Stacking interactions as the principal design element in acyl-transfer catalysts†

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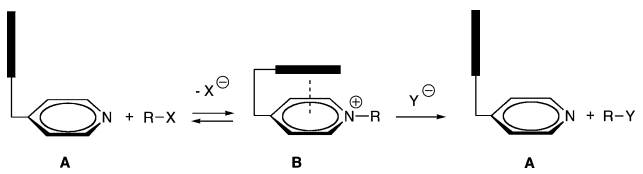
The conformational properties and the stability of acylpyridinium intermediates formed in pyridine-catalyzed acylation reactions have been studied at the SCS-MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G(d) level of theory. It has been shown that stacking interactions can play a decisive role in the stability as well as the conformational preferences of these transient intermediates.

Introduction

Donor-substituted pyridines have been developed as nucleophilic catalysts for a variety of synthetically important transformations such as the acylation of alcohols, amines, and enolates.[1,2] Using chiral pyridine derivatives based on DMAP ((4-dimethylamino)pyridine, **2**) or PPY ((pyrrolidino)pyridine, **3**) major advances have recently been made in kinetic resolution experiments, in particular in those involving secondary alcohols as substrates.[2] The design of these catalysts requires a delicate balance between two partially opposing effects: (a) the use of steric effects for the shielding of parts of the reaction center and thus the control over the conformational space of the selectivity-determining transition states; and (b) the rate enhancement of substrate turnover as compared to the uncatalyzed background reaction. In order to avoid an overly large reduction of the rate of the catalyzed process through steric effects, some of the catalyst designs involve the use of stacking interactions between the core pyridine ring and some side chain functional groups. How these interactions can lead to enhanced rates and to enhanced control of the conformational space at the same time can be illustrated with the minimal two-step sequence for the catalyzed group-transfer process in Scheme 1.



Scheme 1

Initial reaction of the catalyst **A** with the electrophilic reagent RX (with R often being an acyl group) generates the cationic intermediate **B**. Subsequent reaction of **B** with the nucleophilic reagent Y^- regenerates the catalyst **A** and produces the product RY. Intermediate **B** is usually not detected directly under experimental conditions, but most indirect evidence points to the fact that the first of these steps is fast and reversible as compared to the second, product-forming step. Stabilization of intermediate **B** through stacking interactions will under these conditions translate into an overall enhanced rate of reaction. That the stacking interactions are more favorable at the pyridinium cation stage **B** than in the neutral catalyst is plausible in systems containing electron-rich π-systems connected to the pyridine ring through a flexible linker unit.

While this concept appears to be intuitively appealing, there is limited direct experimental evidence supporting its existence and its effectiveness in accelerating group transfer reactions beyond what is known from simpler pyridine catalysts **1–5** already (Scheme 2).[3–6] Kawabata and coworkers have studied catalyst **6** and its acyl intermediate using ^{1}H NMR in $CDCl_3$ at 20 °C.[7a] Based on an analysis of the chemical shift and NOE data, an "open" conformation with little interaction between the pyridine nucleus and the naphthalene π-system was predicted for **6** in its neutral form and a "closed" conformation for the acylpyridinium cation formed from **6** and isobutyryl chloride. The chemical shift data also indicate that the pyridine ring is conformationally flexible in neutral **6** (leading to identical resonances for the C2/C6 and C3/C5 protons), but conformationally restricted in the corresponding acyl intermediate (giving four different signals for the four pyridine protons). No spectroscopic data appear to exist for the acyl intermediates of **7** and **8**. However, **8** has been found to give slightly better selectivities than **7** in kinetic resolution experiments of alcohols.[11] Yamada and coworkers have studied catalyst **9** and its alkyl- and acyl-pyridinium derivatives by ^{1}H NMR measurements.[8] Through comparison to model compounds lacking the thiocarbonyl moiety it was concluded that acylation of **9** leads to a "conformationally locked" pyridinium cation involving stacking interactions between the pyridinium nucleus and the thiocarbonyl bond. Calculations performed on the isobutyrylpyridinium-cation of **9** at the B3LYP/6-31G(d) level of theory also show that these intermediates have clear conformational preferences with respect to the orientation of the *tert*-butyl side chain. Theoretical studies of the conformational space of catalyst **10** at the PM3 level as well as the X-ray crystal structure of protonated **10** show that the π-systems contained in **10** are connected in a rather rigid manner.[9] This excludes the conformational rearrangement described in Scheme 1. According to temperature-dependent ^{1}H NMR studies of the acetyl intermediate of **10** the acetyl C–O bond points away from the substituent at C3. Finally, Connon's PPY derivative **11** represents a synthesis of the motives contained in **8** and **9** in that it replaces

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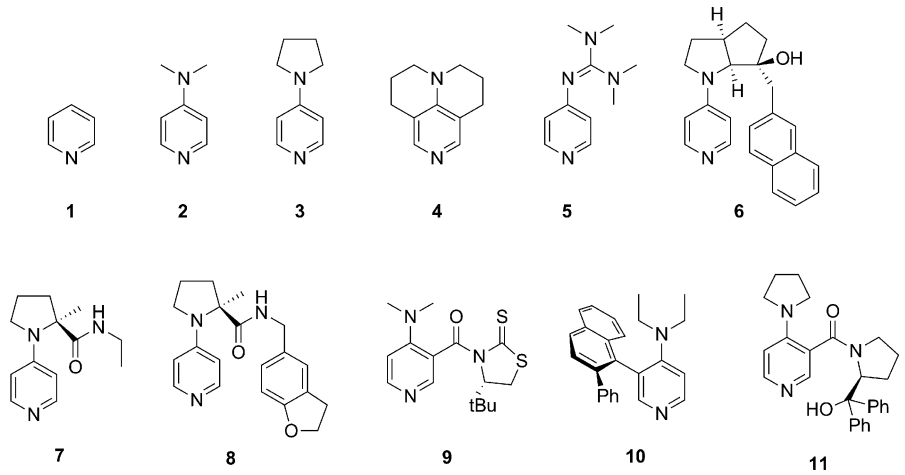


Scheme 2

the thiocarbonyl group of catalyst **9** with aryl substituents, whose π–π stacking interactions with the pyridinium may be more rationally planned.[10] ^{1}H NMR measurements and calculations performed at the B3LYP/6-31G(d) level of theory converge on a preferred conformation of the acyl intermediate of **11** with a side-on conformation of the side-chain phenyl groups and the pyridine ring C(2)–H bond.

In order to probe the involvement of stacking interactions in catalysts based on the pyridine nucleus in a systematic manner, we are studying here a series of these catalysts using several different theoretical methods. For the sake of reference we also include in this study several achiral pyridine derivatives, whose catalytic potential has been tested in the past, such as pyridine (**1**), DMAP (**2**), PPY (**3**), tricyclic DMAP-derivative **4**,[3,5,6] and the 4-guanidylpyridine **5**.[4] The group of chiral pyridine derivatives involves the PPY-derivative **6** by Kawabata and coworkers,[7] two PPY-derivatives **7** and **8** by Campbell and coworkers,[11] the thiourea-substituted system **9** by Yamada and coworkers,[8] and the axially chiral DMAP-derivative **10** by Spivey and coworkers.[9]

Results and discussion

Selection of methods

It is known from theoretical studies of supramolecular complexes of a variety of π-systems such as benzene, naphthalene and the DNA bases that a correct description of dispersion interactions is required already at the stage of geometry optimization.[12,13] It is widely recognized that Hartree–Fock calculations describe dispersion interactions rather poorly due to their neglect of correlation effects. Good results are often obtained already at the MP2 level. An overestimation of dispersion forces observed in some cases at this latter level can be remedied either through more highly correlated single reference approaches such as CCSD(T)[13] or through rescaling the MP2 correlation energies according to the SCS-MP2 procedure.[12b,12c,12e,15] Unfortunately, gradient-corrected density functional methods such as BLYP and hybrid functionals such as Becke3LYP are not able to describe dispersion interactions correctly in a systematic fashion due the essentially local design of these functionals.[12] How far a correlated treatment is also required for the correct description of conformational properties of the catalysts under study here is investigated using catalyst **6** as a test case. A rigorous conformational search has first been performed for **6** and its acetyl intermediate, identifying 24 conformers for neutral **6** and 54 conformers for the corresponding acetyl intermediate **6Ac** at the B3LYP/6-31G(d) level of theory. The potential of this level of theory was tested in earlier studies of the catalytic potential of pyridine bases.[3,5,6] Based on the Boltzmann-averaged enthalpies calculated at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level approximately 30 conformations make a significant contribution (>1%) to the conformational ensemble at 298 K, the energetically most favorable conformer of **6Ac** contributing 9.5%. The existence of stacked conformations in pyridinium cations can be determined in structural terms using the distance between the center of the pyridine ring and the center of the closest lying six membered aromatic ring (as indicated in Fig. 1). This distance amounts to 5.20 Å in the most favorable conformer optimized at the B3LYP/6-31G(d) level, which is NOT a π–π stacking structure and does not agree with the spectroscopic studies mentioned above.[7] More problematic is the fact that none of the other 52 conformational isomers found at the B3LYP level shows any type of stacking interactions. Repeating the conformational search at the RHF/3-21G level[14] again yields a large number of conformational isomers for **6Ac** (52 structures), this time including stacked conformations. Additional consideration of MP2(FC)/6-31G(d) single point energies makes one of the stacked conformations the energetically most favorable one. In order to verify that this single point approach does not lead to artefactual results, the six best conformations obtained at the MP2(FC)/6-31G(d)//RHF/3-21G level have been reoptimized at the MP2(FC)/6-31G(d) level. The results collected for these conformers in Table 1 indicate that the relative ordering is identical at both levels.

The stacked conformation **6Ac-1** is even more stabilized when relative energies are calculated at the MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G(d) level, predicting an energy gap in excess of 10 kJ mol^{-1} between stacked and non-stacked conformations. Application of the SCS-MP2 scaling protocol[15] to the MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G(d) energies for **6Ac** does indeed reduce the energy difference between stacked and other conformations to 4.9 kJ mol^{-1}, while the relative conformational ordering remains approximately the same as before (Table 1).

Table 1 Relative enthalpies (in kJ mol^{-1}) for selected conformers of **6Ac** at different levels of theory

No.	ΔH_{298} HF/ 3-21G	ΔH_{298} HF/ MIDI!	ΔH_{298} MP2/6-31G(d)// HF/3-21G	ΔH_{298} MP2/6-31G(d)// HF/MIDI!	ΔH_{298} MP2/ 6-31G(d)	ΔH_{298} MP2/6-311+G(d,p)// MP2/6-31G(d)	ΔH_{298} SCS-MP2/6-311+G(d,p)// MP2/6-31G(d)
6Ac-1	18.30	12.33	0	0	0	0	0
6Ac-2	0	0	1.24	2.30	0.63	11.53	4.90
6Ac-3	8.95	4.39	3.09	6.24	2.05	14.46	8.25
6Ac-4	2.81	2.79	3.66	5.39	5.79	14.61	9.00
6Ac-5	10.18	5.88	6.05	8.11	12.76	27.63	17.75
6Ac-6	14.27	13.67	6.07	8.33	13.25	24.56	17.94

Fig. 1 Structures of the energetically most favorable conformers of catalyst **6** and its acetylated form **6Ac** as optimized at the MP2(FC)/6-31G(d) level of theory. Distances are given in Ångstroms.

Finally, we have also tested geometry optimizations at the RHF/MIDI! level in combination with MP2/6-31G(d) single point calculations as the basis of conformational searches. Despite the fact that the MIDI! basis set[16] yields better structural data as compared to the smaller 3-21G basis set, there is no significant improvement here as compared to MP2(FC)/6-31G(d)//RHF/3-21G. We may thus conclude that the sequence of full conformational screening at the MP2(FC)/6-31G(d)//RHF/3-21G level, reoptimization of the best conformers at MP2(FC)/6-31G(d) level, and calculation of SCS-MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G(d) single point energies for the best conformers appears to represent the best protocol for the determination of high level results. The following discussion of structural properties of catalysts **6–10** and their acetyl intermediates is therefore based on the results obtained in this fashion.

Conformational properties of acylpyridinium-cations

The energetically most favorable conformer of catalyst **6** is shown in Fig. 1 together with the two best conformers of the acetyl intermediate **6Ac**.

In the more favorable of these latter structures **6Ac-1** the naphthalene ring is positioned quite ideally on top of the pyridinium ring, while the second best conformer **6Ac-2** may best be described as "side-on" in the sense that the C–H bonds of the pyridinium ring point towards the naphthalene π-system. The different relative orientation of the two π-systems is clearly reflected in the different values of the stacking parameter (3.25 *vs.* 4.47 Å, Table 2), but has little effect on other key structural variables such as the C–N bond distance between acetyl group and pyridine ring (1.471 *vs.* 1.473 Å).

This latter bond distance has earlier been found to be a sensitive structural probe for the stability of the acetyl intermediates of differently substituted pyridines as exemplified in Table 2 with the values for catalysts **1–5**.[6] For these latter systems a good correlation is also found between the overall charge of the acetyl group and the C–N bond distance, with shorter bonds correlating with lower overall (positive) charges. However, the charge of the acetyl group is largely constant for the six best conformers of **6Ac** as are the respective C–N bond distances (Table 2). This implies that the energy differences between these conformers (up to 18 kJ mol^{-1}) do not result from differences in the stabilization of the overall positive charge of the system. One further difference between **6Ac-1** and **6Ac-2** concerns the orientation of the acetyl group oxygen atom, which points in the direction of the naphthalene side chain in **6Ac-1** and in the opposite direction in **6Ac-2**. The former orientation had been predicted by Kawabata *et al.* based on NOE measurements between the acetyl group hydrogen atoms and the pyridine ring protons.[7] Aside from the stacked and side-on conformers described in Table 2 and Fig. 1 additional structures of **6Ac** exist in which the naphthalene ring is rotated away from the pyridine ring with stacking parameters beyond 6 Å. These structures contribute very little to the conformational ensemble at 298 K (<1%) and are therefore not explicitly discussed here. In conclusion it is only conformer **6Ac-1** which is in line with all direct and indirect conclusions derived from the NMR data for this system. The most favorable conformer found for the neutral catalyst **6** can best be described as "T-shaped". This structure alone is insufficient to explain the rapid interconversion of the C2–C6 protons of the pyridine ring in **6**, but not in **6Ac**. However, one major difference between these two systems is the much shorter (1.337 *vs.* 1.408 Å) and thus stronger C–N bond connecting the pyridine ring to the amino-substituent at C4. Rotation around this bond (which has partial double bond character in **6Ac**, but not in **6**) is required for rapid equilibration of the hydrogen atoms on the two sides of the pyridine ring and the barrier for rotation around this bond is certainly higher in **6Ac** than in **6**.

The conformational properties of the acetyl intermediates of catalysts **7–10** can easily be classified based on the structures shown in Fig. 2 and the structural and charge data in Table 2.

A comparison of the related systems **7** and **8** shows that **8** contains a π-system capable of stacking interactions, while **7** does not. A close contact between the pyridinium π-system and the benzene ring contained in the amide side chain of **8Ac** is indeed visible in the energetically most favorable conformer of this system displayed in Fig. 2. However, the distance between the ring midpoints of 3.50 Å is significantly longer than the distance between the acetyl group and the oxygen atom of the dihydrobenzofuran side chain of 2.76 Å. This latter contact appears to originate from electrostatic complementarity of the most electronegative center

Table 2 Structural and electronic characteristics of acetyl intermediates of catalysts **1–10**

System	R(C–N)[a]/Å RHF/3-21G	R(C–N)[a]/Å MP2/6-31G(d)	q(Ac)[b] NPA	q(Ac)[c] NPA	Stacking parameters[d]/Å HF/3-21G	Stacking parameters[d]/Å MP2/6-31G(d)	ΔE^e/kJ mol^{-1}	$\Delta E'$/kJ mol^{-1}
1Ac	1.500	1.540	+0.368	+0.380	—	—	—	—
2Ac	1.459	1.486	+0.303	+0.314	—	—	—	—
3Ac	1.456	1.482	+0.296	+0.307	—	—	—	—
4Ac	1.451	1.478	+0.287	+0.298	—	—	—	—
5Ac	1.445	1.472	+0.273	+0.287	—	—	—	—
6Ac-1	1.448	1.471	+0.281	+0.285	3.57	3.25	0.0	0.0
6Ac-2	1.447	1.473	+0.279	+0.287	5.23	4.47	11.53	4.90
6Ac-3	1.448	1.474	+0.280	+0.289	5.18	4.60	14.46	8.25
6Ac-4	1.447	1.471	+0.279	+0.287	5.32	4.29	14.61	9.00
6Ac-5	1.448	1.472	+0.279	+0.288	5.20	4.65	27.63	17.75
6Ac-6	1.451	1.478	+0.285	+0.296	4.70	4.57	24.56	17.94
7Ac	1.453	1.478	+0.291	+0.301	—	—	—	—
8Ac-1	1.458	1.481	+0.290	+0.293	3.68	3.50	0.0	0.0
8Ac-2	1.458	1.482	+0.284	+0.292	4.51	4.41	12.69	7.59
9Ac-1	1.457	1.480	+0.299	+0.307	3.83	3.77	0.0	0.0
9Ac-2	1.458	1.481	+0.301	+0.309	3.83	3.81	0.48	0.78
10Ac-1	1.450	1.477	+0.294	+0.299	4.41	4.44	0.0	0.00
10Ac-2	1.450	1.476	+0.295	+0.298	4.32	4.39	1.86	1.74

[a] Bond distance between pyridine nitrogen and acetyl carbon atoms. [b] NPA/MP2/6-31G(d)//HF/3-21G charges. [c] NPA/MP2/6-31G(d)//MP2/6-31G(d) charges. [d] Distance between the center of the pyridine ring and the center of the closest aromatic ring (or C=S group). [e] Energy differences (in kJ mol^{-1}) between conformers calculated from H_{298}(MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G) data. [f] Energy differences (in kJ mol^{-1}) between conformers calculated from H_{298}(SCS-MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G) data.

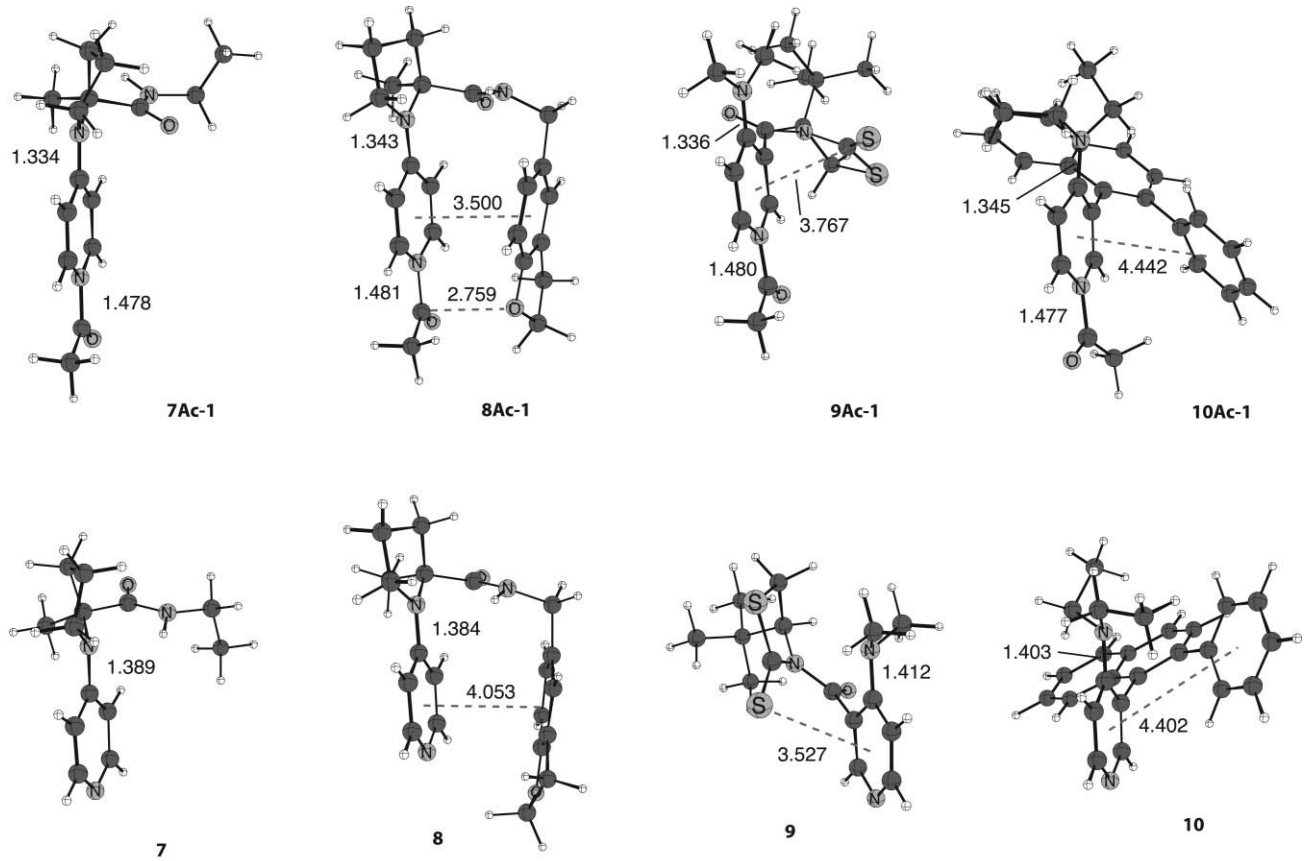
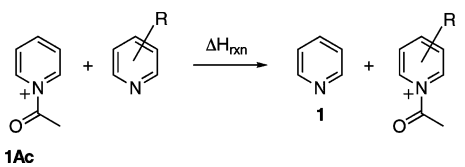


Fig. 2 Structures of the energetically most favorable conformers of catalysts **7**, **8**, **9**, and **10** and their respective acetylated forms as optimized at the MP2(FC)/6-31G(d) level of theory. Distances are given in Ångstroms.

of the side chain and the partially positively charged acetyl group in **8Ac**. It is clear from this description that further variation of the side chain heteroatoms may result in even stronger electrostatic interactions, implying more stable acetyl intermediates and better conformational control. The second best conformer of **8Ac-2** orients the side chain in a side-on fashion to the pyridinium ring and is less stable than **8Ac-1** by 7.6 kJ mol^{-1}. Catalyst **9** differs from the previous systems in that close contacts between the pyridine ring and parts of the side chain (here: the thiocarbonyl group) exist at both the neutral and the cationic stage. The stacking distance is even smaller for neutral **9** than for **9Ac**. One major difference between the neutral and cationic forms of **9** concern the orientation of the *tert*-butyl group, which points towards the dimethylamino group in acetyl-intermediate **9Ac**, and in the opposite direction in neutral catalyst **9**. Non-stacking conformations are energetically very unfavorable for both species. The isobutyryl intermediate of catalyst **9** has been studied earlier by NOE experiments and calculations at the B3LYP/6-31G(d) level.[8] The orientation of the *tert*-butyl side chain is directly comparable to what is found here for the acetyl intermediate. However, while no significant conformational preference exists for the acetyl group in **9Ac** (*syn* and *anti* conformer differ by less than 1 kJ mol^{-1} at all levels studied here), a clear preference for an *anti* conformation (pointing the carbonyl oxygen atom away from the substituent at C3) has been found experimentally for the isobutyryl group. No stacking interactions between the pyridine ring and the phenyl side chain exist in the neutral or cationic forms of catalyst **10**. Still the rigid phenylnaphthyl side chain has clear conformational preferences at both stages, orienting the phenyl substituent towards the acetyl group in cation **10Ac** and towards the diethylamino group in neutral **10**. The most favorable orientation of the acetyl group in **10Ac-1** is in line with the assignment made for the situation in solution based on ^{1}H NMR spectroscopic results.[9d]

Reaction enthalpies for acetyl group transfer

The stability of acetyl intermediates of catalysts **1–10** has been assessed using the reaction enthalpy at 298.15 K for the isodesmic reaction (1) shown in Scheme 3.



Scheme 3

Previous results for catalysts **1–5** have been obtained at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level of theory. Given the problematic performance of this level in describing the conformational properties of the larger catalysts **6–10** we concentrate

here on the results obtained from calculations at Hartree–Fock and MP2 levels of theory (Table 3).

Perusal of the results for the non-stacking catalysts **1–5** shows a clear trend to smaller reaction enthalpies on going from the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) to the MP2(FC)/6-31G(d)//RHF/3-21G level. This reduction is still visible when MP2(FC)/6-31G(d) optimized geometries are used and thus reflects the intrinsic properties of the MP2 method. Additional consideration of SCS-MP2 single point energies calculated with the large 6-311+G(d,p) basis set predicts practically the same values. Comparison of the results obtained from the most economical and the most expensive MP2 versions considered here (MP2(FC)/6-31G(d)//RHF/3-21G *vs.* SCS-MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G(d)) shows these to be strikingly similar for most systems. The relative ordering of the stabilities of catalysts **1–5** is practically identical at all levels selected here with one exception: while catalyst **5** is predicted to give more stable intermediates than catalyst **4** at the Hartree–Fock and B3LYP levels, largely similar values are obtained at the MP2 levels for both systems.

Turning to the results obtained for catalysts **6–10** we note that the two "π-stacking" catalysts **6** and **8** give particularly stable acetyl intermediates. The actual stability values for these two systems depend much more on the computational level than those for all other systems. Concentrating on the results obtained at the SCS-MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G(d) level, the most stable acetyl intermediate is formed by catalyst **6** (−120.9 kJ mol^{-1}). The magnitude of the correlation contribution to this reaction energy of 30.0 kJ mol^{-1} (obtained as the difference between SCS-MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G(d) and RHF/6-311+G(d,p)//MP2(FC)/6-31G(d) energies) is in clear support of strong dispersion interactions[12b] between the naphthalene side chain and the pyridinium ring system in **6Ac**.

The involvement of π-stacking interactions in acyl intermediates of catalyst **8** can be assessed through comparison to catalyst **7**, whose acetyl intermediates differ in stability by 20.5 kJ mol^{-1}. To equate this difference to the magnitude of dispersion interactions is, however, not correct considering the stability difference between **7** and **8** of 20.0 kJ mol^{-1} predicted at RHF/6-311+G(d,p)//MP2(FC)/6-31G(d) level. The absence of a notable correlation effect on the stabilization energies together with the structural characteristics for the acetyl intermediate **8Ac-1** noted above suggests that the higher stabilization energy of **8Ac** as compared to **7Ac** is mainly due to electrostatic effects between the acetyl group and the side chain. Stacking interactions appear not to play a prominent role in catalysts **9** and **10**. In catalyst **9** the balance between the inductive electron-withdrawing power of the acyl substituent at C3 of the pyridine ring and the stacking interactions between thiocarbonyl group and the pyridine ring in its cationic form appear to result in net destabilization compared to DMAP **2**. That dispersion interactions are indeed not decisive for the stabilization of **9Ac** relative to **9** is also reflected in a negative correlation contribution of −2.2 kJ mol^{-1} for this system. In catalyst **10** this is certainly due to the rigid σ-bond framework preventing the large-scale conformational rearrangement described in Scheme 1, but inductive substituent effects appear to be sufficiently large to make the acetyl intermediate **10Ac** quite stable even in the absence of stacking interactions. With respect to the general reaction scheme described in Scheme 1 we may expect

Table 3 Stabilities of acetyl intermediates of catalysts **1–10** as expressed through the heat of reaction ΔH_{rxn} of isodesmic reaction (1) at 298.15 K (in kJ mol^{-1})

System	ΔH_{rxn} RHF-1[a]	ΔH_{rxn} RHF-2[a]	ΔH_{rxn} B3LYP-1[a]	ΔH_{rxn} B3LYP-2[a]	ΔH_{rxn} MP2-1[a]	ΔH_{rxn} MP2-2[a]	ΔH_{rxn} MP2-3[a]	ΔH_{rxn} MP2-4[a]	ΔH_{rxn} MP2-5[a]	ΔH_{rxn} RHF-4
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	−89.24	−85.47	−82.54	−82.08	−78.97	−77.19	−77.67	−76.16	−78.77	−82.79
3	−99.67	−95.15	−93.42	−93.1	−88.49	−89.21	−89.84	−86.20	−89.11	−94.39
4	−110.58	−102.07	−107.06	−108.9	−101.75	−100.60	−101.51	−99.48	−101.41	−107.27
5	−117.76	−106.46	−114.27	−113.1	−99.98	−102.17	−99.22	−94.74	−98.50	−115.73
6	−116.22	−104.36	−110.84	−110.19	−109.77	−109.91	−119.16	−130.32	−120.93	−90.96
7	−87.56	—	—	—	−81.95	—	−84.60	−82.36	−85.37	−90.00
8	−113.30	—	—	—	−114.44	—	−106.08	−110.43	−105.78	−110.01
9	−80.27	—	—	—	−69.48	—	−69.76	−70.28	−74.03	−76.27
10	−109.18	—	−102.89	−105.25	−92.31	—	−92.93	−91.03	−93.09	−96.34

[a] The following abbreviations have been used: "RHF-1" = RHF/3-21G//RHF/3-21G; "RHF-2" = RHF/MIDI!; "B3LYP-1" = B3LYP/6-31G(d)//B3LYP/6-31G(d); "B3LYP-2" = B3LYP/6-311+G(d,p)//B3LYP/6-31G(d); "MP2-1" = MP2(FC)/6-31G(d)//RHF/3-21G; "MP2-2" = MP2(FC)/6-31G(d)//RHF/MIDI!; "MP2-3" = MP2(FC)/6-31G(d)//MP2(FC)/6-31G(d); "MP2-4" = MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G(d); "MP2-5" = SCS-MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G(d); "RHF-4" = RHF/6-311+G(d,p)//MP2/6-31G(d).

catalysts **6**, **7**, **8**, and **10** to be more reactive than DMAP (**2**) at ambient temperature or above since their acetyl intermediates are more stable than that of DMAP.

Conclusions

The conformational preferences of catalysts **6–10** studied at the SCS-MP2(FC)/6-311+G(d,p)//MP2(FC)/6-31G(d) level are in line with the limited existing experimental data available for these systems. Stacking conformations dominate the appearance of the acetylpyridinium intermediates of catalysts **6**, **8**, and **9**. Dispersion interactions are mainly responsible for this situation in **6Ac**, while electrostatic effects dominate in **8Ac**. The conformational preferences of the acetyl intermediates of **9** and **10** are mainly enforced by the rigidity of the σ-framework, leading to a stacking conformation in **9Ac** and a non-stacking conformation in **10Ac**. Still, large conformational changes occur in both of these latter systems on formation of the acetyl intermediate, supporting the "conformational switch" picture derived from experimental ^{1}H NMR studies.

In methodological terms we have shown that studies of the acetyl intermediates of catalysts **6–10** require correlated levels, the MP2(FC)/6-31G(d)//RHF/3-21G level providing a reasonable lower limit of effort. DFT methods such as the popular B3LYP hybrid functional are not able to describe stacking interactions induced through dispersion interactions properly.

Theoretical methods

The conformational space of all systems studied here has initially been studied with the OPLS-AA force field as implemented in BOSS 4.6.[17] Potential parameters for the description of 4-aminopyridines and their acetylpyridinium cations are currently not part of the default OPLS-AA force field.[18] The nitrogen atom attached to C4 of the pyridine ring has therefore been defined as a new nitrogen atom type. Appropriate force field parameters for the neutral catalysts and the acetylpyridinium cations have then been developed from a series of *ab initio* calculations at the B3LYP/6-31G(d) and MP2/6-31G(d) level of theory (see supplemental material for details†). Coulomb parameters have been derived using the CM1 procedure with the AM1 wavefunction. The conformational space of both types of species has then been searched using the Monte Carlo conformational search facility implemented in BOSS 4.6.

All conformers identified in this way have subsequently been reoptimized at the RHF/3-21G(*) level of theory. For some of the systems optimizations at the RHF/MIDI! and B3LYP/6-31G(d) levels of theory have also been performed. Finally, geometry optimizations have been performed at the MP2(FC)/6-31G(d) level for the best conformers identified at the MP2(FC)/6-31G(d)//RHF/3-21G level. For the best conformers identified at fully optimized MP2(FC)/6-31G(d) level additional single point calculations have been performed at the MP2(FC)/6-311+G(d,p) level of theory. The correlation energies calculated at this latter level have been rescaled following the SCS-MP2 procedure described by Grimme.[15]

In all cases default convergence criteria have been used. Thermochemical corrections to enthalpies at 298.15 K (H_{298}) have been calculated at the same level as that used for geometry optimization. The only exception concerns geometries optimized at the MP2(FC)/6-31G(d) level. In this latter case thermochemical corrections have been taken from the HF/3-21G(*) level. All calculations have been performed with Gaussian 03.[19]

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