizations were performed with the Berny (26) algorithm, and Mulliken analysis was used for the charge distributions (27). All the quantum chemical calculations were made with GAUSSIAN94 (28) on an IBM/SP2 computer.

III. RESULTS AND DISCUSSION

In order to check the basicity of DMAN in organic reactions and to compare it with other amines, the condensation of benzaldehyde with molecules containing activated methylenic groups with different pK_a was chosen as a test reaction (Scheme 3). This reaction is a long-standing, mild, and straightforward method for C–C bond formation (29–31) as well as a very convenient reaction test for measuring the basicity of the catalysts (31–33). The reaction proceeds through addition of the carbanionic species resulting from the ionization of the methylene-activated reactant to the carbonyl group, followed by a dehydration step.

However, when primary or secondary amines are used as base catalysts, Knoevenagel condensation is known to

proceed via another mechanism in which the catalyst behaves like a nucleophile, activating the carbonyl function by the formation of the corresponding imine (34).

Depending on the nature of the Z and Z' groups (electroattracting character) proton abstraction is more or less difficult and, therefore, requires a catalyst with a higher or lower basicity. In this case, it is then possible to correlate the basicity of the catalyst with the pK_a of the methylenic group (31). Hence, assuming that the pK_a of 1,8-bisdimethylamino naphthalene is 12.1 (35), deprotonation of methylenic compounds with $pK_a < 12$ should occur when using DMAN as a catalyst. Indeed, condensation of benzaldehyde was not observed with ethyl malonate ($pK_a = 13.3$) but occurred with ethyl cyanoacetate ($pK_a < 9$). However, surprisingly, the reaction did not take place with ethyl acetoacetate ($pK_a = 10.7$) in the range of temperatures in which the reaction was expected to occur.

At room temperature and with only 2% of DMAN as a catalyst, very high conversions were obtained when ethyl cyanoacetate was used as the activated compound (Fig. 1). We compared this basicity with that of compounds with a structure similar to DMAN. Working under the same reaction conditions, we saw that 1,8-diaminonaphthalene ($pK_a = 4.6$), N,N-dimethylaniline ($pK_a = 5.1$), and pyridine ($pK_a = 5.2$) are ineffective catalysts for the condensation of benzaldehyde and ethyl cyanoacetate (Fig. 1). The activity of the bases seems to be related to their pK_a values. As was emphasized by Staab *et al.* (2), our results confirm that the substitution of protons of the 1,8-diaminonaphthalene for methyl groups leads to an exceptionally high basicity of the formed proton sponge, especially considering that the benzaldehyde is activated by the imine formation between the carbonyl group and the primary amine (1,8-diaminonaphthalene). Moreover, using DMAN catalyst instead of N,N-dimethylaniline as a catalyst results not only in the introduction of a second basic site of the same strength, but also to a marked improvement in the basicity due to the stable intramolecular hydrogen bond (Scheme 2).

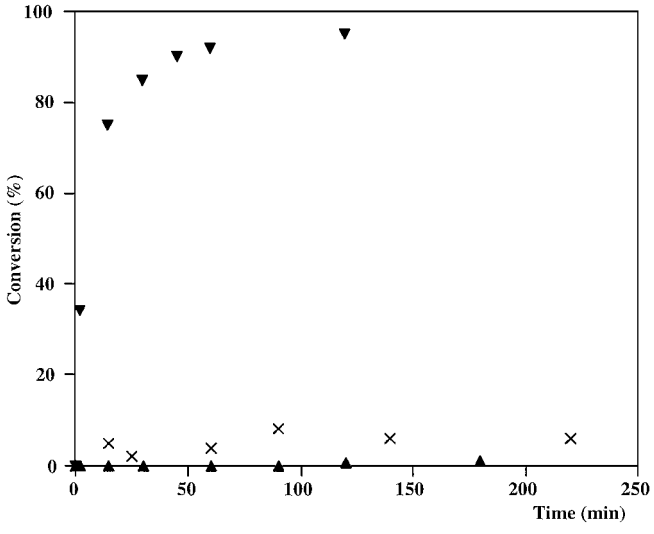
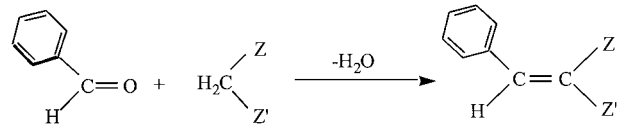


FIG. 1. Condensation of benzaldehyde (8 mmol) and ethyl cyanoacetate (7 mmol) at room temperature using 0.14 mmol of DMAN (▼), 1,8-diaminonaphthalene (▲), and N,N-dimethylaniline (×).



SCHEME 3

The proton affinities of DMAN, ammonia, aniline, pyridine, and 1,8-diaminonaphthalene were calculated at 0 K as the electronic energy differences between the protonated and neutral form. Zero point vibrational corrections were included by calculating the normal vibrational modes of both the neutral and protonated form. We fully optimized the geometry of both the basic and the acidic forms by using DFT and the B3LYP functional with the 6-31G** standard basis set. From the results presented in Table 1, the relative order of basicity is: DMAN > 1,8-diaminonaphthalene > N,N-dimethylaniline ≈ pyridine > aniline > ammonia. To obtain more accurate proton affinities, a better basis set, such as 6-31 + G**, including diffuse functions would be necessary (36). However, the objective of this work is at the semiquantitative level, and, therefore the basis set employed here, 6-31G**, suffices to give reasonable values and to confirm the higher proton affinity of DMAN over the other compounds in Table 1. The results correspond to those expected from a chemical point of view; i.e, ammonia, by not possessing a mechanism to stabilize the cation is the less basic molecule. Stabilization of the protonated form is due to the aromatic ring in the case of pyridine and to a lesser extent in the case of aniline. Stabilization of the N,N-dimethylaniline and DMAN comes from the methyl groups. The results mainly show the extent of stabilization reached by DMAN upon protonation as a consequence of the presence of both the methyl groups and the neighboring N

TABLE 1

Proton Affinities (kcal/mol), Calculated as Differences in Energy in the Neutral and the Protonated Species

Amine	Proton affinities (kcal/mol)
DMAN	258.8
1,8-diaminonaphthalene	233.0
N,N-dimethylaniline	227.3
Pyridine	226.7
Aniline	214.3
Ammonia	208.9

Note. The zero point vibrational energy correction was included in the calculations. The quantum chemical calculations were performed by fully optimizing the geometry of both species at the DFT/B3LYP 6-31G** level.

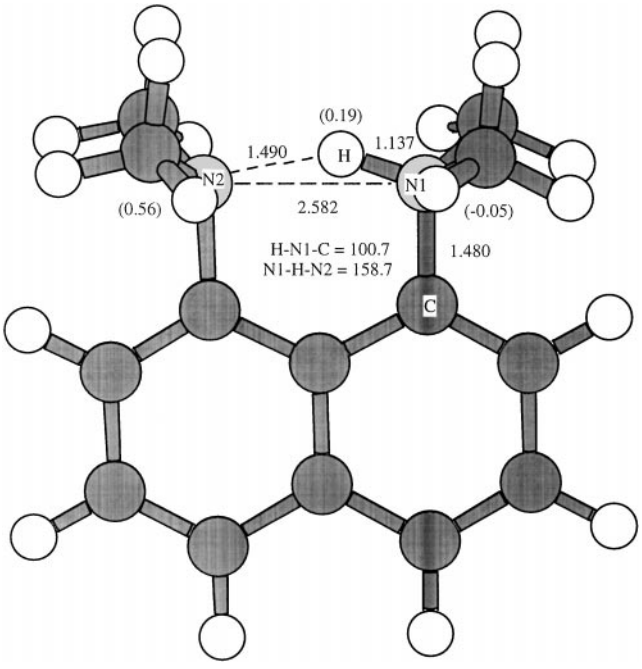
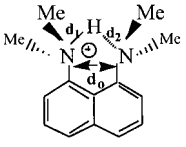


FIG. 2. Optimized geometry of $DMANH^+$ after DFT/B3LYP/6-31G** quantum chemical calculations, showing the more important geometric parameters and the atomic charges of H, N_1,N_2 (in brackets).

atoms. In effect, as previously mentioned, some of the basic properties of this compound are the result of the interaction between the N atoms in the basic and acidic forms. Thus, the basic properties depend partly on the molecular geometry. The relevant geometric parameters derived from the quantum chemical calculation are shown in Fig. 2. A good correlation with previous studies (8, 20) was found, thus also validating our results. The characteristic parameters of proton sponges are shown for previous fits and for our results (Table 2). Again the correlation is good. It can be seen (Fig. 3) how the repulsion of the nitrogen electronic lone pair in the methyl groups is minimized in the neutral compound DMAN, whereas in the protonic form this interaction becomes attractive between the nitrogen lone pair and the proton causing the rotation around the CN bonds. It is also clear from the geometry of $DMANH^+$ that the proton is stabilized by its interaction with the neighboring N atom (the N2–H distance is 1.49 Å). The charge distributions, in particular over the protonic hydrogen, confirm the acidic strength of the $DMANH^+$. The removal of this proton, in order to regenerate the catalyst, is quite easy in the reaction with ethyl cyanoacetate. Thus, the effect of the protonation of the DMAN is considered to be similar to poisoning of the catalyst by the formation of a strong intramolecular hydrogen bond when ethyl acetoacetate is used. In this case, the adduct resulting from the condensation between benzaldehyde and the activated methylene is not basic enough to draw the proton from the $DMANH^+$ in order to form the Knoevenagel product. Therefore, as reported by Alder *et al.* (37), the low proton transfer rates of these molecules make them ineffective bases for carbon deprotonation or E_2 reactions. However, comparison of measurements carried out in H_2O and DMSO–H_2O mixtures (38) shows that the proton transfer from protonated proton sponges to hydroxide ions

TABLE 2

Comparison of the Characteristic Parameters of Previous Fits and Our Results which Correspond to a Quantum Chemical Full Geometry Optimization at the DFT/B3LYP Level by Using the 6-31G Standard Basis Set**

	 (14)	$\alpha = \widehat{NHN}$ our results
$d_1 + d_2$	2.66	2.62
d_0	2.582	2.582
α	154.2	158.71

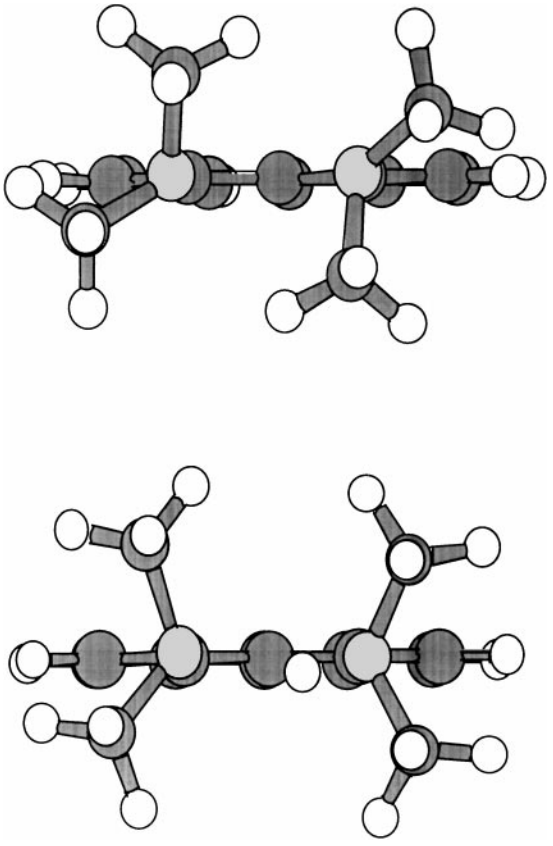


FIG. 3. View of the relative orientation of the methyl groups DMAN (top view) and the $DMANH^+$ (bottom view) as optimized by quantum chemical calculations DFT/B3LYP/6-31G**.

is enhanced in the latter media owing to a weakening of the intramolecular hydrogen bond in the protonated amine.

Solvent Effect on Catalytic Activity

Solvents such as DMSO are known to behave like ligands and can, for example, be easily coordinated to metals such as Pd, Pt (39), or Re (40). The so-formed S-bonded or O-bonded complexes have different properties. Thus, in the case of DMAN one can conceive that the hydrogen bond acceptor power of DMSO will intervene by stabilizing the open form of the protonated amine and increasing the rate of proton transfer.

These kinds of interactions can, nevertheless, be used to facilitate proton release from the $DMANH^+$ when DMSO is used as a solvent. In such a case, the hydrogen acceptor characteristics of this solvent could destabilize the proton in $DMANH^+$, thus making proton release easier and improving the catalytic activity. We have, therefore, modeled the interaction of one molecule of DMSO and the protonated proton sponge by full optimization of all the variables at the Hartree–Fock/3-21G** level (Fig. 4). A relatively large O–H equilibrium distance (2.569 Å) is found due to the steric hindrance presented by the methyl groups in $DMANH^+$ which do not allow the DMSO molecule to adsorb more strongly. In spite of this, the geometric parameters (Fig. 4) show how the proton is destabilized with respect to the isolated $DMANH^+$, as shown by a larger N1–H distance and a shorter N2–H distance. In addition, the larger charge in the proton points to the same effect of stabilizing the "open form" of the protonated sponge.

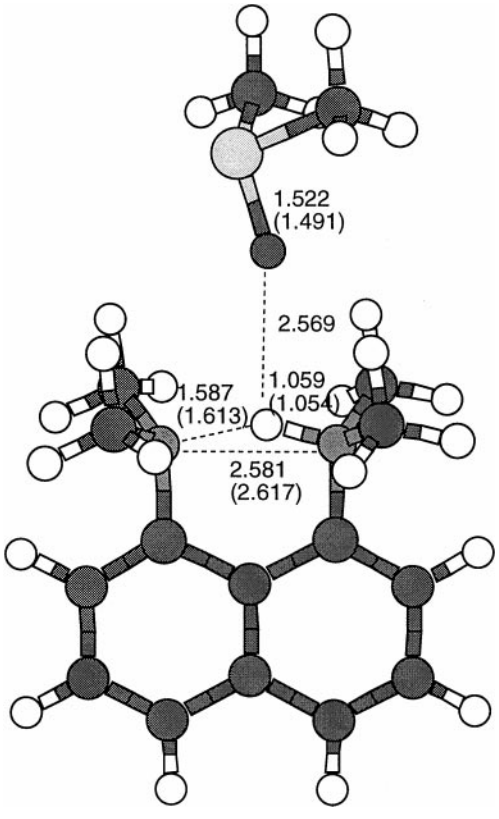


FIG. 4. Geometry of the adsorbed DMSO over $DMANH^+$ as obtained by HF/3-21G** calculations. The numbers in brackets correspond to the isolated $DMANH^+$. It can be seen that interaction with DMSO causes destabilization of the proton. This is also shown by the proton charges which are 0.436 in the isolated $DMANH^+$ and 0.473 a.u. upon interaction with the solvent, DMSO.

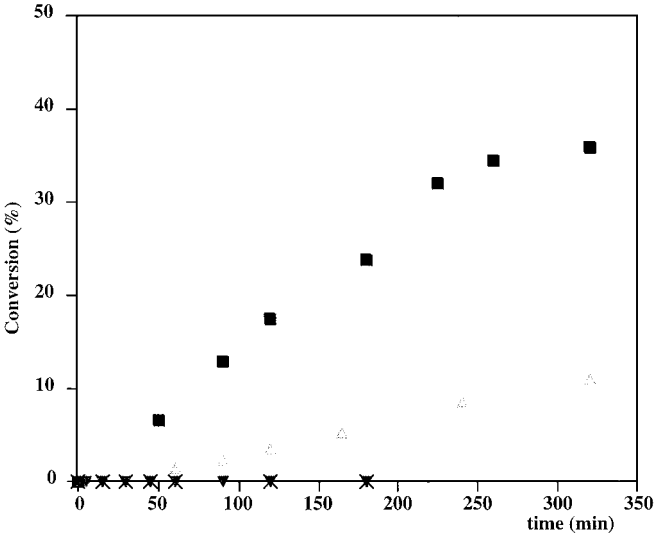
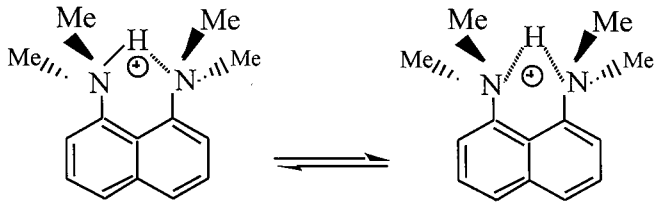


FIG. 5. Condensation of benzaldehyde (8 mmol) and ethyl acetoacetate (7 mmol) at 80°C, catalyzed with DMAN (0.14 mmol) in 5 ml of DMSO (■), DMF (△), and CH_3CN (▼), without solvent (×).

We calculated the strain energy of the DMAN as the energy difference between the DMAN and the geometry when interacting with DMSO minus the energy of the DMAN molecule in its equilibrium geometry. The HF/3-21G** energy difference is 4.04 kcal, indicating the destabilizing effect of the DMSO which activates the DMAN to its open form. It can be seen in Fig. 4 how, in spite of stabilization due to the shorter N2–H distance, destabilization of the N1–H stronger bond dominates; the resulting effect is the higher energy of the open form.

In order to benefit from this solvent effect, reactions between benzaldehyde and ethyl acetoacetate were carried out in DMSO and the results compared with those obtained from reactions in DMF and in CH_3CN. Figure 5 shows the enhancement of DMAN activity at 80°C when using DMSO as the solvent.

As pointed out above, even though the solvent takes no part in the reaction itself, it can play a role in accelerating the overall reaction via an O–H interaction similar to that observed in the adsorption of DMSO over $DMANH^+$. This causes the $DMANH^+$ to become more acidic and increases the rate of proton transfer (41), the controlling step in the condensation reaction involving ethyl acetoacetate.



SCHEME 4

Moreover, it is clear from the nature of the interaction described that, being essentially ionic in nature, it will depend on the charge distributions of the solvent molecules. To test such an effect we compared the charge distributions of two of the solvents used in the study, DMSO and DMF. A more negative density of charge on the oxygen is observed in the case of DMSO (−0.65) with respect to DMF (−0.48). Therefore, the capacity of DMSO to interact with the proton of $DMANH^+$ is greater than that of DMF, which explains the observed increase in the reaction rate. Thus, DMSO would favor the displacement of equilibrium (38) toward the nonbonded hydrogenated form (Scheme 4). In the proton removal process, the intramolecular hydrogen bond must be broken (38) in the transition state, and the open form is deprotonated more easily, allowing the catalyst to be regenerated.

Solvent Effect on the Rate Reaction

Besides the advantage of using the solvent presented above, there is no doubt that changes in the polarity of the media can strongly affect the rate of the reactions involving charged species. Moreover, when the electrostatic field is the only major parameter, it is possible to correlate the effect of the solvent on the kinetic rate constant with the dielectric constant of the solvent (ε_r) by means of Kirkwood's equation,

$$\lg k_{\text{exp}} = A - B\frac{\varepsilon_r - 1}{2\varepsilon_r + 1}, \qquad [1]$$

where k_{exp} is the kinetic rate constant, and A and B are constant parameters and a function of temperature (42).

We examined the influence of several solvents on the reaction between benzaldehyde and ethyl cyanoacetate and focused the study on their polarity. Figure 6 shows the yield of the condensed product versus reaction time. The highest yields are obtained with more polar solvents such as EtOH ($\varepsilon = 24.3$), DMSO ($\varepsilon = 48.9$), DMF ($\varepsilon = 36.7$), and a slightly lower yield with CH_3CN ($\varepsilon = 37.5$). However, in nonpolar solvents such as chlorobenzene ($\varepsilon = 5.6$) and toluene ($\varepsilon = 2.4$), a dramatic decrease in the reaction rate occurs. As shown above, in the case of the reaction between benzaldehyde and ethyl cyanoacetate, 1,8-bisdimethylamino naphthalene acts as an efficient catalyst in the absence of solvent; i.e., the adduct formed is basic enough to undergo the proton removal from the $DMANH^+$. Therefore, the behavior observed with these reactants in the presence of solvents is related to their influence on the reaction mechanism and not to a modification of the capacity of the catalyst for proton transfer. These results are consistent with similar observations using heterogeneous catalysts to catalyze Knoevenagel reactions (43, 44). For dipolar aprotic solvents, this phenomenon is believed to be linked to their high dielectric constant and their dissociating power ($\varepsilon > 15$) (42b), favoring the charge separation during the process (45) that is connected to their low capacity to solvate anions. Therefore, as was observed for ethyl cyanoacetate activation (42b) and for SN_2 substitution in DMSO (46, 47), anion reactivity is enhanced. Moreover, the reaction rate increases with the dielectric constant value of all the aprotic solvents used. However, in spite of a lower dielectric constant, it was shown for EtOH (44) that the amphiprotic properties of this solvent, as demonstrated by its acidic and basic behavior, enhance the reaction rate. Indeed, in addition to the activation of ethyl cyanoacetate and benzaldehyde, due to their relative basic strength, ethanol may induce electrophilic polarization of the carbonyl group of benzaldehyde, related to its moderated acid character, enabling the uncatalyzed reaction to take place. Ethanol is the classical solvent used for Knoevenagel condensations in the homogeneous phase (34).

When polar reactants (like in the Knoevenagel condensation) are involved, the effects of solvation can be described by means of the transition state theory, considering the effects of the solvent on the activity coefficients of the different species. The explanation of the results obtained can be

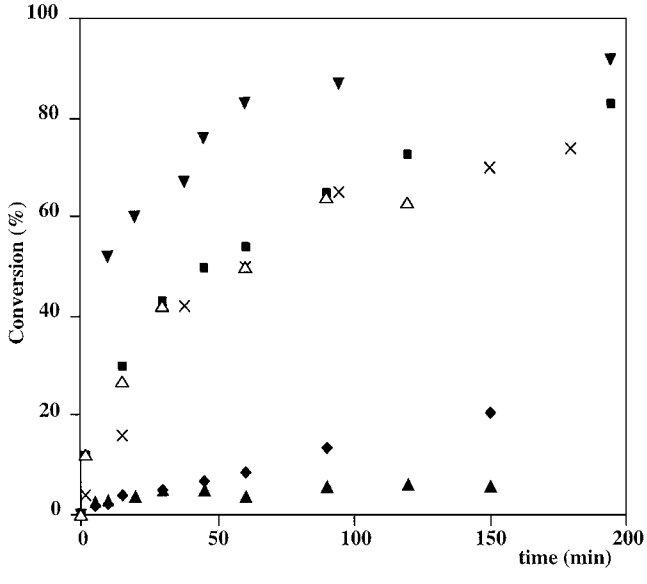


FIG. 6. Condensation of benzaldehyde (8 mmol) and ethyl cyanoacetate (7 mmol) at room temperature with DMAN (0.14 mmol) in EtOH (▼), DMSO (■), DMF (△), CH_3CN (×), chlorobenzene (◆), and toluene (▲).

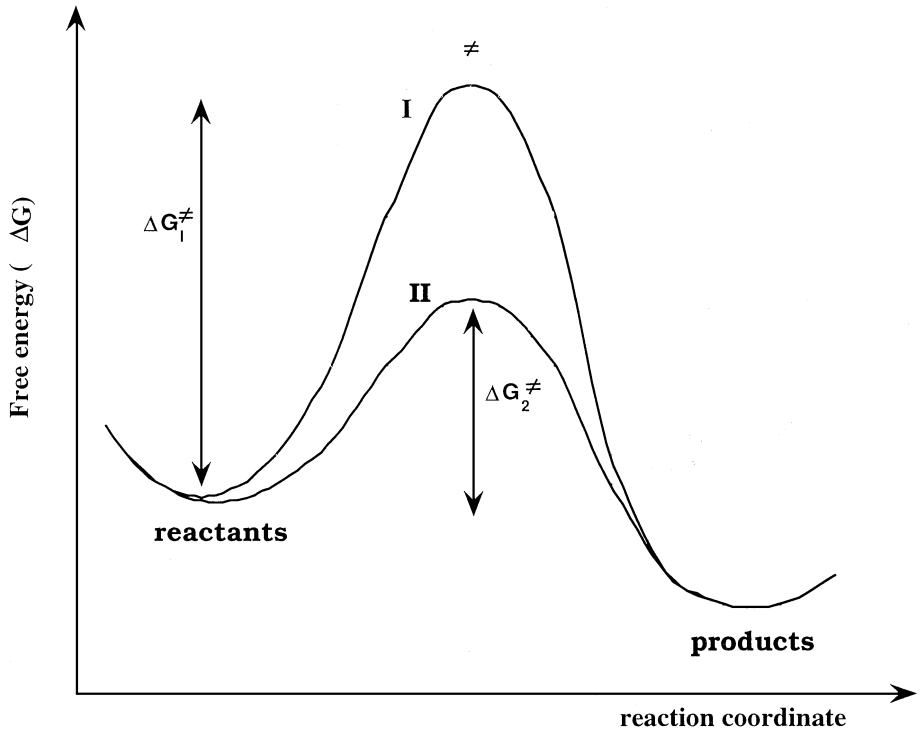


FIG. 7. Theoretical free enthalpy variation as a function of the reaction coordinate: (**I**) without solvation of the reactant or the activated complex; (**II**) with solvation of the transition state by the polar solvent.

attempted on the basis of activation energy of the solvated transition states. To illustrate this concept, the theoretical curve I in Fig. 7 describes the free enthalpy variation profile for a reaction without solvation of the reactant or of the activated complex. If the reaction is performed with a polar solvent, the transition state complex should be solvated, decreasing the activation free enthalpy and so enhancing the reaction rate (Fig. 7, curve II). If this is so, the activation energy of the Knoevenagel reaction in polar solvents (DMSO, DMF, EtOH) should be lower than when the reaction occurs in apolar solvents (chlorobenzene, toluene). Therefore, experiments were carried out in chlorobenzene, DMSO, and without solvent and the activation energies obtained. The following kinetic equation was used:

$$r = k_{\text{exp}}[\text{ECA}]^{\alpha}[\text{BA}]^{\beta} \qquad \text{with } k_{\text{exp}} = k[\text{DMAN}]^{\gamma}. \quad [2]$$

Experiments and previous studies (28, 30) have shown that the reaction is first order with respect to the reactants, i.e, $\alpha = \beta = \gamma = 1$. Then,

$$r = k_{\text{exp}}[\text{ECA}][\text{BA}] \qquad \text{with } k_{\text{exp}} = k[\text{DMAN}]. \quad [3]$$

Thus, varying the concentration of the reactants, and following the changes of conversion with time at different temperatures, the kinetic rate constants and activation energies can be obtained (Table 3).

The low activation energy values, obtained for the condensation catalyzed by DMAN, indicate the ease with which this reaction takes place.

It can be seen that Ea (DMSO) < Ea (chlorobenzene) agrees with a stabilization of the transition state by polar solvents.

DMAN allows the condensation reaction to be carried out by proton abstraction from ethyl cyanoacetate, which is certainly favored by polar solvents. This assumption is supported by the results obtained when N,N-dimethylaniline ($pK_a = 5.6$) is used as a catalyst. The basic strength of this tertiary amine with a structure similar to that of DMAN is insufficient to undergo the reaction, even when DMSO is used as a solvent.

The rate law (Eq. [3]) gives the transition state composition corresponding to the rate-controlling step. However,

TABLE 3

Activation Energy and Rate Constant for Knoevenagel Condensation between Benzaldehyde and Ethylcyanoacetate as a Function of the Nature of the Solvent

Solvent	Ea (kcal/mol)	k (min^{-1}) at RT
DMSO	5	1.47
Chlorobenzene	8.5	0.05
Without	7–7.3	0.68

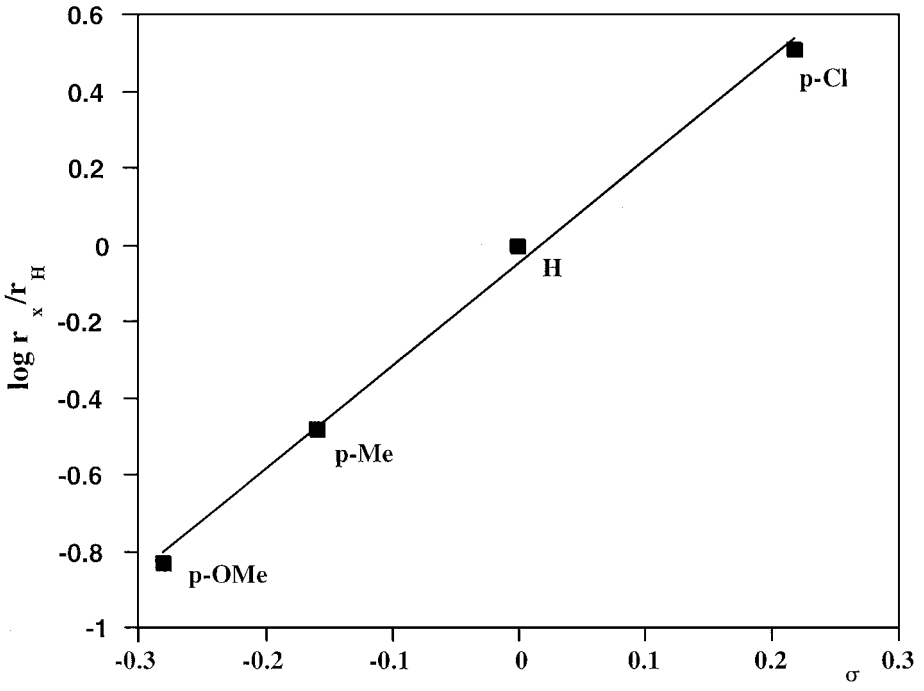
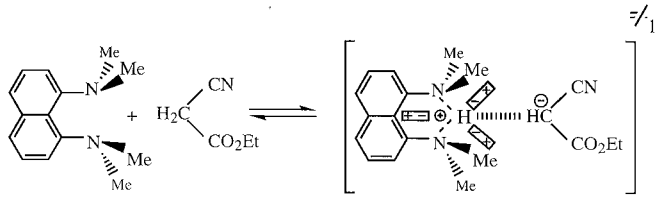


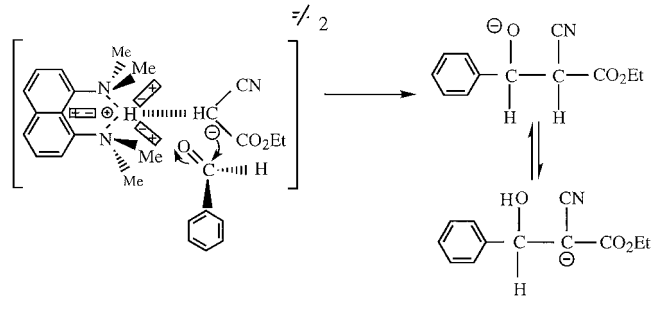
FIG. 8. Hammett correlation for the reaction between ethyl cyanoacetate and para-substituted benzaldehyde *X*-ΦCHO (*X* = *p*-Cl, H, *p*-Me, *p*-OMe) at room temperature.

of all the steps in the Knoevenagel reaction (ionization of the methylene-activated reactant, addition of the so-formed carbanion to the carbonyl group, and dehydration), only the addition step agrees with Eq. [3], because the dehydration step is rarely assumed to be rate-determining (34). In order to specify the nature of this transition state, the $\sigma\rho$ Hammett relationship was examined through the condensation reaction of ethyl cyanoacetate and para-substituted benzaldehydes (*p*-OMe ($\sigma = -0.28$), *p*-Me ($\sigma = -0.16$) and *p*-Cl ($\sigma = 0.2$)) in DMSO with 2% DMAN as the catalyst at room temperature. Figure 8 shows the plot of $\log(r_x/r_H)$ versus σ values. The slope of the linear correlation leads to a reaction constant ρ equal to 2.7. This positive value indicates that electron-withdrawing substituents favor the reaction by drawing electron density from the carbon atom (48). The high value of ρ compared with that obtained ($\rho = 1.45$) with piperidine as the catalyst in EtOH (49) indicates a stronger influence of the nature of the para-substituents, probably due to the different mechanism involved when secondary amines are used as catalysts. Indeed, the imines formed in this case are more reactive than the corresponding benzaldehydes. Moreover, electrophilic polarization induced by the solvent EtOH may favor this reaction and may result in a decrease in the ρ parameter value.

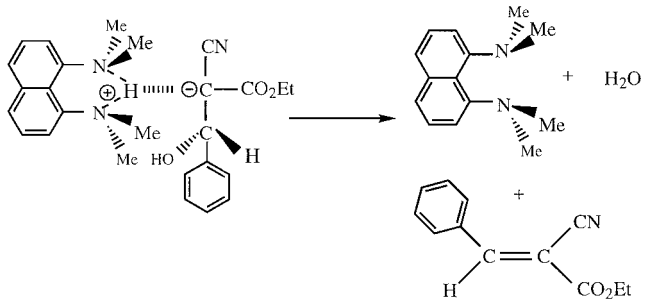
The observed reactivity pattern can be explained by the reaction shown in Schemes 5–7. In a first step, the rapid abstraction of a proton from ECA leads to an intermediate stabilized by solvent molecules represented as a dipole ($\boxed{+-}$) in Scheme 5. The formed anion, the reactivity of which was enhanced, attacks the carbonyl group of the benzaldehyde giving the transition state of the reaction (Scheme 6). In the last step, the abstraction of the proton from $DMANH^+$ by the adduct formed between ethyl cyanoacetate and benzaldehyde gives the olefin product after removing the water while the catalyst is regenerated (Scheme 7).



SCHEME 5



SCHEME 6



SCHEME 7

A different Knoevenagel mechanism is involved when primary amines are used as the catalyst. This is found when the reaction rates of the condensation with 1,8-diaminonaphthalene, performed with and without solvent, are compared (Fig. 9). While there is no reaction without solvent, the condensation between BA and ECA occurs when it is carried out in DMSO, in spite of the low pK_a of 1,8-diaminonaphthalene ($pK_a = 4.6$). As mentioned above, the mechanism in this case involves an imine intermediate formed between benzaldehyde and 1,8-diaminonaphthalene (Scheme 8). This intermediate has a more basic character than the amine. A solvent such as DMSO would be an advantage for N–H bond polarization during imine formation by favoring the reaction, as was suggested by Laspéras *et al.* (50).

IV. CONCLUSIONS

When ethyl acetoacetate is used as a reactant the proton sponge can abstract the proton from the activated methyl-

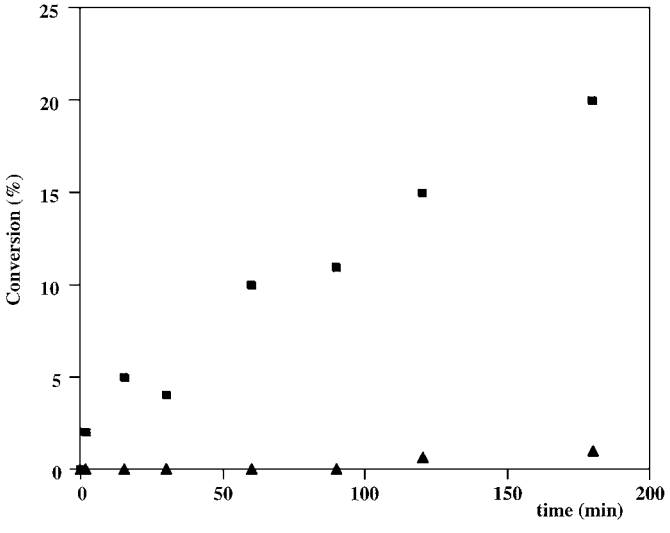
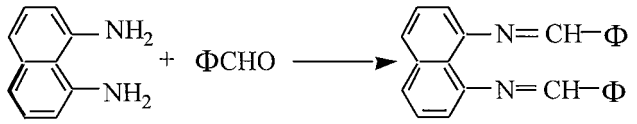


FIG. 9. Condensation between benzaldehyde (8 mmol) and ethyl cyanoacetate (7 mmol) at room temperature with 1,8-diaminonaphthalene (0.14 mmol): without solvent (▲) and in DMSO (■).



SCHEME 8

enic group. However, the protonated DMAN is so stable that the proton is not returned, and the catalyst becomes inactive. The presence of a solvent such as DMSO polarizes the -N-H^+-N- bond, weakening the intramolecular hydrogen bond of the protonated amine, and modifying the activity of DMAN. If the active methylene component is substituted for a more acidic reactant as ethyl cyanoacetate, the adduct formed with benzaldehyde can give back the proton from $DMANH^+$ to form the olefinic product. This study has shown that DMAN undergoes proton abstraction from ECA during a reaction favored by polar solvents.

In conclusion, this work showed the optimum conditions for using such an amine as a basic catalyst. It may be an advantage to anchor this or other proton sponges (with pK_a up to 25) onto solid supports.

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