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Methyl Cation Affinities of Commonly Used Organocatalysts

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Abstract: Methyl cation affinities (MCAs) and proton affinities (PAs) of a variety of N- and P-based organocatalysts have been calculated at the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level of theory. Correlations between MCA and PA values have been used to identify factors leading to the potentially poor predictive value of PA data for organocatalytic activity. One of the relevant factors concerns steric effects between organocatalysts and the reactant electrophiles, which are not well-modeled by reaction with a proton. A second important factor concerns systematic differences in bond strengths between second- and third-row elements. This latter point makes MCA values much better descriptors of the catalytic activity of phosphanes than PA or pK_a data.

Introduction

Organocatalytic transformations have recently developed into a new, rapidly growing facet of stereoselective catalysis.[1] The catalysts used in these reactions are often directly taken from the chiral pool (such as amino acids or cinchona alkaloids) or are simple nitrogen or phosphorus bases. Rationalization of the selectivity and activity of these catalysts is made difficult due to the mechanistic complexity of these transformations and a dearth of appropriate quantitative studies. Most of these catalysts are nucleophilic in nature and questions of relative activity have therefore been approached on the basis of relative proton affinity (PA) or basicity data. However, most of the organocatalytic transformations involve nucleophilic attack at carbon and we are showing here that methyl cation affinity (MCA) values are much better descriptors of catalytic activity than either proton affinity (PA) or pK_a values. MCA and PA data are defined in this context as the reaction enthalpies for the transformations shown in eqs 1a and 1b. Using a theoretical procedure recently identified to provide accurate methyl cation affinities even for large molecular systems,[2] we provide here a set of computed MCA values for a wide variety of N- and P-based organocatalysts. Correlations between MCA and PA values have then been used to identify factors leading to the potentially poor predictive value of PA or pK_a data (Scheme 1).

Results and Discussion

Figure 1 compiles the MCA values for nitrogen and phosphorus nucleophiles listed in Table 1 in a graphical manner.

Scheme 1

$$\text{H-Nuc}^+ \xrightarrow{\text{PA}} \text{H}^+ + \text{Nuc} \qquad (1a)$$

$$\text{CH}_3\text{-Nuc}^+ \xrightarrow{\text{MCA}} \text{CH}_3^+ + \text{Nuc} \qquad (1b)$$

The MCA of pyridine (**1**) is rather low at 518.7 kJ mol^{-1} but can be enhanced considerably by donor substituents at the C4-position as in 4-(dimethylamino)pyridine (4-DMAP, **27**), 4-pyrrolidinopyridine (PPY, **29**), 4-(tetramethylguanidyl) pyridine (**25**), anellated pyridine derivative **32**, and the 3,4-diaminopyridine **33**.[3] Enlargement of the π-system through benzoanellation as in quinoline (**4**) also leads to higher MCA values, as does substitution of **4** with methyl and methoxy substituents (as in **10** and **16**). The MCA value for **10** of 542.7 kJ mol^{-1} is significantly smaller than that for methyl cation addition to the quinoline nitrogen in the cinchona alkaloids cinchonidine (**12**) and cinchonine (**13**).

In the absence of any specific interactions between the methyl group attached to the quinoline nitrogen and the chiral substituent located at C4, this difference of around 10 kJ mol^{-1} reflects differences in the polarizability of **10** and **12**/**13**. The very similar values obtained for **12** and **13** (552.1 vs 552.4 kJ mol^{-1}) indicate that the stereochemistry at the C8/C9 centers has little influence on the stability of methyl cation adducts. This observation can also be made for the MCA values for the quinoline nitrogen atoms in quinidine (**18**) and quinine (**22**) at 561.8 and 563.9 kJ mol^{-1}. The absolute values are now much larger than those for **12** and **13** due to the methoxy substituent

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(1) For reviews see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811−891. (b) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985−3012. (c) List, B. *Acc. Chem. Res.* **2004**, *37*, 548−557. (d) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601−610. (e) Method, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035−1050. (f) Vedejs, E.; Jure, M. *Angew. Chem.* **2005**, *117*, 4040−4069; *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 3971−4001. (g) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719−724.
(2) Wei, Y.; Singer, T.; Mayr, H.; Sastry, G. N.; Zipse, H. *J. Comput. Chem.* **2008**, *29*, 291−297.
(3) The MCA differences between pyridines **1**, **25**, **27**, **29**, and **32** are slightly smaller than those found earlier for reaction with the acetyl cation.[4,5] The MCA values for **1**, **27**, and **29** are much larger in absolute terms than the affinity of these pyridines toward the benzhydrylium cation,[6] but the affinity differences are rather comparable for both cations.
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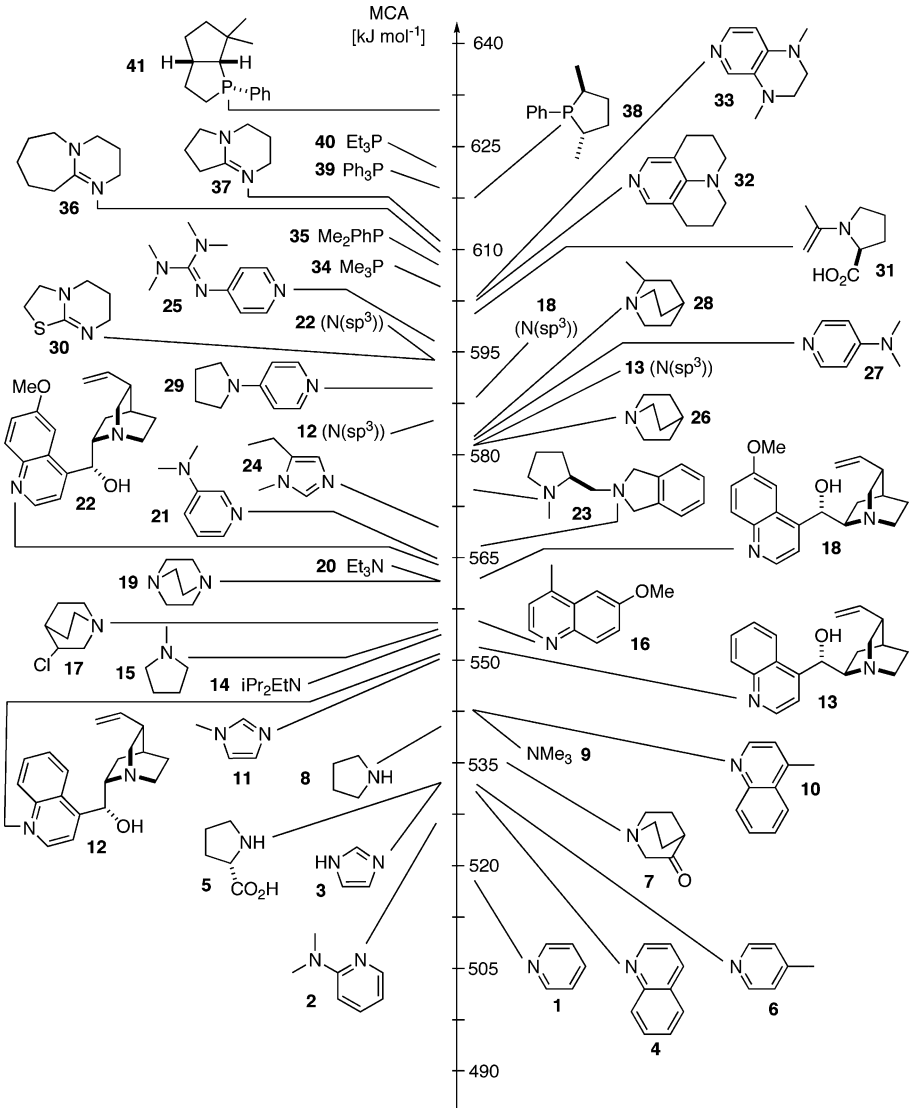

Figure 1. Structures of N- and P-centered organocatalysts ordered by their MCA values.

at C6 position of the quinoline ring. The MCAs of imidazoles are intrinsically somewhat higher than those of pyridines. Addition of alkyl substituents to the parent system **3** as in *N*-methylimidazole (**11**) and in 1-methyl-5-ethylimidazole (**24**) enhance the methyl cation affinity quite significantly, leading to a MCA of 569.1 kJ mol^{-1} for **24**.[1d] The methyl cation affinities of tertiary aliphatic amines are mainly guided by the structure of the alkyl groups and their potential to stabilize positive charge through inductive effects. The lowest MCA is therefore obtained for trimethylamine (**9**), the values for triethylamine (**20**) and quinuclidine (**26**) being larger by 19.7 and 38.0 kJ mol^{-1}, respectively. The MCA of Huenig base (**14**) is actually lower than that for **20**, due to steric repulsion between the methyl cation and the isopropyl substituents. The cation-stabilizing effects of alkyl substituents can be reduced through introduction of electron-withdrawing substituents as in DABCO (**19**), 3-chloroquinuclidine (**17**), and 3-quinuclidinone (**7**). The MCA values for the quinuclidine nitrogen centers in the cinchona alkaloids **12** and **13** are both very similar to that of quinuclidine (**26**) itself, again indicating little influence of the stereochemistry at the C8 and C9 positions on adduct formation. Addition of a methoxy substituent to the quinoline ring has a surprisingly large influence on the methyl cation affinities of the quinuclidine nitrogen atom in cinchona alkaloids. This enhancement amounts to 8 kJ mol^{-1} in **13**/**18** and to 10 kJ mol^{-1} in **12**/**22**. The quinuclidine nitrogen atom in quinine (**22**) thus represents the center of highest MCA at 594.7 kJ mol^{-1} in the cinchona alkaloid systems considered here. A similar observation has been made in binding affinity measurements of cinchona alkaloids toward OsO_4.[7] The much higher MCA values of the quinuclidine nitrogen atoms in cinchona alkaloids as compared to the respective quinoline nitrogen atoms are, of course, in agreement with the outcome of alkylation reactions, which exclusively favor alkylation of the N(sp^3) nitrogen atom.

The largest MCA values calculated here are those for the amidine bases such as DBU (**36**) and DBN (**37**), the sulfur-substituted derivative **30**,[8] and tertiary phosphanes. A very large difference in MCA values exists between phosphanes and amines of identical substitution pattern, the difference between trimethylamine (**9**) and trimethylphosphane (**34**) amounting to 61.6 kJ mol^{-1}. The MCA of phosphanes can be enlarged further

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Table 1. Methyl Cation Affinity (MCA) and Proton Affinity (PA) Values of Organocatalysts (in kJ mol^{-1})

system	MCA (MP2[a])	PA (MP2[a])	MCA/PA (MP2[a])
1	518.7	922.6	0.562
2 (pyridyl N)	526.7	961.3	0.548
3 (N3)	531.7	935.8	0.568
4	531.8	941.7	0.565
5 (N)	532.4	939.2	0.567
6	532.8	938.7	0.567
7	535.2	934.7	0.573
8	539.8	949.8	0.568
9	542.6	948.0	0.572
10	542.7	954.2	0.569
11 (N3)	550.0	956.5	0.575
12 (N(sp^2))	552.1	964.1	0.573
13 (N(sp^2))	552.4	964.8	0.573
14	553.8	994.1	0.557
15	554.6	959.9	0.578
16	555.7	967.9	0.574
17	555.9	955.0	0.582
18 (N(sp^2))	561.8	974.9	0.576
19	562.2	962.1	0.584
20	562.3	979.2	0.574
21 (pyridyl N)	563.4	970.8	0.580
22 (N(sp^2))	563.9	976.5	0.577
23 (isoindolyl N)	565.6	1006.0	0.562
24	569.1	976.5	0.583
23 (pyrrolidyl N)	574.8	1009.7	0.569
25 (guanidyl N)	576.2	1000.9	0.576
26	580.6	980.8	0.592
13 (N(sp^3))	580.8	995.0	0.584
27 (pyridyl N)	581.2	994.1	0.585
28	582.0	989.9	0.588
12 (N(sp^3))	584.8	993.0	0.589
18 (N(sp^3))	588.6	1002.3	0.587
29 (pyridyl N)	590.1	1004.4	0.588
30 (N(sp^2))	594.4	1010.9	0.588
22 (N(sp^3))	594.7	1001.8	0.594
25 (pyridyl N)	597.5	1013.5	0.590
31 (C(sp^2))	599.2	1008.9	0.594
32 (pyridyl N)	602.4	1017.0	0.592
33	602.5	1014.5	0.594
34	604.2	950.9	0.635
35	608.5	957.8	0.635
36 (N(sp^2))	609.6	1044.8	0.583
37 (N(sp^2))	611.3	1032.5	0.592
38	617.8	968.8	0.638
39	618.4	966.4	0.640
40	622.4	972.9	0.640
41	630.7	981.7	0.642

[a] MP2(FC)/6-31+G(2d,p)//B98/6-31G(d).

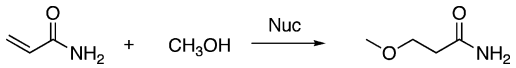
through introduction of appropriate aromatic and aliphatic substituents. How these motifs can be combined into the design of chiral catalysts has recently been demonstrated with phosphanes **38** and **41**.[9]

How do these MCA values compare to the respective proton affinities? The correlation of MCA and PA values in Figure 2 shows that there is a good qualitative correlation of both measures of electrophilic affinity.

However, two factors appear to lead to deviations from this correlation. The first of these factors concerns steric effects, which are larger for the addition of methyl cations than for protons. As indicated in Figure 2 for **2**, **14**, **23**, and **36** these effects lead to MCA values smaller than would be expected on the basis of their PA.[10] This is hardly surprising for Huenig base **14**, whose design implies its use as a sterically hindered, nonnucleophilic base. Compounds **23** and **36**, however, are frequently used in organocatalytic processes, and the steric effects visible in Figure 2 may thus affect the rates.

Most carbon electrophiles used in organocatalytic transformations are certainly larger than the methyl cation, and one must anticipate that steric effects will be even larger in synthetically relevant transformations than calculated here. The second factor concerns electronic effects when comparing nitrogen and phosphorus bases. The latter are located on a different correlation line shifted to lower PA values by approximately 70 kJ mol^{-1}.[10,11] This implies that tertiary phosphanes such as PPh_3 (**39**) or PEt_3 (**40**) will have much higher affinities toward carbon electrophiles as compared to amine bases of comparable proton basicity. The much higher affinity of tertiary phosphanes for carbon electrophiles than for protons is also reflected in reaction rates measure recently for the addition to benzhydrylium cations in apolar solvents.[6]

In how far the MCA values shown in Figure 1 correlate with catalytic rate measurements involving nucleophilic organocatalysts has subsequently been explored for all currently available experimental data.[12−14,18,19] The nucleophile-induced addition of methanol to acrylamide studied by Connon et al.[12] represents one of the examples in which rate data cannot be readily correlated with aqueous pK_a values of the involved nucleophiles ($R^2 = 0.39$, Figure 3).



Already using gas-phase PA data yields a much better correlation ($R^2 = 0.64$) with experimental rate constants, implying that the polarity of solvent-free or high-concentration reaction conditions may not be described well by aqueous phase data. By far the best correlation ($R^2 = 0.91$) is obtained when using MCA data, which is due to the results for trialkyl phosphanes and DABCO. The organocatalytic activity of both compounds correlates much better with their affinity toward carbon than with their affinity toward protons. The transformation shown in Figure 3 has also been studied in the presence of triethylamine (**20**) and Huenig base (**14**), but no rate acceleration has been observed for these two compounds. This likely implies that for many substrates employed under organocatalytic conditions steric effects will be larger than reflected in the MCA values presented here. Similar observations have also been made

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(10) For all nitrogen-based compounds (but excluding the sterically most congested systems **2**, **14**, **23**, and **36**), the following correlation exists: PA = 343.33 + 1.1175 × MCA (kJ mol^{-1}). This is the solid correlation line shown in Figure 2. The regression line shifts upward by 13 kJ mol^{-1} on consideration of all nitrogen-containing compounds: PA = 357.19 + 1.0989 × MCA (kJ mol^{-1}).

(11) For phosphanes **34**, **35**, **38**, **39**, **40**, and **41**, the following correlation exists: PA = 264.64 + 1.1374 × MCA (kJ mol^{-1}).

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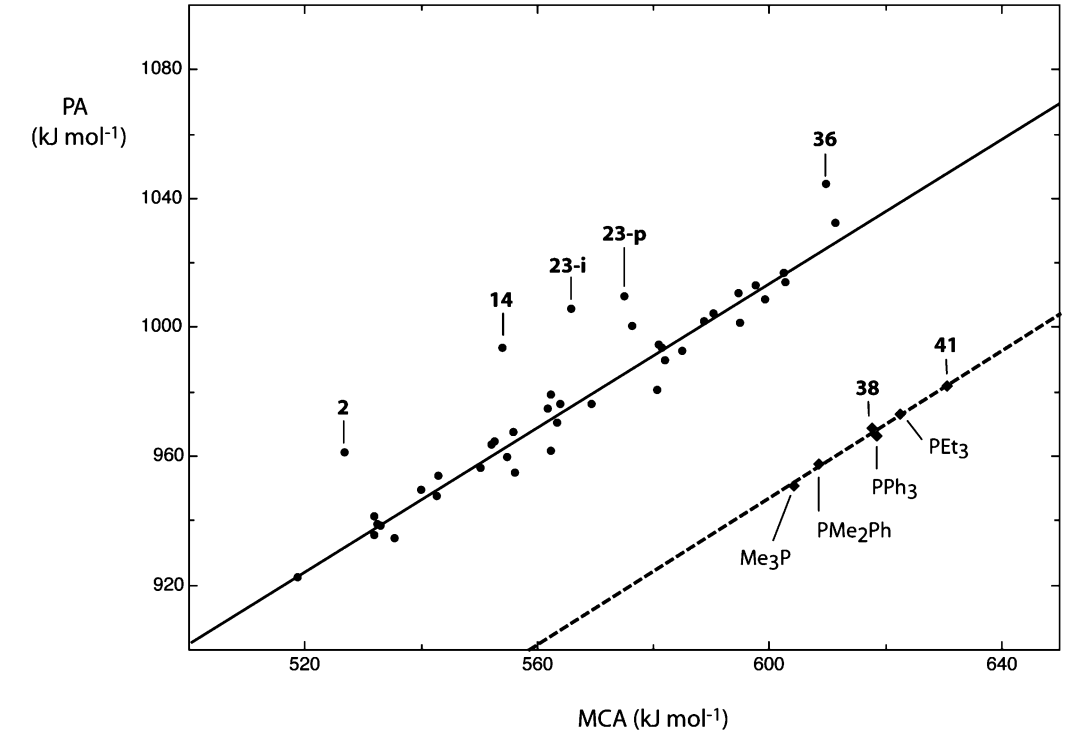

Figure 2. Correlation of MCA and PA values for the systems shown in Figure 1.

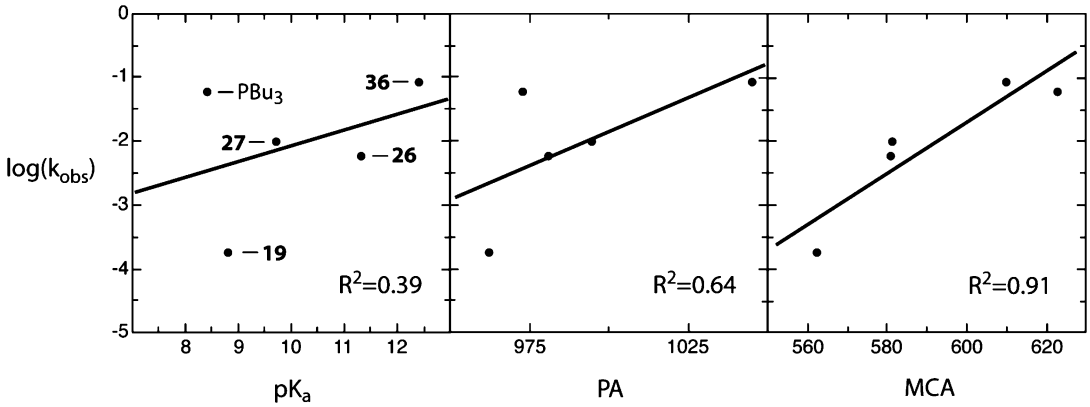

Figure 3. Correlation of observed rate constants k_{obs} for the nucleophile-induced addition of methanol to acrylamide[12] with the corresponding pK_a, PA (kJ mol^{-1}), and MCA (kJ mol^{-1}) values. The PA and MCA values of PEt_3 (**40**) have been used for PBu_3.

for the mechanistically more complex Baylis−Hillman reaction. Comparing the activities of quinuclidine derivatives **7**, **17**, **26**, and DABCO (**19**) in the Baylis−Hillman reaction with acrylate esters as substrates, Aggarwal et al. noted that DABCO is a much better catalyst than would be expected on the basis of its aqueous pK_a value.[13,14] This was ultimately traced back to a reordering of pK_a values in apolar solvents, but we note that the observed catalytic efficiency is again fully in line with the relative MCA values of these compounds presented here (see Supporting Information). That tertiary phosphanes such as Me_3P (**34**) exceed the catalytic activity of 4-DMAP (**27**) (in agreement with the MCA values of these systems) has been shown for intramolecular Baylis−Hillman reactions.[15] DBU (**36**) as the nitrogen base with the highest MCA value in Table 1 has also been tested in these reactions but appears to be basic enough to deprotonate the protic solvent (ethanol) to such a degree as to favor addition of alkoxide anions instead. This phenomenon has been observed in related reactions before, but it is very difficult indeed to find one mechanistic scheme fitting all published cases.[12,14,16,17] The high basicity of DBU may also be at the heart of its low activity as a catalyst in the acylation of alcohols with anhydrides.[8] The acidic side products generated in these reactions will, even when neutralized with a large excess of an auxiliary amine base, protonate (and thus deactivate) DBU in the course of the reaction. This together with the steric effects hindering the formation of a planar, resonance-stabilized acyliminium cation will limit the use of DBU as an organocatalyst to some selected cases. No such problems can be expected from catalysts combining high MCA with comparatively low PA values, and we may use the ratio MCA/PA as a quantitative guideline in this respect. A survey of these ratios in Table 1 immediately shows that tertiary phosphanes fare much better in this respect than all nitrogen-based compounds, underlining the promising prospects of this class of compounds in organocatalysis. Reaction rates for the acylation of tertiary alcohols with anhydrides in apolar solution catalyzed by pyridines **25**, **27**, **29**, and **32** are in full agreement with the relative MCA values of these compounds.[18−20] Most interest-

ingly, Bu_3P has been shown to be slightly more effective than 4-DMAP (**27**) in acylation reactions of secondary alcohols.[21] This observation is at variance with the proton affinities of 4-DMAP and, for example, Et_3P (**40**) but readily accommodated with respect to the MCA values of these two systems.

A wide range of results exist for the base-catalyzed hydrolysis of carboxylic acid derivatives in water.[22] For some catalysts the mechanism has been clearly established to proceed through initial formation of acylammonium intermediates.[23−25] The reaction rates determined for the quinuclidine derivatives **7**, **17**, **26**, and DABCO (**19**) in their reaction with organic carbonates, for example, are in full agreement with their MCA values. We should, however, not forget that aqueous solvation leads to a dramatic reduction of nucleophilic reactivity in general and also, in part, a reordering of relative reactivities as compared to less polar organic solvents.[6]

Aside from correlating catalytic efficiencies with the MCA values of the corresponding catalysts and thus establishing a Brønsted-type correlation between reaction rates and ground-state affinity data, the MCA values in Table 1 can also be used in a more qualitative way to understand the basis of organocatalytic processes. This can be exemplified using the proline-catalyzed aldol reaction between acetone and aromatic aldehydes.[1b] The uncatalyzed background reaction corresponds in this case to the nucleophilic addition of acetone (or, more likely, its enol) to the aromatic aldehyde. The hope for a catalytic process rests on the assumption that the enamine **31** formed by reaction of acetone and proline is more reactive toward the electrophilic aldehyde than the enol of acetone. The MCA value for enamine **31** (599.2 kJ mol^{-1}) is much higher than that of acetone enol (459.0 kJ mol^{-1}) or that of proline (**5**) itself (532.4 kJ mol^{-1}). Even when present in equal amounts in the reaction mixture **31** will react much faster with electrophiles than acetone enol or proline and thus enable a catalytic cycle. Under most experimental conditions, however, the true side reaction to proline catalysis will most likely be that of unspecific base catalysis.[27] The acetone enolate involved in this process will be a much better nucleophile than either acetone enol or enamine **31**. A direct comparison of these ionic and neutral nucleophiles through their MCA values will not be meaningful due to the large role played by environmental factors (solvent, counterion) in the reaction of anionic nucleophiles.

Conclusion

The MCA values presented here can be used as a guideline for the optimization of organocatalytic transformations. The mechanistic complexity of many such reactions, the presence of numerous side reactions, and the broad variety of solvents used under experimental conditions make it unlikely that quantitative predictions can be made for structurally different organocatalysts with only one single parameter. However, if the general limitation of a single parameter approach has been accepted, it is clear that the currently known catalytic activities of nitrogen and phosphorus bases are much more readily correlated with MCA than with PA or pK_a data.

Methods

The geometries of all systems have been optimized at the B98/6-31G(d) level of theory. The conformational space of flexible organocatalysts has first been searched using the MM3 force field and the systematic search routine in the TINKER program.[26] All stationary points located at force field level have then been reoptimized at B98/6-31G(d) level as described before. Starting geometries for the cationic adducts have been generated from the neutral structures through addition of a proton or methyl cation, followed by subsequent reoptimization at B98/6-31G(d) level. Thermochemical corrections to 298.15 K have been calculated for all minima from unscaled vibrational frequencies obtained at this same level. The thermochemical corrections have been combined with single-point energies calculated at the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level to yield enthalpies H_{298} at 298.15 K. In conformationally flexible systems enthalpies have been calculated as Boltzmann-averaged values over all available conformers. This procedure has recently been found to reproduce G3 methyl cation affinity values of selected small- and medium-sized organocatalysts within 4.0 kJ mol^{-1}.[2] Thermochemical data obtained for some of the catalysts described here at G3 level has been included as Supporting Information. All quantum mechanical calculations have been performed with Gaussian 03.[28]

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Supporting Information Available: Comparison of published experimental data with pK_a, PA, and MCA values (part A) and structures and energies of all stationary points described in the text at various levels of theory, including the full ref 28 (part B). This material is available free of charge via the Internet at http://pubs.acs.org.

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