The DMAP-Catalyzed Acetylation of Alcohols—A Mechanistic Study (DMAP = 4-(Dimethylamino)pyridine)

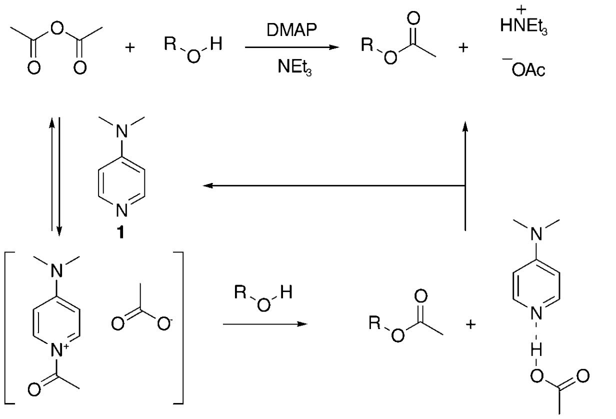
Shangjie Xu, Ingmar Held, Bernhard Kempf, Herbert Mayr, Wolfgang Steglich, and Hendrik Zipse*[a]

Abstract: The acetylation of *tert*-butanol with acetic anhydride catalyzed by 4-(dimethylamino)pyridine (DMAP) has been studied at the Becke3LYP/6-311+G(d,p)//Becke3LYP/6-31G(d) level of theory. Solvent effects have been estimated through single-point calculations with the PCM/UAHF solvation model. The energetically most favorable pathway proceeds through nucleophilic attack of DMAP at the anhydride carbonyl group and subsequent formation of the corresponding acetylpyridinium/acetate ion pair. Reaction of this ion pair with the alcohol substrate yields the final product, *tert*-butylacetate. The competing base-catalyzed reaction pathway can either proceed in a concerted or in a stepwise manner. In both cases the reaction barrier far exceeds that of the nucleophilic catalysis mechanism. The reaction mechanism has also been studied experimentally in dichloromethane through analysis of the reaction kinetics for the acetylation of cyclohexanol with acetic anhydride, in the presence of DMAP as catalyst and triethylamine as the auxiliary base. The reaction is found to be first-order with respect to acetic anhydride, cyclohexanol, and DMAP, and zero-order with respect to triethyl amine. Both the theoretical as well as the experimental studies strongly support the nucleophilic catalysis pathway.

Keywords: acylation • density functional calculations • dimethylaminopyridine • kinetics • nucleophilic catalysis

Introduction

4-(Dimethylamino)pyridine (DMAP, **1**) is a catalyst of outstanding utility in a variety of group-transfer reactions, such as the acylation of alcohols and amines.[1–5] Despite the frequent use of DMAP itself and the recent development of chiral DMAP derivatives for applications in stereoselective catalysis,[6–13] the mechanisms of even the most simple DMAP-catalyzed reactions, such as the acetylation of alcohols with acetic anhydride, have not yet been studied in detail. A recent review of the mechanistic characteristics of this reaction highlighted the importance of the deprotonation step as well as the influence of the auxiliary base on the catalytic activity of DMAP.[3f] The currently accepted mechanism for acylation reactions of alcohols involves the pre-equilibrium formation of an acylpyridinium cation through reaction of DMAP with the acyl donor (Scheme 1). The alcohol then reacts with the acylated catalyst in the rate-determining second step to form the ester product together with the deactivated (protonated) catalyst. Regeneration of the latter requires an auxiliary base such as triethylamine. An alternative mechanism, the deprotonation of the alcohol by DMAP and subsequent attack of the alkoxide at the acyl



Scheme 1.

[a] Dr. S. Xu, Dipl.-Chem. I. Held, Dr. B. Kempf, Prof. H. Mayr, Prof. Dr. W. Steglich, Prof. Dr. H. Zipse
Department Chemie und Biochemie, LMU München
Butenandtstrasse 5–13, 81377 München (Germany)
Fax: (+49) 89-2180-77738
E-mail: zipse@cup.uni-muenchen.de

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

 DOI: 10.1002/chem.200500398

donor, has been ruled out because of the lack of correlation between the catalytic reactivity and the pK_a of amines.[3a,5]

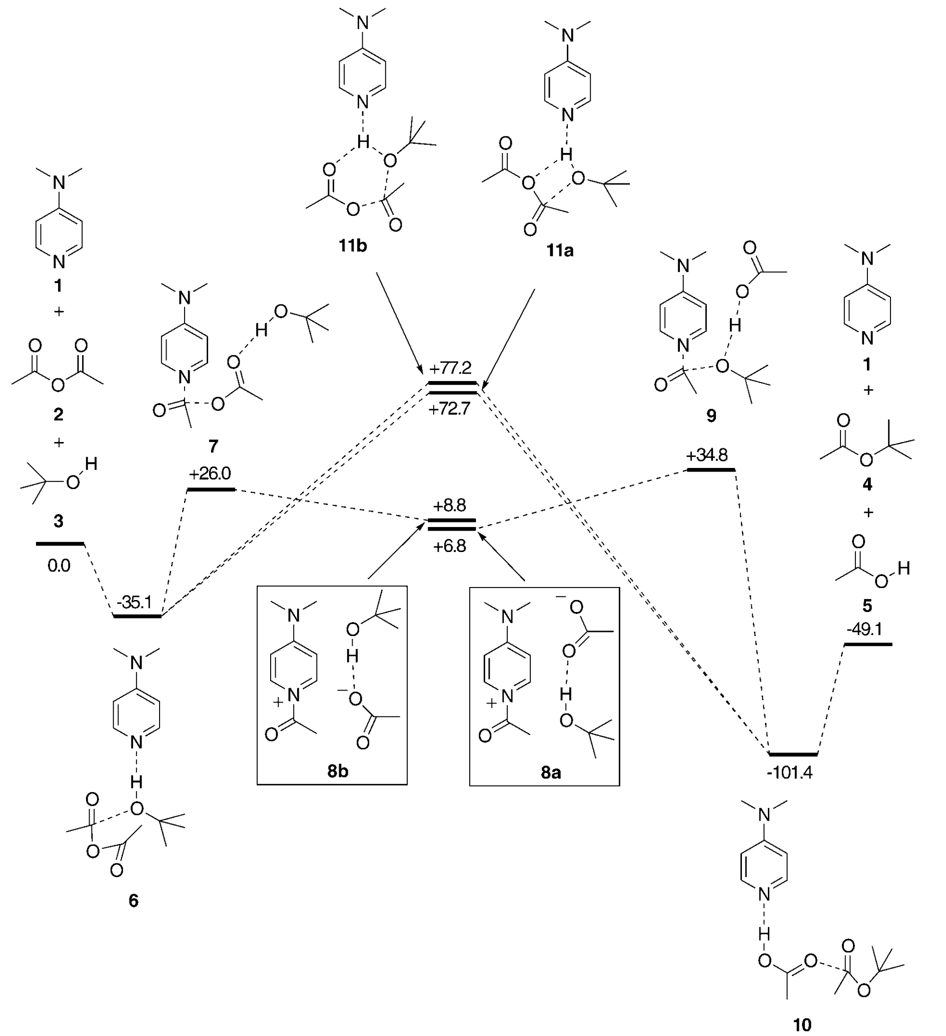
One of the open questions in this nucleophilic catalysis mechanism concerns the base required to deprotonate the alcohol in the rate-determining step. Possible options include the acetate counterion, the auxiliary base triethylamine, and the catalytic base DMAP. The involvement of the acetate counterion has been suggested, based on the low reactivity of acyl pyridinium salts containing less basic anions (chloride, tosylate, and tetrafluoroborate).[14–16]

To shed light on the mechanism of this acylation reaction, we have now studied the reaction mechanism of acetic anhydride with *tert*-butanol in the presence of DMAP with theoretical methods. In how far the model system chosen for theoretical study is representative for the situation under experimental conditions has subsequently been verified through determination of the reaction order for all reactants.

Results and Discussion

All stationary points have been optimized at the B3LYP/6-31G(d) level of theory and relative enthalpies have been obtained at the B3LYP/6-311+G-(d,p)//B3LYP/6-31G(d) level.

The DMAP-catalyzed reaction of acetic anhydride and *tert*-butanol is initiated through formation of a ternary complex **6** of all three components, which is common to both the nucleophilic and the general base catalysis pathway (Scheme 2, Table 1). Along the former pathway the pyridine-ring nitrogen atom reacts with acetic anhydride **2** in a concerted acyl-transfer mechanism without the intermediacy of a tetrahedral intermediate.[17–21] Expulsion of the acetate leaving group is facilitated at this stage through formation of a hydrogen bond to the hydroxy group of alcohol **3** (Figure 1). Passing through transition state **7**, the system arrives at intermediate **8b**, which can best be described as a loose complex of the acetylpyridinium cation of DMAP and a complex between acetate and *tert*-butanol.[22] Reorientation of the two components of this complex yields intermediate **8a**, in which the alcohol is now poised to attack the acetylpyridinium cation. The reactivity of the alcohol is enhanced through hydrogen bonding to the acetate counterion in this second step of the reaction. Transition state **9** thus witnesses the concerted cleavage and formation of overall four bonds: the C–N bond connecting the acetyl and the pyridine moiety in **8a**, the C–O ester bond in ester **4**, the O–H bond in alcohol **3**, and the O–H bond in acetic acid (**5**) (Figure 1). Transition state **9** is located $+69.9\,\mathrm{kJ\,mol^{-1}}$ above the reactant complex **6** and $+8.8\,\mathrm{kJ\,mol^{-1}}$ above transition state **7**. This is in agreement with the assumption of rate-limiting acyl transfer to the alcohol as described in Scheme 1. The surprisingly exothermic formation of product complex **10** derives from a strong hydrogen bond between DMAP and acetic acid **5**. Cleavage of this complex to yield the separate components **1**, **4**, and **5** is therefore endothermic by approximately $52\,\mathrm{kJ\,mol^{-1}}$. The most favorable variant of the competing general base catalysis mechanism leads in one single step from reactant complex **6** to product complex **10**. The most favorable transition



Scheme 2. Gas-phase enthalpy profile (ΔH_{298}) for the competing nucleophilic and base catalysis mechanisms in the DMAP-catalyzed reaction of acetic anhydride with *tert*-butanol as calculated at the B3LYP/6-311+G-(d,p)//B3LYP/6-31G(d) level of theory.

Table 1. Relative enthalpies [in kJ mol^{-1}] for stationary points located on the potential-energy surface of DMAP (**1**)+acetic anhydride (**2**)+*tert*-butanol (**3**). Solvent effects have been estimated through PCM/UAHF/Becke3LYP/6-31G(d) single-point calculations.

	H_{298}(gas)[a]	H_{298}(CCl_4)[a]	H_{298}($CHCl_3$)[a]	H_{298}(CH_2Cl_2)[a]
nucleophilic catalysis				
1+2+3	0.0	0.0	0.0	0.0
6	-35.1	+2.7	+7.8	+13.3
7	+26.0	+52.2	+51.3	+54.0
8a	+8.03	+32.7	+32.0	+34.6
8b	+6.84	+36.8	+36.5	+39.0
9	+34.8	+55.1	+57.1	+60.9
10	−101.4	−66.4	−61.0	−56.1
1+4+5	−49.1	−47.4	−46.5	−45.9
base catalysis (concerted)				
1+2+3	0.0	0.0	0.0	0.0
6	-35.1	+2.7	+7.8	+13.3
11a	+72.7	+91.7	+93.5	+97.0
11b	+77.2	+95.6	+96.3	+99.1
10	−101.4	−66.4	−61.0	−56.1
1+4+5	−49.1	−47.4	−46.5	−45.9
base catalysis (stepwise)				
1+2+3	0.0	0.0	0.0	0.0
6	-35.1	+2.7	+7.8	+13.3
16	+120.5	+150.8	+152.9	+157.3
15	+113.2	+143.6	+145.5	+149.8
14	+154.7	+169.0	+166.9	+168.7
13	−11.3	+5.2	+20.4	+25.3
12	+4.4	+23.5	+26.0	+29.5
10	−101.4	−66.4	−61.0	−56.1
1+4+5	−49.1	−47.4	−46.5	−45.9

[a] B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level.

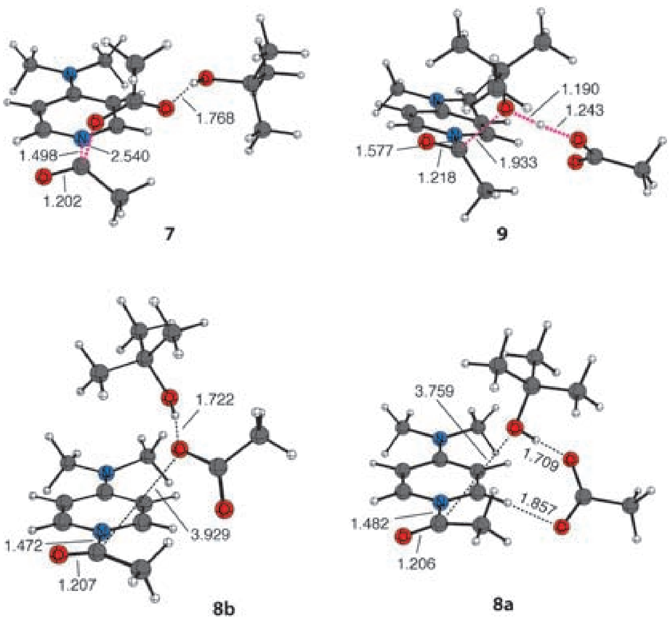
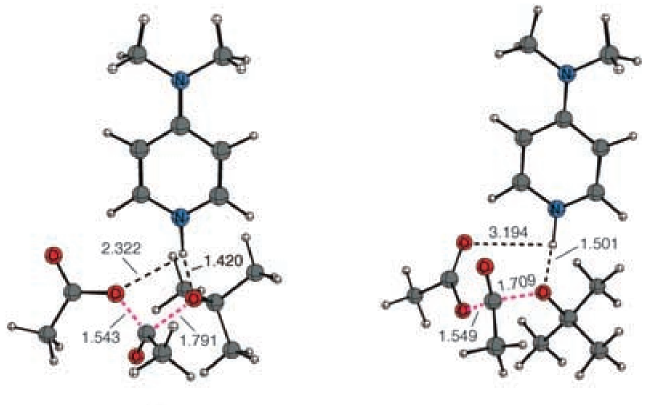


Figure 1. Structures of transition states **7** and **9** located along the nucleophilic catalysis reaction pathway together with the corresponding zwitterionic complexes **8a** and **8b** as calculated at the Becke3LYP/6-31G(d) level of theory.

state for this step (**11a**) is located +107.9 kJ mol^{-1} above reactant complex **6** and thus +37.9 kJ mol^{-1} above transition state **9**. The base-catalyzed pathway can also proceed through a six-membered-ring transition state **11b**, which is 4.5 kJ mol^{-1} less favorable than the four-membered-ring transition state **11a**. As highlighted in Figure 2 the terms

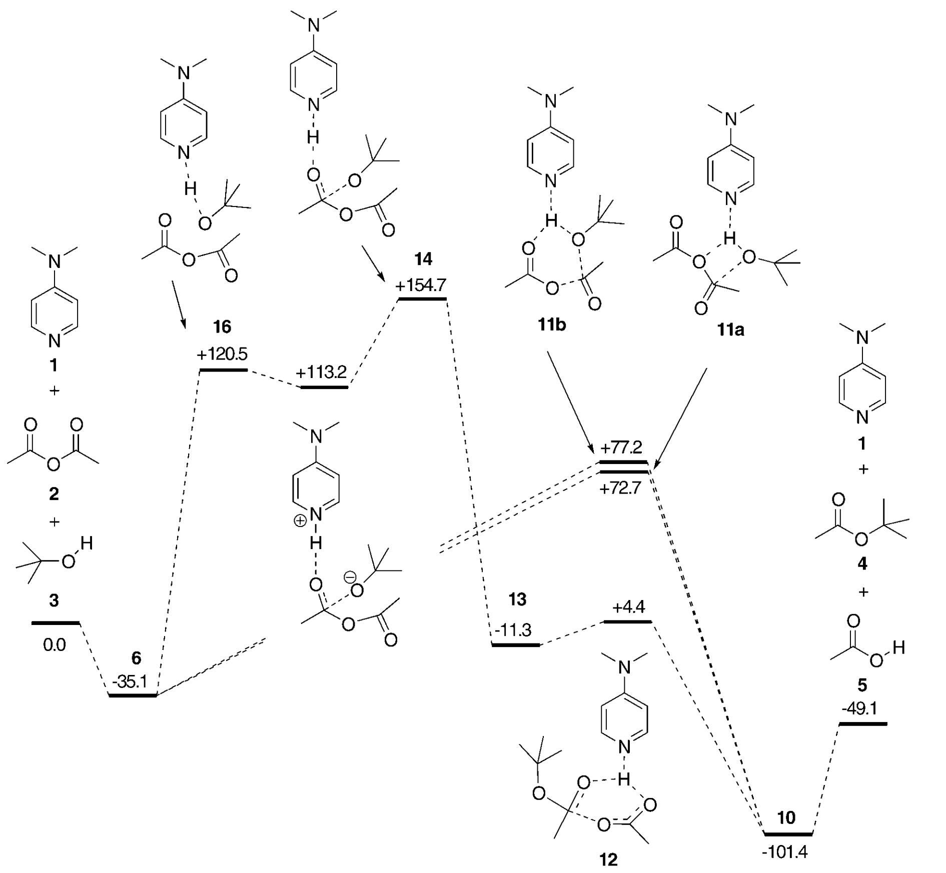


11a **11b**

Figure 2. Structures of transition states **11a** and **11b** located along the base catalysis reaction pathway as calculated at the Becke3LYP/6-31G(d) level of theory.

"four-membered" and "six-membered" describe the overall changes in bonding between the reacting centers. However, the distances included in Figure 2 show that the reactions are far from synchronous, the deprotonation of *tert*-butanol being far advanced, while protonation of acetate is still in a very early stage. The very unfavorable energies of the transition states **11a** and **11b** clearly rule out any participation of the base-catalyzed pathway at typical reaction temperatures. The base-catalyzed pathway can also proceed in a stepwise fashion, involving full deprotonation of the alcohol as the first (and energetically also most demanding) step (Scheme 3). The barrier for this deprotonation step as well as its subsequent addition to the C−O double bond of acetic anhydride is, however, even less favorable than that of the concerted base-catalyzed pathway.

The presence of partially or fully charge-separated zwitterionic intermediates described in Schemes 2 and 3 suggests that solvent effects may potentially have a large influence on the energetics of these reactions, polar solvents possibly leading to lower reaction barriers. Experimentally observed solvent effects indicate, however, that the oppopsite is true.[3a,5] A larger series of solvents has been tested by Hassner and co-workers in the acetylation of 1,1-diphenylethanol with triethylamine as the auxiliary base and pyrrolidinopyridine (PPY) as the catalyst.[5] The reaction was found to proceed most readily in hexane and carbontetrachloride, more slowly in dichloromethane and diethyl ether, and to no appreciable extent in DMF or acetonitrile. To test the influence of solvent effects on the three pathways outlined in Schemes 2 and 3, we have estimated solvent effects for carbontetrachloride, chloroform, and dichloromethane through PCM/UAHF single-point calculations and combined them with gas-phase enthalpy differences to construct a solution-phase enthalpy profile (Table 1). The results obtained in this



Scheme 3. Gas-phase enthalpy profile (ΔH_{298}) for the competing concerted and stepwise base catalysis mechanisms in the DMAP-catalyzed reaction of acetic anhydride with *tert*-butanol as calculated at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level of theory.

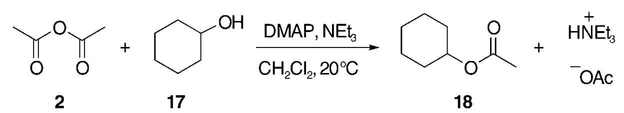
have therefore studied the kinetics of the DMAP-catalyzed reaction of acetic anhydride with alcohols in dichloromethane at ambient temperature in the presence of triethylamine as the auxiliary base. These studies have been performed with cyclohexanol (**17**) as the alcohol component in order to allow for a sufficiently large variation of concentrations (Scheme 4).[23]

For all concentrations studied here the reaction rate can be expressed through a rate law that contains two terms, one for the DMAP-catalyzed process and one for the uncatalyzed background process [Eq. (1)]. If one of the two reactants, for example, Ac_2O, is chosen in large excess over the other, and DMAP is accompanied by an excess of a more basic and catalytically inactive amine, the rate law can be simplified to that of a pseudo-first-order reaction as in Equations (2) and (3).

fashion show that even moderately polar solvents such as dichloromethane raise the reaction barrier through solvating the reactants substantially better than the intermediates or transition states. In line with the observations made by Hassner and co-workers, the reaction is predicted to proceed most readily in the least polar solvent CCl_4, while reaction in chloroform is slightly less favorable, and reaction in dichloromethane even more so. The rate-limiting step is still predicted to be the same as in the gas phase, as solvent effects are comparable for transition states **7** and **9**. In all three solvents the base-catalyzed mechanisms are as uncompetitive as they are in the gas phase.

One remarkable feature of transition state **9** is the concertedness of acetyl and proton transfer. This is illustrated in detail in Figure 1 showing transition states **7** and **9**.

In case the deprotonation of the alcohol through the acetate anion in transition state **9** is a realistic description of the rate-limiting step of the overall reaction, one must expect that deprotonation through auxiliary bases, such as triethylamine (NEt_3) or through a second equivalent of DMAP, plays no role under preparative conditions. In how far the reaction rate depends on the concentrations of DMAP or triethylamine to first or higher order has, however, not yet been clarified for the acylation of alcohols. We



Scheme 4. Reaction chosen for kinetic studies.

$$\frac{-\mathrm{d}[\text{cyclohexanol}]}{\mathrm{d}t} = k_3[\mathrm{Ac_2O}][\text{cyclohexanol}][\mathrm{DMAP}] + k_2[\mathrm{Ac_2O}][\text{cyclohexanol}] \tag{1}$$

$$\frac{-\mathrm{d}[\text{cyclohexanol}]}{\mathrm{d}t} = k_{1\Psi}[\text{cyclohexanol}] \tag{2}$$

$$k_{1\Psi} = k_3[\mathrm{Ac_2O}]_0[\mathrm{DMAP}]_0 + k_2[\mathrm{Ac_2O}]_0 \tag{3}$$

Measurement of the reaction rate under appropriately controlled conditions yields the results shown in Figures 3 and 4. In line with the rate law expressed in Equations (2) and (3), and the consensus nucleophilic catalysis mechanism, the rate of reaction depends linearly on the concentration of DMAP (Figure 3a). This excludes the possibility of a second molecule of DMAP acting as the catalytic base in the rate-

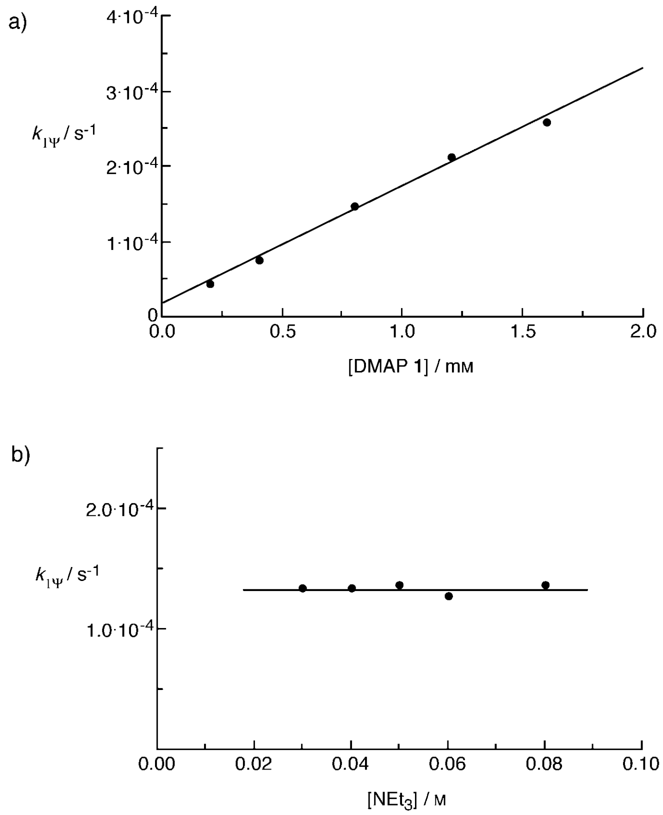


Figure 3. Variation of the pseudo-first-order rate constant $k_{1\psi}$ as a function of the reaction conditions (20°C, CH_2Cl_2). a) Dependence of $k_{1\psi}$ on the concentration of DMAP with $[Ac_2O]_0 = 0.12$ M, $[\text{cyclohexanol}]_0 = 0.02$ M, $[NEt_3]_0 = 0.06$ M. b) Dependence of $k_{1\psi}$ on the concentration of NEt_3 with $[\text{cyclohexanol}]_0 = 0.02$ M, $[Ac_2O]_0 = 0.20$ M, $[DMAP]_0 = 0.0004$ M.

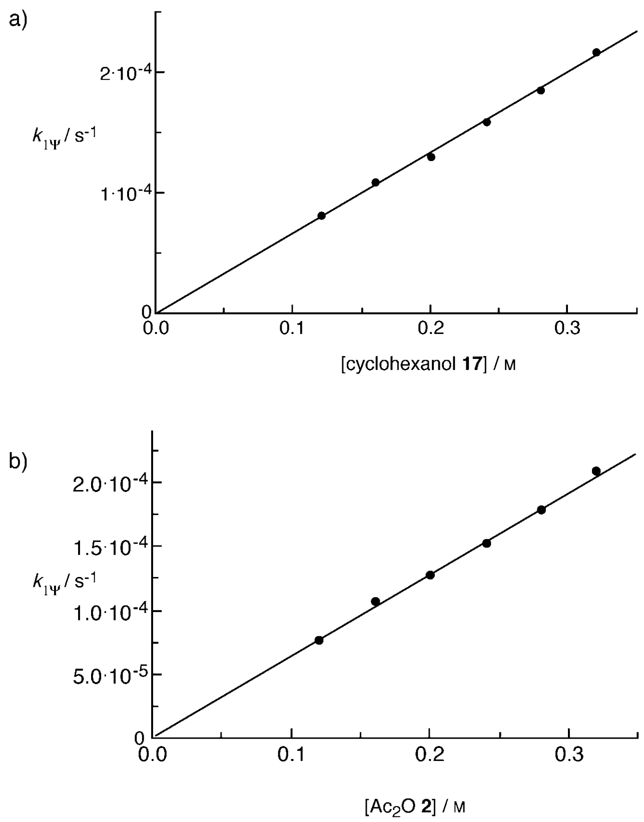


Figure 4. Variation of the pseudo-first-order rate constant $k_{1\psi}$ as a function of the reaction conditions (20°C, CH_2Cl_2). a) Dependence of $k_{1\psi}$ on the concentration of cyclohexanol with $[Ac_2O]_0 = 0.02$ M, $[NEt_3]_0 = 0.06$ M, $[DMAP]_0 = 0.0004$ M. b) Dependence of $k_{1\psi}$ on the concentration of Ac_2O with $[\text{cyclohexanol}]_0 = 0.02$ M, $[NEt_3]_0 = 0.06$ M, $[DMAP]_0 = 0.0004$ M.

limiting step of the acylation reaction. No dependence of the reaction rate on the concentration of the auxiliary base triethylamine could be found in the concentration range of 0.03–0.08 M (Figure 3b). The horizontal line shown in Figure 3b is only included to guide the eye. This result is in full support of the consensus mechanism and implies that triethylamine does not participate in the rate-limiting step of the acylation reaction.

The reaction rate depends linearly on both reactants, cyclohexanol (Figure 4a) and acetic anhydride (Figure 4b), up to concentrations of 0.32 M. Preliminary measurements with alcohol concentrations exceeding 1 M indicate, however, that higher concentrations of this polar component will lead to a deviation from the linear dependence predicted by Equations (2) and (3) towards slower rates. This is in line with earlier observations of reduced reaction rates in polar solvents and also the continuum solvation calculations described above.[3a,5] Fitting all data points to Equation (1) yields rate constants of $k_2 = 1.42 \pm 0.07 \times 10^{-4}\,\mathrm{L\,mol^{-1}\,s^{-1}}$ and $k_3 = 1.30 \pm 0.07\,\mathrm{L^2\,mol^{-2}\,s^{-1}}$. This indicates a rate difference of 9154 at a DMAP concentration of 1 M. At the much lower concentrations of DMAP used here (mM range), however, the uncatalyzed background reaction represents up to 10% of the reaction rate. While this is of no practical consequence for the reaction studied here, the rate ratio of the catalyzed and the uncatalyzed pathway is highly critical for kinetic resolutions with chiral DMAP derivatives.

Conclusion

In conclusion the theoretical examination of the nucleophilic and the base catalysis pathways and the experimental studies of the reaction kinetics of the DMAP-catalyzed acylation of cyclohexanol fully support the consensus mechanism described in Scheme 1. Solvation through organic solvents of moderate polarity is predicted to increase the barrier relative to apolar solvents. Based on the kinetic measurements neither the auxiliary base NEt_3 nor the catalytic base DMAP appear to be involved in the deprotonation of the alcohol during the acylation process. This leaves us with the acetate counterion contained in the acylpyridinium ion pair as the most likely base.

Experimental Section

General: Dichloromethane was vigorously stirred over concentrated H_2SO_4 to remove traces of olefins (3 days), and was then washed with water, 5% aqueous K_2CO_3 solution, and water again. After drying over $CaCl_2$ for 2 days, it was distilled from CaH_2. 4-Dimethylaminopyridine (DMAP) was purchased from Acros Corporation and used without further purification. Cyclohexanol and nonane (used as an internal standard) were purchased from Acros Corporation and distilled from sodium before use. Triethylamine was distilled from CaH_2; acetic anhydride was refluxed with MgC_2 at 80–90 °C for 5 days and distilled.

Kinetic measurements: Reaction solutions were prepared through mixing stock solutions of DMAP with a calibrated solution containing cyclohexanol, acetic anhydride, and triethylamine. Reactions were performed under a nitrogen atmosphere at 20 °C. All kinetic measurements were performed by using gas chromatography (FISONS 8130, Column: SE30) with nonane as internal standard. Rate measurements were performed through following the disappearance of the minor reaction component under pseudo-first-order conditions.

Computational details: All stationary points were optimized at the Becke3LYP/6-31G(d) level of theory. For all stationary points a number of conformational isomers exist. Only the energetically most favorable conformer was used to generate the enthalpy profile discussed in the text. An overview of all isomers is available in the Supporting Information. The nature of all stationary points was verified through calculation of the vibrational frequency spectrum. Thermochemical corrections to calculate enthalpies at 298 K were obtained by using the rigid rotor/harmonic oscillator model and the force constants calculated at Becke3LYP/6-31G(d) level. Single-point calculations were subsequently performed at the Becke3LYP/6-311+G(d,p) level of theory. Combination of the single-point energies with thermochemical corrections calculated at Becke3-LYP/6-31G(d) level yields the "H_{298}" values cited in the text. Solvent effects have been estimated through single-point calculations for the Becke3LYP/6-31G(d) gas-phase structures. The PCM/UAHF model was used for this purpose, again in combination with the Becke3LYP/6-31G(d) method.[24] Solvent effect calculations were performed for carbontetrachloride (CCl_4, $\varepsilon=2.23$), chloroform ($CHCl_3$, $\varepsilon=4.90$), and methylenechloride (CH_2Cl_2, $\varepsilon=8.93$) by using Gaussian 03, Rev. B.03. All other calculations were performed with Gaussian 98, Rev. A.11.[25]

[1] a) W. Steglich, G. Höfle, *Angew. Chem.* **1969**, *81*, 1001; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 981; b) G. Höfle, W. Steglich, *Synthesis* **1972**, 619–621.
[2] L. M. Litvinenko, A. I. Kirichenko, *Dokl. Akad. Nauk SSSR* **1967**, *176*, 97–100.
[3] For reviews see: a) G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602–615; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569–583; b) E. F. V. Scriven, *Chem. Soc. Rev.* **1983**, *12*, 129–161; c) A. Hassner, in *Encyclopedia of Reagents for Organic Synthesis*, Wiley, Chichester, **1995**, pp. 2022–2024; d) U. Ragnarsson, L. Grehn, *Acc. Chem. Res.* **1998**, *31*, 494–501; e) D. J. Berry, C. V. Digiovanna, S. S. Metrick, R. Murugan, *Arkivoc* **2001**, 201–226; f) A. C. Spivey, S. Arseniyadis, *Angew. Chem.* **2004**, *116*, 5552–5557; *Angew. Chem. Int. Ed.* **2004**, *43*, 5436–5441.
[4] M. R. Heinrich, H. S. Klisa, H. Mayr, W. Steglich, H. Zipse, *Angew. Chem.* **2003**, *115*, 4975–4977; *Angew. Chem. Int. Ed.* **2003**, *42*, 4826–4828.
[5] A. Hassner, L. R. Krepski, V. Alexanian, *Tetrahedron* **1978**, *34*, 2069–2076.
[6] For reviews see: a) G. C. Fu, *Acc. Chem. Res.* **2000**, *33*, 412–420; b) A. C. Spivey, A. Maddaford, A. Redgrave, *Org. Prep. Proced. Int.* **2000**, *32*, 331–365; c) G. C. Fu, *Acc. Chem. Res.* **2004**, *37*, 542–547; d) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5178.
[7] S. Tabanella, I. Valancogne, R. F. W. Jackson, *Org. Biomol. Chem.* **2003**, *1*, 4254–4261.
[8] K.-S. Jeong, S.-H. Kim, H.-J. Park, K.-J. Chang, K. S. Kim, *Chem. Lett.* **2002**, 1114–1115.
[9] a) T. Kawabata, M. Nagato, K. Takasu, K. Fuji, *J. Am. Chem. Soc.* **1997**, *119*, 3169–3170; b) T. Kawabata, K. Yamamoto, Y. Momose, H. Yoshida, Y. Nagaoka, K. Fuji, *Chem. Commun.* **2001**, 2700–2701; c) T. Kawabata, R. Stragies, T. Fukaya, K. Fuji, *Chirality* **2003**, *15*, 71–76; d) T. Kawabata, R. Stragies, T. Fukaya, Y. Nagaoka, H. Schedel, K. Fuji, *Tetrahedron Lett.* **2003**, *44*, 1545–1548.
[10] a) E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1996**, *118*, 1809–1810; b) S. A. Shaw, P. Aleman, E. Vedejs, *J. Am. Chem. Soc.* **2003**, *125*, 13368–13369.
[11] a) A. H. Mermerian, G. C. Fu, *Angew. Chem.* **2005**, *117*, 971–974; *Angew. Chem. Int. Ed.* **2005**, *44*, 949–952; b) J. E. Wilson, G. C. Fu, *Angew. Chem.* **2004**, *116*, 6518–6520; *Angew. Chem. Int. Ed.* **2004**, *43*, 6358–6360; c) I. D. Hills, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4051–4054; *Angew. Chem. Int. Ed.* **2003**, *42*, 3921–3924; d) Ara H. Mermerian, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 4050–4051; e) B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 10006–10007; f) B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579; g) S. Bellemin-Laponnaz, J. Tweddell, J. C. Ruble, F. M. Breitling, G. C. Fu, *Chem. Commun.* **2000**, 1009–1010; h) J. C. Ruble, J. Tweddell, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 2794–2795; i) J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492–1493.
[12] a) A. C. Spivey, T. Fekner, S. E. Spey, H. Adams, *J. Org. Chem.* **1999**, *64*, 9430–9443, and references therein; b) A. C. Spivey, T. Fekner, S. E. Spey, *J. Org. Chem.* **2000**, *65*, 3154–3159; c) A. C. Spivey, A. Maddafort, T. Fekner, A. J. Redgrave, C. S. Frampton, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3460–3468; d) A. C. Spivey, A. Maddafort, T. Fekner, D. P. Leese, A. J. Redgrave, C. S. Frampton, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1785–1794; e) A. C. Spivey, D. P. Leese, F. Zhu, S. G. Davey, R. L. Jarvest, *Tetrahedron* **2004**, *60*, 4513–4525.
[13] G. Priem, B. Pelotier, S. J. F. Macdonald, M. S. Anson, I. B. Campbell, *J. Org. Chem.* **2003**, *68*, 3844–3848.
[14] E. Guibe-Jampel, G. Le Corre, M. Wakselman, *Tetrahedron Lett.* **1979**, *20*, 1157–1160.
[15] E. Kattnig, M. Albert, *Org. Lett.* **2004**, *6*, 945–948.
[16] G. Lamaty, F. Mary, J. P. Roque, *J. Chim. Phys. Phys.-Chim. Biol.* **1991**, *88*, 1793–1810.
[17] a) S. Ba-Saif, A. K. Luthra, A. Williams, *J. Am. Chem. Soc.* **1987**, *109*, 6362–6368; b) S. Ba-Saif, A. K. Luthra, A. Williams, *J. Am. Chem. Soc.* **1989**, *111*, 2647–2652; c) A. Williams, *Acc. Chem. Res.* **1989**, *22*, 387–392; d) A. Williams, *Chem. Soc. Rev.* **1994**, *23*, 93–100.
[18] S. Stefanidis, S. Cho, S. Dhe-Paganon, W. P. Jencks, *J. Am. Chem. Soc.* **1993**, *115*, 1650–1656.
[19] a) A. C. Hengge, R. A. Hess, *J. Am. Chem. Soc.* **1994**, *116*, 11256–11263; b) R. A. Hess, A. C. Hengge, W. W. Cleland, *J. Am. Chem. Soc.* **1997**, *119*, 6980–6983; c) R. A. Hess, A. C. Hengge, W. W. Cleland, *J. Am. Chem. Soc.* **1998**, *120*, 2703–2709.
[20] J. I. Braumann, M. Zhong, *J. Am. Chem. Soc.* **1999**, *121*, 2508–2515.
[21] J. F. Marlier, *Acc. Chem. Res.* **2001**, *34*, 283–290.
[22] A tetrahedral intermediate as proposed in reference [3f] could not be located on the reaction pathway between reactant complex **6** and acyl intermediate **8**.
[23] Preliminary measurements with *tert*-butanol as the alcohol indicated that at the lowest concentrations needed for full kinetic analysis, half-lives would exceed 14 days.
[24] a) C. Amovilli, V. Barone, R. Cammi, E. Cances, M. Cossi, B. Mennucci, C. S. Pomelli, J. Tomasi, *Adv. Quantum Chem.* **1998**, *32*, 227–262; b) M. Cossi, G. Scalmani, N. Rega, V. Barone, *J. Chem. Phys.* **2002**, *117*, 43.
[25] a) Gaussian 03 (Revision B.03), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda,

O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., **2004**; b) Gaussian 98 (Revision A.11), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.

Received: April 7, 2005
Published online: May 27, 2005

