The Stability of Acylpyridinium Cations and Their Relation to the Catalytic Activity of Pyridine Bases

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This manuscript is dedicated to Bernd Giese on the occasion of his 65th birthday, for being a great teacher, a role model for the modern physical-organic chemist, and a good friend.

Abstract: The stability of acylpyridinium cations can be used as a predictive tool for the development of catalysts for acyl transfer reactions based on the 4-aminopyridine motive. Substituents in 2-position of the pyridine ring are detrimental to both, the catalytic activity of pyridine catalysts as well as the stability of the respective acetylpyridinium cations. Alkyl substituents located in 3-position of the pyridine ring and at the nitrogen substituent in 4-position lead to higher catalytic activity as well as more stable acetylpyridinium cations. This is, of course, only true as long as steric effects do not hinder the proper alignment of the 4-amino substituent and the pyridine ring.

Keywords: nucleophilic catalysis, DMAP, acyl intermediates

Nucleophilic catalysts such as DMAP (1) have found widespread application not only in the synthesis of esters and amides, but also in silylation and even C–C bond forming reactions.2 Recently, considerable effort has been directed towards the development of chiral catalysts based on the DMAP motive in order to effect enantioselective transformations.3–10 While some of these catalysts achieve high catalytic activity, others are catalytically almost inactive and achieve stereoselective transformations only in a single turnover experiment. We have recently shown that DMAP derivatives of enhanced catalytic activity can be developed through anellation of aliphatic ring systems and that the activity of these new catalysts correlates well with their relative acylation enthalpies.11 This correlation becomes understandable when considering the current consensus mechanism for the DMAP catalyzed acetylation of alcohols with acetic anhydride (Scheme 1).1 In the first step of the catalytic cycle DMAP (1) reacts with acetic anhydride (2) to form ion pair intermediate 3 composed of the 4-dimethylamino-N-acetylpyridinium cation and the acetate anion. Formation of the ion pair 3 is usually considered to be rapid and reversible in comparison to the follow-up step, in which reaction with alcohol 4 occurs. The products of this (rate-limiting) second step are ester 5 and the protonated catalyst 6. Multiple catalytic turnovers are only possible after regeneration of the unprotonated catalyst 1 [pKₐ(water, 25 °C) = 9.58] from ion pair 6 through proton transfer to an auxiliary base such as Et₃N

\[
\begin{align*}
&\text{N} \quad \text{O} \\
&\text{O} \\
&\text{O} \\
&\text{1} \quad \text{K} \\
&\text{2} \\
&\text{R–OH} \\
&\text{4} \quad k_2 \\
&\text{R} \\
&\text{5} \\
&\text{6} \\
&\text{N} \quad \text{O} \\
&\text{OAc} \\
&\text{N} \quad \text{O} \\
&\text{OAc} \\
&\text{R} \\
&\text{7Ac}
\end{align*}
\]

Scheme 1

Isodesmic reaction (Equation 1) is based on pyridine 7 and the acetylpyridinium cation 7Ac as the reference. The reaction enthalpies calculated for reaction (Equation 1) therefore reflect the potential of the substitution pattern (here symbolized through substituent R) to stabilize an acetylpyridinium cation relative to its neutral parent.
All structures have been optimized at the Becke3LYP/6-31G(d) level of theory. A rigorous conformational search has been performed in each case in order to cover the conformational space available to the more flexible systems. Enthalpies at 298.15 K have then been calculated for each conformer based on its harmonic vibrational frequencies. Single point energy calculations have also been performed at the Becke3LYP/6-311+G(d,p) level of theory. Combination of these single point energies with the enthalpy values at the Becke3LYP/6-31G(d) level allows the calculation of Becke3LYP/6-311+G(d,p)/Becke3LYP/6-31G(d) reaction enthalpies at 298.15 K. Finally, average enthalpies at 298.15 K have been calculated for each system through Boltzmann-averaging over all conformers. Atomic charges have been calculated using the Natural Population Analysis (NPA) scheme at the Becke3LYP/6-31G(d) level of theory.14

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While DMAP as well as other pyridine derivatives of high catalytic activity lack substituents in the C2 and C6 positions, this is not so for many of the chiral DMAP derivatives. We have therefore subdivided the systems investigated in this study into those carrying no substituents in the critical C2/C6 positions (I and 7–21) and those that do (22–31). While the substituents must be expected to exert steric as well as electronic effects in the latter class of catalysts, the substituent effects will be mainly electronic in nature in the former. The structures of all systems are shown in Figure 1, ranked by their heats of reaction for the acetyl transfer reaction in Equation 1. Enthalpies, charge parameters, and selected structural data have been collected in Table 1.

The presence of a donor substituent in 4-position of the pyridine ring leads to a strong stabilization of the acetylpyridinium cation. For the 4-dimethylamino substituent present in DMAP, this effect amounts to –82.1 kJ/mol. The pyrrolidino substituent present in 4-pyrrolidinopyridine (PPY, 8) is even more effective and stabilizes the acetylpyridinium cation by –93.1 kJ/mol. These substituent effects have in the past been rationalized with respect to stabilization of the acetylpyridinium cation through additional resonance forms as depicted in Scheme 2. Here the resonance forms A and B are the main contributors to the overall wavefunction in the absence of powerful donor-substituents, and resonance form C is the main addition brought about by substituents in 4-position. That the overall charge of the acetyl group \( q(\text{Ac}) \) as well as the length of the C–N bond connecting the acetyl group and the pyridine ring \( r(\text{C–N}) \) vary significantly with the substitution pattern of the pyridine ring indicates, however, that the no-bond resonance form D is also significant.

The charge parameter \( q(\text{Ac}) \) and the distance parameter \( r(\text{C–N}) \) are particularly well suited for the characterization of the acetylpyridinium cations, since they are directly related to the acetyl group transfer process and since they are likely not to depend on steric effects exerted by substituents in 3- and 4-position of the pyridine ring. Inspection of the results in Table 1 shows that for the known catalysts DMAP (1) and PPY (8) the partial charge of the acetyl group is significantly less positive at +0.298 and +0.291 as compared to the acetylpyridinium cation 7Ac with \( q(\text{Ac}) = +0.366 \). This may be understood as a reduction of the relevance of resonance form D and increased importance of the other three resonance forms A–C for these donor-substituted pyridines. This interpretation is

<table>
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<tr>
<th>System</th>
<th>( \Delta H_{\text{mol}} ) [kJ/mol]</th>
<th>( q(\text{Ac})^a,b )</th>
<th>( r(\text{C–N}) ) [pm]</th>
<th>( d(\text{O/C/N/C}) ) [°]</th>
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<td>148.52</td>
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<td>147.99</td>
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<td>+0.275</td>
<td>147.29</td>
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<td>0.4</td>
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<td>147.11</td>
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</tr>
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<td>+0.272</td>
<td>147.02</td>
<td>0.3</td>
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<td>–128.0</td>
<td>+0.228</td>
<td>144.34</td>
<td>5.2</td>
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</table>

\( ^a \) In units of elemental charge e.  
\( ^b \) Acetyl group charge of the most favorable conformer.
also supported by a rather long C–N bond of 151.6 pm in acylpyridinium cation 7Ac, which is significantly shortened in the acylpyridinium cations of 1 (at 148.2 pm) and 8 (at 147.9 pm).

The enhanced stabilization of the acetylpyridinium cations through anellation of 5-, 6-, or 7-membered rings as present in pyridines 9–14 is mainly a consequence of inductive electron-donating effects of the alkyl substituents, either through the nitrogen substituent in 4-position or directly through connection to the pyridine ring in 3- and 5-positions. As a consequence the stability order of the corresponding acetylpyridinium cations follows roughly the number of carbon atoms present in the 3-/5- and 4-substituents. This may be exemplified using the pyridines PPy (8), 12, and 10, all of which carry four carbon atoms in the substituent pattern and whose acetylation enthalpy values are within 4.5 kJ/mol. This simple explanation fails where steric effects or ring strain prevent the proper alignment of the nitrogen substituent in 4-position and the pyridine ring as in 7-membered ring system 14 or the 3-methyl substituted system 21. Still, the simple model of inductive effects through alkyl substituents can be utilized to predict more stable pyridinium cations such as those of pyridines 15ci (cis-dimethyl substitution), 15tr (trans-dimethyl substitution), and 16. The additional methyl groups attached to the methylene groups in 3- and 5-positions of the doubly-anellated system 11 lead to an increased stability of the acetylpyridinium cation of 3.9, 5.5, and 10 kJ/mol, respectively.

While alkyl substituents attached to the 4-amino substituent are clearly stabilizing, the opposite is true for phenyl substituents as present in 17 and 18. The first of these systems differs from doubly-anellated system 11 through introduction of a single phenyl substituent, leading to a decrease of the stability of the pyridinium cation by 20.4 kJ/mol. Introduction of two phenyl substituents into pyridine 12 yields system 18, with the difference in the stability of the pyridinium cations now amounting to 29.8 kJ/mol. That more potent electron-donors in 4-position lead to more highly stabilized pyridinium cations can nicely be illustrated with the 4-tetramethylguanidinium-substituted system 19, whose cation is stabilized by –113.1 kJ/mol relative to pyridine, 31 kJ/mol more than for DMAP and 20 kJ/mol more than for PPY. That anellation of substituents does not always translate into enhanced stability of the acetylpyridinium cation is apparent from the comparison of 19 and 20. In the latter system one of the four methyl groups present in 19 has been used to form a direct connection to the 3-position of the pyridine ring. This anellation step leads to a reduction of the cation stability by almost 10 kJ/mol.

All of the effects discussed above are based on the assumption that substituent effects are essentially electronic in nature, without direct influence on the local geometry of the acetyl group present in the acetylpyridinium cations. The validity of this assumption is supported by the relative orientation of the acetyl group and the pyridine ring. This is most conveniently expressed through the dihedral angle d(O/C/N/C) describing the relative orientation of the carbonyl O–C double bond and the adjacent N–C bond of the pyridine ring. This angle is rather close to 0.0 in all cases lacking substituents in 2- and 6-positions, indicating perfect alignment of the π-systems of

Figure 1 Structures of pyridine derivatives 1 and 7–31, ranked by their relative acetylation enthalpy at 298.15 K as defined by Equation 1

Scheme 2
the acetyl group and the pyridinium ring. Introduction of a single methyl group as in 22 leads to partial rotation of the acetyl group out of the plane defined by the pyridine ring, amounting to 20.0 degrees in 22. This structural perturbation is accommodated by a decrease in the stability of the acetylpyridinium cation by almost 16 kJ/mol. The acetylation energies of the systems 30, 31, 28, 29, and 25 containing 4-, 5-, or 6-membered anellated rings in 2-/3-position of the pyridine ring are influenced by an interplay of several effects, the steric hindrance of the acetyl group as well as the inductive electron-donation being the most dominant. Anellation of a 6-membered aromatic ring as in 25 prevents the optimal alignment of both the acetyl group as well as the 4-dimethylamino substituent at the acetylpyridinium stage, resulting in a rather low acetylation energy of –60.4 kJ/mol. The hindrance of the alignment of the dimethylamino substituent can be quantified to ca 20 kJ/mol through comparison of the acetylation energies of quinolines 24 and 25 (a difference of 61.5 kJ/mol) with those of pyridine (7) and DMAP (a difference of 82.1 kJ/mol). Anellation of 5-membered rings as in 28 and 29 still leads to a perturbation of the acetyl group orientation, but to a much smaller degree as that observed for 24 and 25. This is also reflected in the acetylation energies, which are rather close to those calculated for DMAP. Further reduction of the ring size as in cyclobutyl-anellated system 31 leads to a structurally unperturbed acetylpyridinium cation with enhanced stability over that of DMAP. The large destabilizing effect observed on introduction of a double bond in the anellated cyclobutyl ring as in 30 is obviously not a steric effect, but rather reflects the reluctance of the cyclobutene ring to form an antiaromatic cyclobutadiene system on formation of the acetylpyridinium cation.

The small acetylation enthalpy obtained for chiral DMAP derivative 23\textsuperscript{1} of –56.6 kJ/mol is in full agreement with the hypothesis of steric compression between the acetyl moiety and the substituent in 2-position. That the effects of steric compression are comparable in 22 and 23 may seem surprising at first due to the significantly different absolute size of the 2-substituent. However, the most favorable conformation of the acetylated form of 23 (termed here 23Ac-a) positions the methoxy group and the tert-butyl substituent above and below the pyridine ring plane, leaving only the C–H bond at the chiral center to face the acetyl group (Figure 2). The chiral DMAP derivative 26 is based on the highly successful ligands developed by Braese and coworkers for the addition of dialkylzinc reagents to aldehydes and imines.\textsuperscript{17,18} The acetylation enthalpy of 26 is predicted to be rather low at –59.1 kJ/mol, the result of severe steric interactions between the paracyclophane bridge atoms and the acetyl group. The highest acetylation energies calculated in this study are predicted for DMAP derivative 27, which has recently been utilized by Fu and coworkers in a series of base-catalyzed processes.\textsuperscript{5,6} That the acetylation energy is dramatically larger (more negative) than for pyridines 28 and 29, which also contain an anellated cyclopentadiene ring in 2,3-position of the pyridine ring, is due to the electron-donating ability of the ferrocenyl moiety. This is also responsible for the rather low positive charge of the acetyl group of +0.228 and the rather short C–N bond. The anellated cyclopentadienyl ring in 27 is small enough to avoid repulsive interactions with the acetyl group bound to the pyridine ring. The most favorable conformation of the acetylpyridinium cation 27Ac-a shows the carbonyl oxygen atom oriented towards the (partially positively charged) hydrogen atom bound to the neighboring cyclopentadienyl ring (Figure 2). This is practically identical to the conformation present in an X-ray crystal structure of the acetylpyridinium cation of the pentaphenyl derivative of 27.\textsuperscript{34} How do the calculated enthalpies correlate with the observed catalytic reactivity of the pyridine bases? An answer to this question is made difficult through the lack of reliable rate data, even for the most common DMAP-catalyzed reactions such as the acetylation of alcohols. The recent determination of reaction half lives for the acetylation of tertiary alcohol 32 (Figure 3) with acetic anhydride and Et\textsubscript{3}N as the auxiliary base in CHCl\textsubscript{3} of 151 minutes for DMAP, 69 minutes for PPY, 63 minutes for 10, and 26 minutes for tricyclic derivative 11 nicely correlate with the increasingly negative acetylation enthalpies of –82.1, –75.8, –69.5, and –65.8 kJ/mol, respectively.

![Figure 2](image_url) Three-dimensional structures of the energetically most favorable conformers of acetylpyridinium cations 23Ac and 27Ac as optimized at the Becke3LYP/6-31G(d) level of theory.
−93.1, −96.0, and −108.9 kJ/mol calculated for these four catalysts, respectively. Relative to the alcohol substrate 0.1 equivalent of the catalysts have been used in these studies.11 Earlier estimates of the relative catalytic activity of PPY and DMAP arrive at a value of 2.5 at room temperature using equimolar amounts of catalyst and alcohol substrate.16

Relative catalytic efficiencies of various pyridine derivatives (0.1 equiv relative to the alcohol) have previously been reported by Hassner et al. for the acetylation of 1,1-diphenylethanol (33) with acetic anhydride and Et₃N as the auxiliary base in the absence of additional solvent. Relative catalytic efficiencies of 1.0, 0.90, and 0.63 have been determined for PPY, pyridine 19, and DMAP, respectively. No catalytic effect has been found for pyridine (7), 4-pyrrolidinoquinoline, and a series of 2-substituted pyridines.16 While the results for PPY, DMAP, and pyridine parallel the acetylation energies calculated here, a significantly higher reactivity would have been expected for 19 based on its acetylation enthalpy of −113.1 kJ/mol. The chiral DMAP derivative 23 appears not to be catalytically active in acyl transfer reactions, but has shown good selectivities in its fully acylated form in the kinetic resolution of secondary alcohols.4a The low catalytic activity of 23 is paralleled by a relatively small acetylation enthalpy of −56.6 kJ/mol. The catalytic potential of ferrocene derivative 27 (0.05 equiv) has been quantified for the acylation of secondary alcohol 34 (Figure 3) with diketene in CH₂Cl₂ at room temperature.5 While a half-life of less than 3 minutes has been determined for 27, a half-life of less than two minutes has been reported for DMAP. Since these half-lives are at the limit of what may be determined reliably by the NMR-method, one may conclude that DMAP and 27 show comparable catalytic reactivity in this case. While a significant catalytic activity had to be expected for 27 based on its acetylation enthalpy of −128.0 kJ/mol, the difference in acetylation enthalpies of DMAP and 27 would have suggested the latter to be much more potent.

The relative acetylation enthalpies for various DMAP derivatives as defined through Equation 1 can be used as a qualitative measure of the catalytic potential of these derivatives in acylation reactions. Steric effects through substituents in 2-position of the pyridine ring appear to be much more detrimental to the reaction kinetics than to the stability of the acetylypyridinium intermediates. This implies that pyridine derivatives with acetylation enthalpies in the range of 0 kJ/mol and −60 kJ/mol will not be catalytically active. The correlation between acetylation enthalpy and reaction rate appears to work well up to values around −110 kJ/mol. Beyond this region further increases in acetylation enthalpy appear not to translate into rate increases as neither 19 nor 27 exceeds the catalytic activity of PPY or 11. Considering the high catalytic efficiency of 11, the comparable efficiency of 19 and PPY, and the comparable catalytic efficiency of DMAP and 27, one may even be tempted to predict a peak in catalytic efficiency at acetylation enthalpies of around −110 kJ/mol. This is also what would be expected to happen in case the equilibrium constant for formation of the acetylypyridinium intermediate $K$ as described in Scheme 1 assumes values much larger than unity. A clear picture can, however, only be obtained from experimental studies using all catalysts under exactly comparable conditions.

**Acknowledgment**

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**References**


(18) Bräse, S. private communication.