ORGANIC LETTERS

2008
Vol. 10, No. 23
5413−5416

Estimating the Stereoinductive Potential of Cinchona Alkaloids with a Prochiral Probe Approach

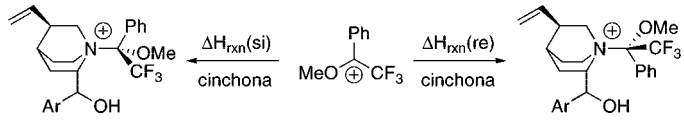
Yin Wei,[†] G. Narahari Sastry,[‡] and Hendrik Zipse*[,†]

Department of Chemistry and Biochemistry, LMU München, Butenandtstrasse 5-13, D-81377 München, Germany, and Indian Institute of Chemical Technology, Hyderabad-500 007, India

zipse@cup.uni-muenchen.de

Received October 6, 2008

ABSTRACT



Cinchona alkaloids occupy a privileged status due to their optimal possession of two desirable properties, namely catalytic efficiency and stereoselectivity. This paper proposes a new quantitative measure, the energy difference between the adducts formed by *re* and *si* face attack to Mosher's cation ($\Delta MOSCA_{re-si}$) as a measure of stereoinductive potential, by taking the example of cinchona alkaloids. Other descriptors such as methyl cation affinities and the one based on continuous symmetry measures are also estimated and correlated with $\Delta MOSCA_{re-si}$ values.

Cinchona alkaloids and their derivatives play an important role in stereoselective catalysis, both as actual catalysts as well as building blocks for ligands in transition-metal complexes.[1] The frequent use of these compounds in a variety of chemically distinct transformations suggests that the intrinsic structural and electronic properties of these alkaloids make them suitable as reagents and catalysts for a variety of stereoselective processes.[2] The most frequently used compounds of this class include cinchonidine (**1**), cinchonine (**2**), quinine (**5**), and quinidine (**6**). One of the inherently useful properties of these compounds is their commercial availability. Using two different cationic probes we are testing what other properties make these compounds superior to the known, but much less frequently used C9-epimers **3**, **4**, **7**, and **8**. For the sake of comparison we also include the (*S*)-proline-derived[3] diamine **9** and sparteine **10** (Figure 1).

We have recently shown that a variety of N- and P-centered bases can be ranked according to their affinity toward the methyl cation (CH_3^+). In selected organocatalytic processes this methyl cation affinity (MCA) was shown to correlate better with the experimentally observed catalytic efficiencies than proton affinities (PA).[4,5] We extend these studies to include affinity values toward prochiral cation **11**, formally derived from α-methoxy-α-trifluoromethyl-α-phenylacetic acid (MTPA, Mosher's acid, $Ph(OCH_3)(CF_3)C-CO_2H$) through decarboxylation. The success of this latter acid as a derivatizing reagent for a multitude of chiral alcohols suggests that the three substituents connected to C2 (Ph, CF_3, OCH_3) provide an optimally dif-

[†] LMU München.
[‡] IICT Hyderabad.

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10.1021/ol8023067 CCC: $40.75
Published on Web 11/08/2008

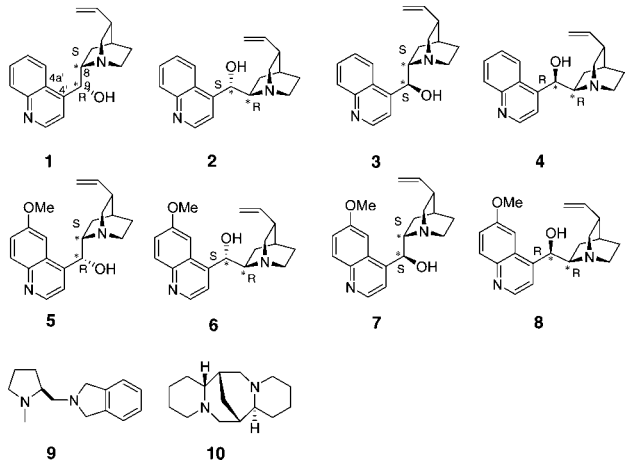
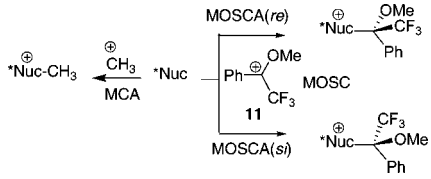


Figure 1. Cinchona alkaloids **1**−**8** and selected tertiary amines **9** and **10**.

ferentiated environment in steric and electronic terms.[6,7] In order to emphasize the resemblance to Mosher's acid we will refer to cation **11** as "Mosher's cation" (or MOSC) and to the corresponding reaction enthalpies at 298 K then as "MOSCA" values. As described in Scheme 1, reaction of MOSC with chiral nucleophiles can occur from the *re* or *si* face of the cation, leading to two diastereomeric adducts with two different affinity values: MOSCA(*re*) and MOSCA(*si*).

Scheme 1



The development of new chiral descriptors for stereoselective organocatalytic transformations is interesting in its own right, and the prochiral MOSCA probe proposed here is a practical approach in this direction.

Figure 2 compiles the MCA values of compounds **1**−**10** listed in Table 1 in a graphical manner. The analysis concentrates here on the properties of the quinuclidine substructure in alkaloids **1**−**8** as it has been shown earlier[4] that the MCA values of the respective N(sp^3) center is significantly higher than that of the N(sp^2) center in the quinoline ring. The MCA values of natural cinchona alkaloids **1**, **2**, **5**, and **6** are in the range of 580−595 kJ mol^{-1}, which are similar to those of some commonly used organocatalysts such as DMAP, 4-pyrrolidinopyridine (PPY), and quinuclidine.[4] The MCA values differ by only 4 kJ mol^{-1} in the cinchona alkaloids **1** and **2** and by about 6 kJ mol^{-1} in alkaloids **5** and **6**. However, the MCA value of *epi*-cinchonidine **3** is lower than that of **1** by more than 20 kJ mol^{-1}, and similarly, the MCA value of *epi*-quinine **7** is also lower than that of **5** by more than 20 kJ mol^{-1}. The MCA values of *epi*-cinchonine **4** and *epi*-quinidine **8** are lower than the MCA values of **2** and **6** by more than 16 kJ mol^{-1}, respectively. Comparing the relative energies for neutral molecules and adducts, respectively, the neutral epimers **3** and **7** are more stable by more than 10 kJ mol^{-1} than **1** and **5**, and the cations are less stable by 8 kJ mol^{-1}. Addition of a methoxy substituent to the quinoline ring has a surprisingly large influence on enhancing the MCA values of the quinuclidine nitrogen atom in cinchona alkaloids. This enhancement amounts to 10 kJ mol^{-1} in **1**/**5**, 8 kJ mol^{-1} in **2**/**6**, 9.3 kJ mol^{-1} in **3**/**7**, and 8 kJ mol^{-1} in **4**/**8**. The MCA value of tertiary amine **9**, frequently used in organocatalytic

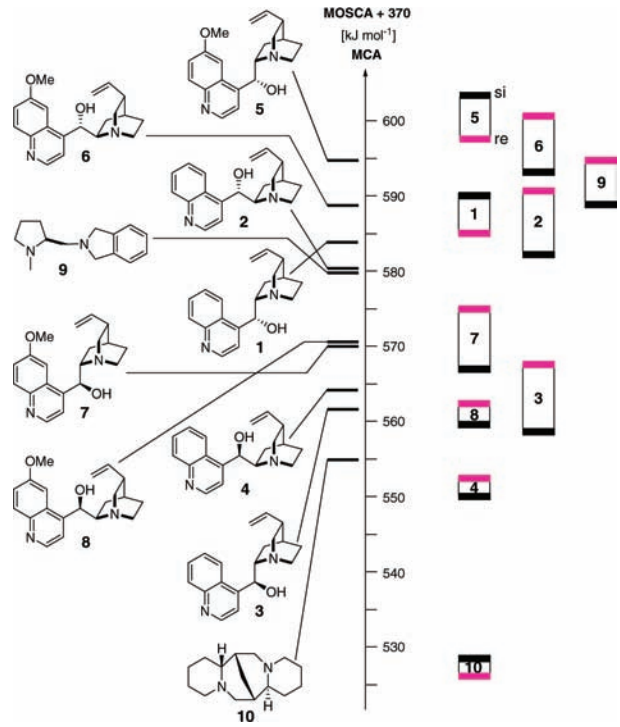


Figure 2. MCA and MOSCA values of compounds **1**−**10**. Black bars correspond to *si* face attack and magenta bars correspond to *re* face attack, respectively.

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(8) Using geometries optimized at the MP2(FC)/6-31G(d) level (instead of B98/6-31G(d)) leaves the MCA value of **1** unchanged. For compound **3**, the MCA value amounts to 565.4 kJ mol^{-1} with MP2(FC)/6-31G(d) geometries and to 562.4 kJ mol^{-1} with B98/6-31G(d) geometries. These small changes indicate that the use of B98/6-31G(d) geometries is very reliable for the calculation of MCA values.

(9) Using geometries optimized at the MP2(FC)/6-31G(d) level (instead of B98/6-31G(d)), the MOSCA*re* and MOSCA*si* of **1** are 218.5 and 224.1 kJ mol^{-1}, respectively, differing from the values using B98/6-31G(d) geometries by only 3 kJ mol^{-1}. ΔMOSCA*re*−*si* using MP2(FC)/6-31G(d) geometries is −5.6 kJ mol^{-1}, which is slightly different from −5.5 kJ mol^{-1} using B98/6-31G(d) geometries. These small changes indicate that the use of B98/6-31G(d) geometries is very reliable for the calculation of MOSCA values.

Table 1. MCA, PA, MOSCA Values[a] (in kJ mol^{-1}), and CCM for Systems **1**−**10**

			MOSCA			CCM			μ (D)		
	MCA	PA	*re*	*si*	ΔMOSCA *re*−*si*	*re*	*si*	ΔCCM *re*−*si*	*re*	*si*	Δμ (D) *re*−*si*
1	584.8	993.0	215.2	220.7	−5.5	13.8	15.2	−1.4	6.98	4.51	2.47
2	580.8	995.0	220.7	212.3	8.5	16.8	10.1	6.7	4.16	7.04	−2.88
3	562.4	990.1	197.6	188.4	9.2	16.1	10.6	5.5	3.51	6.68	−3.17
4	564.4	991.1	183.7	180.0	3.7	16.8	17.2	−0.4	2.99	5.37	−2.38
5	594.7	1001.8	227.3	233.7	−6.4	16.2	20.2	−4.0	6.49	3.72	2.77
6	588.6	1002.3	231.2	223.3	7.9	16.2	9.6	6.6	3.42	6.57	−3.15
7	571.7	999.6	205.6	196.9	8.7	15.9	13.1	2.8	3.14	6.31	−3.17
8	572.3	998.9	193.1	189.3	3.8	18.8	19.7	−0.9	6.05	6.6	−0.55
9	574.8	1009.7	224.9	217.6	7.3	9.1	4.3	4.8	4.53	8.34	−3.81
10	554.9	1044.4	156.3	158.6	−2.3	12.4	8.8	3.6	1.61	2.86	−1.25

[a] Calculated at the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level.[8,9]

processes, is 574.8 kJ mol^{-1}. The MCA value of **10** is 554.9 kJ mol^{-1}, somewhat lower than the MCA values of commonly used organocatalysts.[4] The proton affinities of all cinchona alkaloids are much less affected by changes in the stereochemistry than the MCA values, resulting in rather similar values for compounds **1**−**4** and for **5**−**8** (Table 1).

The MOSCA*re* and MOSCA*si* values of compounds **1**−**10** (Table 1) are substantially smaller in absolute terms than the respective MCA values. The difference appears to be close to 370 kJ mol^{-1} for the nucleophiles selected here, but the steric bulk and internal structure of the MOSC cation leads to a significantly larger spread of MOSCA than of MCA values. The highest MOSCA values are calculated here for quinine (**5**) and quinidine (**6**), which are also the compounds with highest MCA values. Also in line with the MCA results is the finding that all natural alkaloids **1**, **2**, **5**, and **6** have higher MOSCA values than their C9 epimers. However, the MOSCA values for the non-natural alkaloids **7**/**8** and **3**/**4** are farther apart than expected based on their respective MCA data. If the qualitative correlation of carbocation affinity values with catalytic activity in Lewis base-catalyzed reactions observed earlier[4] holds, one would conclude that **5** and **6** are the most reactive compounds and that the respective C9 epimers are significantly less reactive.

This has indeed been observed experimentally by Oda et al. in the alkaloid-catalyzed alcoholysis of cyclic anhydrides.[10] These studies, together with subsequent work by Aitken et al.[11] and by Bolm et al.,[12] also illustrate that numerous other factors contribute to the experimentally observed selectivity, one of the critical parameters being the catalyst concentration. The generally higher selectivity observed in the presence of higher catalyst concentrations indicates the presence of an unselective background process, a general phenomenon of base-catalyzed reactions of alcohols with anhydrides.[13] In addition, a catalytic effect of the protonated cinchona alkaloids cannot also be excluded. The intrinsic stereoinductive potential of the bases considered here is quantified through the difference between *re* and *si* face MOSC affinity values as listed in Table 1, a negative value indicating preference for *si* face attack. Negative values are found here for the natural alkaloids **1** and **5**, while positive values of similar size are found for the alkaloids **2** and **6**. The opposite preferences for quinine (**5**) and quinidine (**6**) parallel numerous experimental observations in the alcoholysis of anhydrides, in which catalysis by **5** and **6** yield opposite product enantiomers.[10−12] Experimental studies involving the C9 epimeric cinchona alkaloids are much less frequent and appear to indicate the same absolute stereochemical preferences for stereochemical pairs **2**/**4** and **6**/**8**, but with lower absolute ee % values for **4** and **8**. The stereofacial preference as well as the lower absolute selectivity are closely matched by the MOSCA values computed here, predicting the same *re* facial addition preference for all four of these compounds, with ΔMOSCA values being much smaller for **4**/**8** than for **2**/**6** (Table 1). It is only for compounds **3** and **7** that the experimental results observed by Oda (near-racemic product) are in clear contrast to the large positive ΔMOSCA values calculated here. In light of these results, reexamination of the catalytic performance of these compounds under the conditions developed by Bolm et al. appears highly desirable.

The analysis of geometrical parameters of MOSC adducts reveals only small differences in dihedral angle $d_{C8-N-C-O}$ between MOSC*re*$^+$ and MOSC*si*$^+$ adducts, implying that the MOSC methoxy group is restricted to essentially one orientation in all adducts. The structures of the most stable conformers for **1**−MOSC*re*$^+$ and **1**−MOSC*si*$^+$ also show that the methoxy group in MOSC is oriented toward the quinoline moiety, and the same observation can again be

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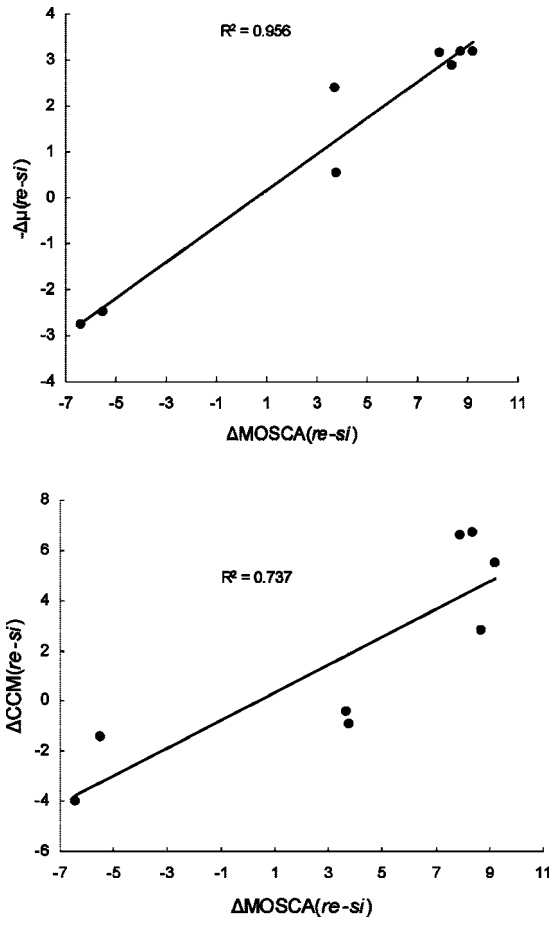

Figure 3. Correlation of ΔMOSCA values for cinchona alkaloids **1**−**8** with other parameters.

made for the other cinchona alkaloids except for **4**−MOSC-*si*$^+$ and **8**−MOSC*si*$^+$ (see the detailed conformational analysis in the Supporting Information). One further finding concerns the overall dipole moment of MOSC adducts for the cinchona alkaloids (Table 1), which shows a moderate correlation with the MOSCA values (see Figure 3). This correlation implies that the energetically most favorable MOSC adducts are those with overall lower dipole moments. However, as exemplified by the results for **9**, such a correlation appears not to be of general validity.

The continuous chirality measure (CCM) developed by Avnir[14] is a general approach to measure the deviation of the structure of a chiral molecule from having an achiral point group. The CCM can be used as a quantitative measurement of the intrinsic chirality of molecular systems. CCM values have been calculated for the lowest energy conformations of **1**−**10**, and also for their respective methyl cation and MOSC adducts. There is no quantitative correlation between MOSCA values and CCM for the set of compounds studied here. However, there is a moderate correlation between $\Delta MOSCA_{re-si}$ of cinchona alkaloids **1**−**8** and their respective ΔCCM_{re-si} values (see Figure 3).

Taken together, the MOSCA values determined here for a series of tertiary amines represent a quantitative and easily computable measure of the stereoinductive potential of these nucleophiles. These data, together with the methyl cation affinity (MCA) values, are expected to facilitate the development of new, more effective and more selective catalysts, in particular in an area where initial experiments have already been performed. The stereoinductive potential is one of the key factors determining the stereoselectivity in catalytic processes. Whether or not such a process is successful depends on a host of additional factors, the absolute catalytic efficiency being one of the most relevant. The MOSCA probe proposed here appears to capture both the catalytic efficiency as well as the stereoselectivity. For the systems studied here the most reactive and selective compounds appear to be quinine (**5**) and quinidine (**6**), while sparteine (**10**) appears to be neither particularly selective nor reactive.

Acknowledgment. Financial support for this project by the DFG through the focus program SPP 1179 "organocatalysis" and by the DST-DAAD Indo-German PPP exchange program is gratefully acknowledged.

Supporting Information Available: Computational details and the energies for all compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8023067

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