Powerful Acylation Catalyst

Enhancing the Catalytic Activity of 4-(Dialkylamino)pyridines by Conformational Fixation**

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Dedicated to Professor Heinrich Nöth on the occasion of his 75th birthday

4-(Dimethylamino)pyridine (DMAP, **1**) was introduced to synthetic chemistry as a powerful nucleophilic group-transfer catalyst more than three decades ago[1,2] and has become a standard reagent[3] for acylation, esterification,[4] macrolactonization,[5] and silylation reactions,[6] to mention only a few applications. DMAP has since served as a basis for several research groups for the development of chiral acylation catalysts.[7] Herein we report on the enhanced

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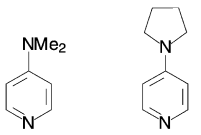
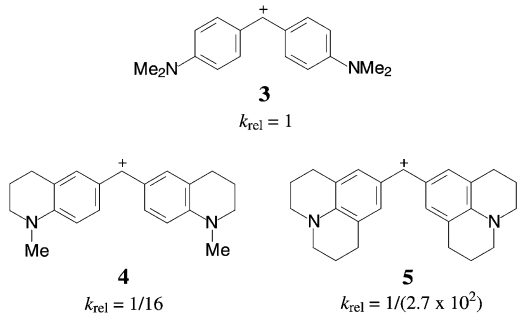


1 **2**

catalytic activity of 4-(dialkylamino)pyridines in which the 4-amino group is conformationally fixed in a ring fused to the pyridine ring.

Previous work showed that 4-pyrrolidinopyridine (PPY, **2**)[3a,8,9] is a more effective acylation catalyst than DMAP. Evidently the catalytic activity depends on the stabilization of the *N*-acyl pyridinium ion by interaction with the lone pair of electrons of the 4-amino group.[10] Therefore, an increase in this interaction should lead to enhanced catalytic performance.

Studies on 4,4′-bis(dialkylamino)benzhydryl cations showed a dramatic increase in stabilization when the nitrogen atom was part of a conformationally fixed ring system. This is illustrated by the series of benzhydryl cations **3**–**5** (Scheme 1),

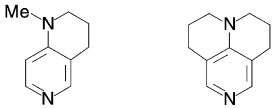


3 $k_{rel} = 1$

4 $k_{rel} = 1/16$ **5** $k_{rel} = 1/(2.7 \times 10^2)$

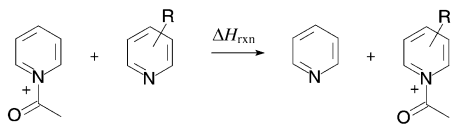
Scheme 1. Relative reactivities of benzhydryl cations derived from the rate constants of their reactions with π nucleophiles (20 °C).[11]

in which the bisjulolidinyl derivative **5** is about 300 times less electrophilic than the simple bis(dimethylamino) derivative **3**.[11] We reasoned that conformational fixation combined with the inductive electron-donating effect of an alkyl group in the *meta* position might have a similar effect on the corresponding (4-dialkylamino)pyridines and cause an increase in electron density at the pyridine nitrogen atom, thus resulting in stabilization of the *N*-acyl pyridinium ion derivative. We used the 4-(dialkylamino)pyridines **6** and **7** for this study.



6 **7**

The expected enhanced stability of the *N*-acyl intermediates derived from the DMAP analogues **6** and **7** can be verified through theoretical evaluation of the reaction enthalpies for the acetyl-transfer reaction shown in Equation (1). Reaction enthalpies at 298 K were calculated for a



(1)

number of DMAP derivatives at the B3LYP/6-311 + G(d,p)// B3LYP/6-31G(d) level of theory,[12] whereby more negative values indicate better stabilization of the acetyl group relative to pyridine (Table 1). As expected, a strongly negative

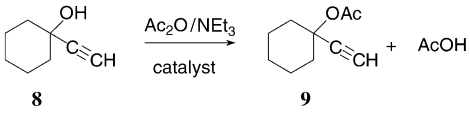
Table 1: Calculated reaction enthalpies ΔH_{rxn} for the acetyl-transfer reaction (1) and experimental half-lives $t_{1/2}$ for the reference reaction (2).

	DMAP (**1**)	PPY (**2**)	**6**	**7**
ΔH_{rxn} [kJ mol^{-1}]	−82.1	−93.1	−96.0	−108.9
$t_{1/2}$ [min]	151	69	63	26

reaction enthalpy was calculated for DMAP, which confirms the special properties of this compound from the viewpoint of the stability of the acyl intermediate. Reaction enthalpies more negative by 11–14 kJ mol^{-1} were predicted for the singly annulated DMAP analogue **6** and PPY (**2**). Annulation of an additional six-membered ring as in **7** lowers the reaction enthalpy by 27 kJ mol^{-1}. These results suggest that the DMAP derivative **7** may be a significantly better acyl-transfer catalyst than DMAP itself or even **2**.

The known pyridonaphthyridine derivative **7**[13] was prepared from 1,6-naphthyridine in four steps according to a literature procedure.[13b] The bicyclic analogue **6** was synthesized by reaction of the *ortho*-lithiated derivative of 4-(*tert*-butoxycarbonylamino)pyridine[7e] with 1-chloro-3-iodopropane and reduction of the resulting *tert*-butoxycarbonyl (Boc) derivative[14] with diisobutylaluminum hydride.[15]

To test the catalytic activity of the 4-aminopyridines **1, 2, 6**, and **7**, the acetylation of 1-ethynylcyclohexanol (**8**) with acetic anhydride in the presence of triethylamine as the auxiliary base was studied in $CDCl_3$ at 20 °C [standard reaction, Eq. (2)].[3a] The reaction was monitored by



8 **9** (2)

^{1}H NMR spectroscopy under the conditions described, based on the increase in the intensity of the CH_3CO signals. The results are illustrated in Figure 1 and summarized in Table 1.

The results indicate that the incorporation of the 4-amino group in one single six-membered ring (as in **6**) leads to an enhancement of the catalytic activity similar to that observed for **2** relative to **1**. Compound **7**, in which the amino group is incorporated in two six-membered rings, exhibits a substantial increase in activity and appears to be about six times more active than DMAP (**1**). It even outperforms PPY (**2**), until now the best catalyst known for this transformation, by a factor of 2.5. The acylation of the sterically hindered alcohol **8** was complete within 2 to 3 h under the catalysis of **7**, whereas the DMAP- or PPY-catalyzed reactions were far from completion after the same amount of time (Figure 1).[16]

In conclusion, we have shown that it is possible to develop nucleophilic acylation catalysts that are superior to the

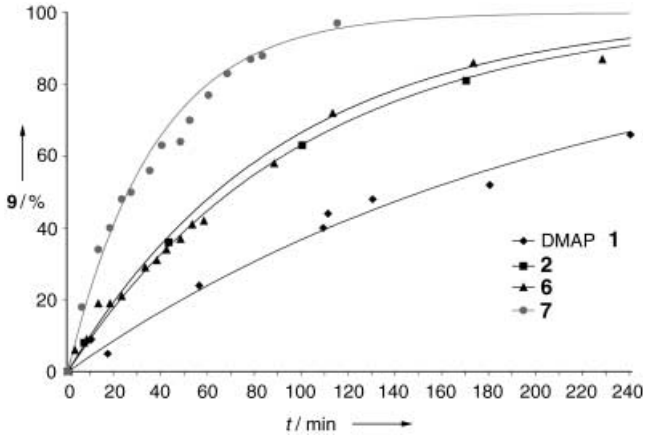


Figure 1. Acetylation of **8** ($c = 0.2$ mol L^{-1}) with Ac_2O ($c = 0.4$ mol L^{-1}) in the presence of NEt_3 ($c = 0.6$ mol L^{-1}) and various (4-dialkylamino)-pyridine catalysts ($c = 0.02$ mol L^{-1}) in $CDCl_3$ at 20 °C.

familiar DMAP. Compounds such as **7** are of potential value for acylations that proceed in low yields because of undesired side reactions when the less active catalysts **1** or **2** are used. Moreover, the annulated derivative **7** provides a rigid, highly reactive scaffold upon which new generations of chiral DMAP derivatives can be built.

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Keywords: ab initio calculations · acylation · dimethylaminopyridine · kinetics

[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] For kinetic evidence for the high catalytic activity of DMAP in the benzoylation of aryl amines, see: L. M. Litvinenko, A. I. Kirichenko, *Dokl. Akad. Nauk SSSR Ser. Khim.* **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, Vol. 3* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 2022 – 2024.

[4] a) B. Neises, W. Steglich, *Angew. Chem.* **1978**, *90*, 556 – 557; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 552; b) A. Hassner, V. Alexanian, *Tetrahedron Lett.* **1978**, 4475 – 4478.

[5] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989 – 1993; b) E. P. Boden, G. E. Keck, *J. Org. Chem.* **1985**, *50*, 2394 – 2395.

[6] S. K. Chaudhary, O. Hernandez, *Tetrahedron Lett.* **1979**, 99 – 102.

[7] a) E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1996**, *118*, 1809 – 1810; b) J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1996**, *61*, 7230 – 7231; c) T. Kawabata, M. Nagato, K. Takasu, K. Fuji, *J. Am. Chem. Soc.* **1997**, *119*, 3169 – 3170; d) B. Tao, J. C. Ruble, D. A. Hoic, G. C. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 5091 – 5092; e) A. C. Spivey, T. Fekner, S. E. Spey, H. Adams, *J. Org. Chem.* **1999**, *64*, 9430 – 9443, and references therein; f) A. C. Spivey, T. Fekner, S. E. Spey, *J. Org. Chem.* **2000**, *65*, 3154 – 3159; g) A. C. Spivey, A. Maddaford, T. Fekner, A. J. Redgrave, C. S. Frampton, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3460 – 3468; h) G. C. Fu, *Acc. Chem. Res.* **2000**, *33*, 412 – 420, and references therein; i) A. C. Spivey, A. Maddaford, T. Fekner, D. P. Leese, A. J. Redgrave, C. S. Frampton, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1785 – 1794; j) G. Priem, B. Pelotier, S. J. F. Macdonald, M. S. Anson, I. B. Campbell, *J. Org. Chem.* **2003**, *68*, 3844 – 3848; k) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985 – 3012.

[8] W. Steglich, G. Höfle, *Tetrahedron Lett.* **1970**, *54*, 4727 – 4730.

[9] A. Hassner, L. R. Krepski, V. Alexanian, *Tetrahedron* **1978**, *34*, 2069 – 2076.

[10] Compare the analogous effects in the enamine series: a) S. Hünig, H. Hoch, *Fortschr. Chem. Forsch.* **1970**, *14*, 235 – 293; b) B. Kempf, N. Hampel, A. R. Ofial, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 2209 – 2218.

[11] a) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *123*, 9500 – 9512; b) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66 – 77.

[12] All structures were first optimized at the Becke3LYP/6-31G(d) level of theory. Zero-point vibrational energies and thermochemical corrections to enthalpies at 298 K were calculated based on the rigid-rotor/harmonic-oscillator model at the same level of theory. Single-point energies were then calculated at the Becke3LYP/6-311 + G(d,p) level of theory. Combination of the Becke3LYP/6-311 + G(d,p) total energies with the previously calculated thermochemical data yielded the enthalpies termed "B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d)" in the text. Boltzmann averaging of enthalpies was performed for those systems that display more than one low-energy conformation. All calculations were performed with the Gaussian 98 (Rev. A.7) package.[17] Energy data and structural parameters for pyridine, the pyridine bases **1, 2, 6**, and **7**, and their *N*-acetyl derivatives are given in the Supporting Information.

[13] a) K. Tsuda, S. Saeki, S. Imura, S. Okuda, Y. Sato, H. Mishima, *J. Org. Chem.* **1956**, *21*, 1481 – 1486; b) T. Sakomoto, N. Miura, Y. Kondo, H. Yamanaka, *Chem. Pharm. Bull.* **1986**, *34*, 2018 – 2023.

[14] J. N. Reed, J. Rotchford, D. Strickland, *Tetrahedron Lett.* **1988**, *29*, 5725 – 5728.

[15] The synthesis of **6** and the spectroscopic data of compounds **6** and **7** are described in the Supporting Information.

[16] The importance of the auxiliary base is illustrated by the fact that the half-life for the acetylation of **8** under the catalysis of **7** is increased from 151 to 465 min if pyridine is used instead of triethylamine.

[17] Gaussian 98 (Revision A.7), 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**.

