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Organocatalytic Activity of Cinchona Alkaloids: Which Nitrogen Is More Nucleophilic?

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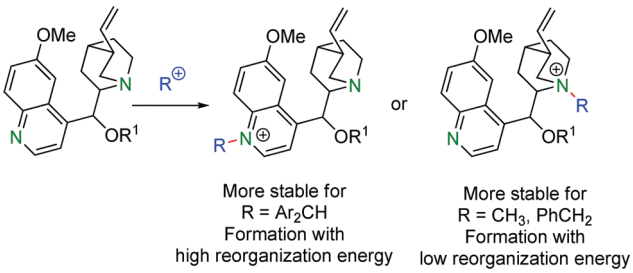

The cinchona alkaloids **1a**−**d** react selectively at the quinuclidine ring with benzyl bromide and at the quinoline ring with benzhydrylium ions (diarylcarbenium ions). The kinetics of these reactions have been determined photometrically or conductimetrically and are compared with analogous reactions of quinuclidine and quinoline derivatives. Quantum chemical calculations [MP2/6-31 + G(2d,p)// B3LYP/6-31G(d)] show that the products obtained by attack at the quinuclidine ring (N_{sp3}) of quinine are thermodynamically more stable when small alkylating agents (primary alkyl) are used, while the products arising from attack at the quinoline ring (N_{sp2}) are more stable for bulkier electrophiles (Ar_2CH). In some cases, rate and equilibrium constants for their reactions with benzhydrylium ions could be determined. These data gave access to the Marcus intrinsic barriers, which are approximately 20 kJ mol^{-1} lower for attack at the N_{sp3}-center than at the N_{sp2}-center.

Introduction

Since the beginning of the 20th century, alkaloids, such as quinine or quinidine, have been used as catalysts for asymmetric syntheses.[1a,b] A breakthrough were Pracejus' alcoholyses of disubstituted ketenes in the presence of cinchona alkaloids.[1c] Though numerous other classes of tertiary amines have since been investigated with respect to their catalytic efficiencies,[1] the naturally occurring cinchona alkaloids **1a,b**

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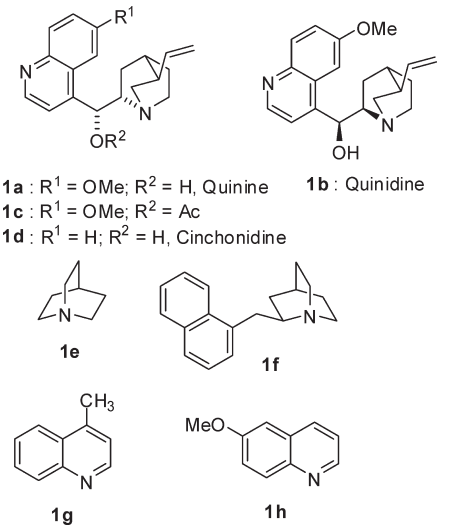
and derivatives thereof (Chart 1) have remained in the focus of interest.[2−15]

Nucleophilic attack of quinine at the carbonyl groups of the intermediate ketenes has been suggested to rationalize the asymmetric halogenations of carboxylic acid derivatives[2] and of the enantioselective syntheses of β-lactams[3] and β-lactones[4] via [2 + 2] cycloadditions of ketenes.[5] Asymmetric syntheses of 1,4-benzoxazinones have been achieved via [4 + 2] cycloaddition of benzoquinone imides with chiral ketene enolates derived from acid chlorides and catalytic amounts of cinchona alkaloids.[6] Cinchona alkaloids were reported to catalyze asymmetric cyanations and cyanosilylations of ketones and aldehydes[7] as well as desymmetrizations of *meso*-anhydrides.[8] Chiral ammonium enolates, obtained by nucleophilic attack of cinchona alkaloids and their derivatives at Michael acceptors, were involved in enantioselective Baylis−Hillman reactions.[9] Conjugate additions of cinchona alkaloids to Baylis−Hillman carbonates[10] and allylic trichloroacetimidates[11] were suggested to account for the enantioselective synthesis of α-substituted methyl acrylates and trichloroacetylated allyl amides, respectively. Nucleophilic attack of cinchona alkaloids at α-haloketones or esters in the presence of carbonates generates chiral ammonium ylides, which were used for asymmetric cyclopropanation reactions.[12] Sharpless et al. employed cinchona alkaloids for osmium-catalyzed asymmetric dihydroxylations of alkenes and reported that the binding strengths to OsO_4 are very sensitive to steric effects.[13]

Though Adamczyk and Rege reported that 1,3-propane sultone reacts with quinine selectively at the N_{sp2} center of the quinoline ring,[14,15] it is generally assumed that the catalytic activity of the cinchona alkaloids is due to the nucleophilicity of the N_{sp3} center of the quinuclidine ring. During our efforts to characterize the nucleophilic reactivity of cinchona alkaloids in comparison with other organocatalysts, we had noticed that in contrast to most other electrophiles, benzhydrylium ions (diarylcarbenium ions) attack selectively at the N_{sp2} center of the quinoline ring. This observation prompted us to systematically investigate the nucleophilic reactivity of the two basic positions in cinchona alkaloids.

CHART 1. Cinchona Alkaloids and Related Compounds



Results

Product Identification. In agreement with earlier reports,[16,17] compounds **1a**−**d** react with benzyl bromide at the quinuclidine ring (Scheme 1). The quaternary ammonium salts resulting from benzylation of **1a** and **1d** are commercially available and are used as phase-transfer catalysts.

In contrast, benzhydrylium ions attack cinchona alkaloids at the quinoline nitrogen. Comparison of the ^1H and ^{13}C NMR chemical shifts of the adducts of quinuclidine (**1e**), 6-methoxyquinoline (**1h**), and *O*-acetylquinine (**1c**) with $(mfa)_2CH^+$ and $(ani)_2CH^+$ (Chart 2) reveals exclusive attack of benzhydrylium ions at the N_{sp2} center of cinchona alkaloids.

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SCHEME 1. Reactions of Quinine (1a) with Benzyl Bromide and Benzhydrylium Salts

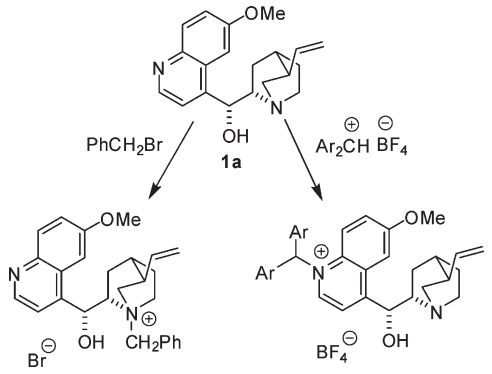
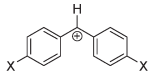
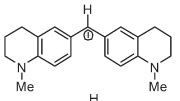
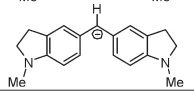


CHART 2. Abbreviations and Electrophilicity Parameters (E) of Benzhydrylium Ions (Ar_2CH^+)



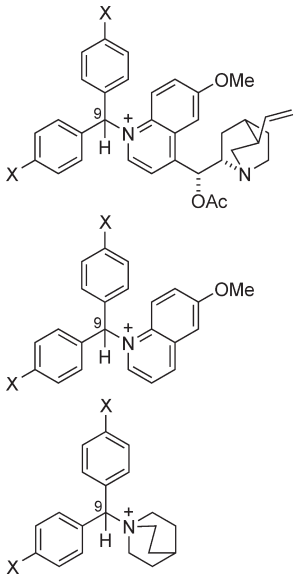
	X	E [a]
Ph_2CH^+	H	5.90
$(tol)_2CH^+$	Me	3.63
$(ani)_2CH^+$	OMe	0.00
$(pfa)_2CH^+$	$N(Ph)CH_2CF_3$	–3.14
$(mfa)_2CH^+$	$N(CH_3)CH_2CF_3$	–3.85
$(dpa)_2CH^+$	NPh_2	–4.72
$(mor)_2CH^+$	$N(CH_2CH_2)_2O$	–5.53
$(mpa)_2CH^+$	$N(Ph)CH_3$	–5.89
$(dma)_2CH^+$	$N(CH_3)_2$	–7.02
$(pyr)_2CH^+$	$N(CH_2)_4$	–7.69
$(thq)_2CH^+$		–8.22
$(ind)_2CH^+$		–8.76

[a] Empirical electrophilicity parameter from ref. 19b.

While the reactions of quinuclidine (**1e**) ($\delta_H(NCH_2) = 2.78$ ppm) with $(mfa)_2CH^+$ and $(ani)_2CH^+$ are accompanied by a 0.6–0.8 ppm deshielding of the NCH_2-protons, the chemical shifts of the quinuclidine protons remained unaffected when *O*-acetylquinine (**1c**) was combined with these benzhydrylium ions. On the other hand, benzhydrylation of **1c** led to distinct changes in the chemical shifts of the quinoline moiety similar to those observed upon treatment of 6-methoxyquinoline (**1h**) with benzhydrylium salts (see Supporting Information).

A further argument for the attack of benzhydrylium ions at the quinoline ring of **1c** comes from the comparison of the chemical shifts of 9-H and C-9 of the adducts in Scheme 2, which have been assigned by COSY and HSQC. The NMR chemical shifts of the benzhydryl proton 9-H and the benzhydryl carbon C-9 in the adducts obtained from benzhydrylium ions and *O*-acetylquinine (**1c**) are very similar to those of the corresponding adducts with 6-methoxyquinoline (**1h**), indicating the same environment of the benzhydryl center in both pairs of adducts. In contrast, the corresponding chemical shifts of the adducts with quinuclidine (**1e**) differ significantly. While the benzhydryl proton resonates at much

SCHEME 2. Comparison of ^1H and ^{13}C NMR Chemical Shifts (in ppm, solvent = CD_3CN) of the Benzhydryl Center in Different Adducts with Amines



X	δ(9-H)	δ(C-9)
$N(CH_3)CH_2CF_3$	7.77	72.8
OMe	8.20	72.8
$N(CH_3)CH_2CF_3$	7.80	73.5
OMe	8.20	72.9
$N(CH_3)CH_2CF_3$	5.20	83.5
OMe	6.28	80.1

higher field ($\Delta\delta = 2-2.6$ ppm), the benzhydryl carbon is more deshielded ($\Delta\delta = 7-10$ ppm).

Kinetics. To rationalize the contrarian selectivities of different electrophiles, we have studied the kinetics of the reactions of benzhydrylium ions and of benzyl bromide with quinine (**1a**) and compared them with the corresponding reactions of related compounds (Chart 1).

In a first set of experiments we determined the kinetics of the reactions of the amines **1** (Chart 1) with benzhydrylium ions (Chart 2), which have been used as reference electrophiles for characterizing the reactivities of σ-, n-, and π-nucleophiles.[19,20]

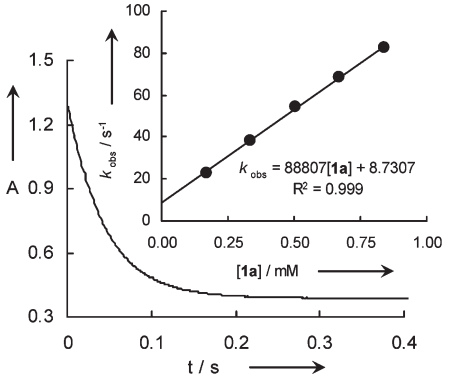


FIGURE 1. Exponential decay of the absorbance A at 590 nm and linear correlation of the pseudo-first-order rate constants k_{obs} with [**1a**] for the reaction of $(mfa)_2CH^+BF_4^-$ ($c_0 = 1.8 \times 10^{-5}$ M) with amine **1a** in CH_2Cl_2 at 20 °C (as the reaction is reversible, the final absorbance is not zero).

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TABLE 1. Second-Order Rate Constants for Reactions of Amines 1a−h with Benzhydrylium Tetrafluoroborates at 20 °C

			$k/M^{-1}\,s^{-1}$	
amine	N/s	Ar_2CH^+	CH_2Cl_2	CH_3CN
1a	10.46/0.75 (CH_2Cl_2)	$(mfa)_2CH^+$	8.88×10^4	
		$(dpa)_2CH^+$	1.76×10^4	
		$(mor)_2CH^+$	4.98×10^3	
		$(dma)_2CH^+$	no rxn	
1b	10.54/0.74 (CH_2Cl_2)	$(mfa)_2CH^+$	9.36×10^4	
		$(dpa)_2CH^+$	1.74×10^4	
		$(mor)_2CH^+$	5.38×10^3	
		$(dma)_2CH^+$	no rxn	
1c		$(mfa)_2CH^+$	8.23×10^4	2.68×10^4
1e	20.54/0.60[a] (CH_3CN)	$(mfa)_2CH^+$		9.97×10^{8a}
		$(mor)_2CH^+$		3.34×10^{8a}
		$(dma)_2CH^+$		1.18×10^{8a}
		$(pyr)_2CH^+$		5.22×10^{7a}
		$(ind)_2CH^+$		1.08×10^{7a}
1f	15.66/0.62 (CH_3CN)	$(dma)_2CH^+$		1.84×10^5
		$(pyr)_2CH^+$		1.13×10^5
		$(thq)_2CH^+$		4.12×10^4
		$(ind)_2CH^+$		1.63×10^4
		$(jul)_2CH^+$		no rxn
		$(lil)_2CH^+$		no rxn
1g	11.60/0.62 (CH_3CN)	$(pfa)_2CH^+$		1.78×10^5
		$(mfa)_2CH^+$	1.23×10^5	4.22×10^4
		$(dpa)_2CH^+$		3.46×10^4
		$(mor)_2CH^+$		3.34×10^3
		$(mpa)_2CH^+$		4.04×10^3
		$(pyr)_2CH^+$		no rxn
1h	10.86/0.66 (CH_3CN)	$(pfa)_2CH^+$		1.37×10^5
		$(mfa)_2CH^+$	7.96×10^4	2.16×10^4
		$(dpa)_2CH^+$		2.10×10^4
		$(mor)_2CH^+$		2.33×10^3
		$(dma)_2CH^+$		no rxn

[a]From ref 18.

The decay of the benzhydrylium absorbances has been followed photometrically after combining benzhydrylium tetrafluoroborates with variable excesses of the amines. Pseudo-first-order rate constants k_{obs} were obtained by fitting the decay of the absorbances to the monoexponential function $A = A_0\,e^{-k_{obs}t} + C$. Plots of k_{obs} versus the concentrations of the amines were linear (Figure 1), with the second-order rate constants (Table 1) being the slopes of the correlation lines. Because of solubility problems, different solvents had to be used for the different reaction series. Comparison of rate constants in CH_3CN and CH_2Cl_2 reveals a 3- to 4-times higher reactivity in CH_2Cl_2.

Plots of $\log k$ versus the electrophilicity parameter E of the benzhydrylium ions (Figure 2) are linear as required by eq 1, where $k_{20\,°C}$ ($L\,mol^{-1}\,s^{-1}$) is the second-order rate constant, E is the electrophilicity parameter, N is the nucleophilicity parameter, and s is a nucleophile-specific slope parameter.[19,20]

$$\log k_{20\,°C} = s(N + E) \quad (1)$$

From the slopes and the intercepts on the abscissa, we can derive the nucleophile-specific parameters s and N, respectively, which are listed in the second column of Table 1.

The kinetics of the reactions of benzyl bromide with quinine (**1a**) and several of its substructures have been followed conductimetrically. In all cases, pseudo-first-order conditions were employed with the amines **1** in high excess.

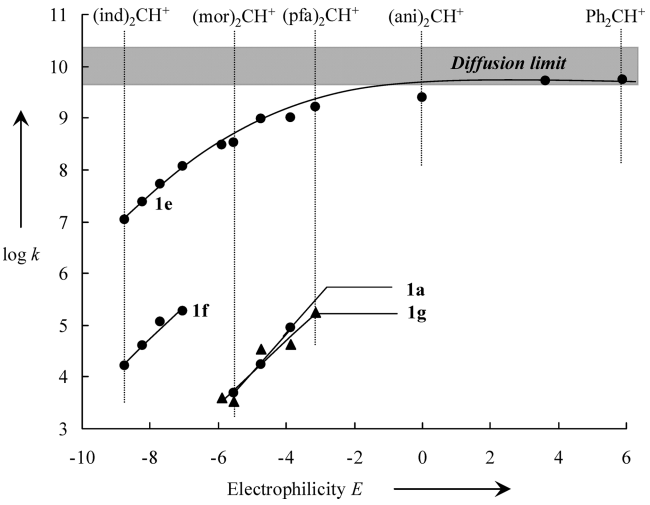


FIGURE 2. Plots of $\log k$ versus E for the reactions of amines with benzhydrylium ions Ar_2CH^+.

TABLE 2. Second-Order Rate Constants for the Reactions of Amines with Benzyl Bromide at 20 °C

	$k/M^{-1}\,s^{-1}$	
amine	DMSO	CH_3CN
1a	2.88×10^{-2}	
1d	3.68×10^{-2}	
1e	17.3	6.32
1f		6.16×10^{-2}
1g		1.7×10^{-4}

As a consequence of the previously reported proportionality between salt concentration and conductance in acetonitrile, the formation of the ammonium salts gave rise to an exponential increase of the conductances G (eq 2).[21] The second-order rate constants (Table 2) were obtained from plots of k_{obs} versus [**1**].

$$dG/dt = G_{max}(1 - e^{-k_{obs}t}) + C \quad (2)$$

Discussion

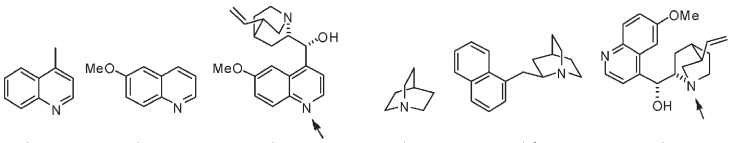
The similarity of the slope parameters s in Table 1 implies that the relative reactivities of the different amines depend only slightly on the nature of the benzhydrylium ions. For that reason, the relative reactivities toward $(mfa)_2CH^+$ given in Scheme 3 can be considered to be representative also for reactions with other benzhydrylium ions.

As shown in Scheme 3, the quinoline ring in quinine (**1a**) has a similar reactivity toward benzhydrylium ions as the 4-methyl- and 6-methoxy-substituted quinolines **1g** and **1h**. Quinuclidine (**1e**) reacts >4 orders of magnitude faster with benzhydrylium ions, and the 50-fold reduced reactivity of **1f** can be assigned to the steric shielding by the neighboring naphthylmethyl group. The additional hydroxy group in the naphthylmethyl group of **1a** must be responsible for a further $>10^3$-fold reduction of reactivity which is derived from the exclusive attack of benzhydrylium ions at the quinoline ring of **1a** (with $k_{rel} = 0.70$). Though unlikely, one cannot

(20) (a) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77. (b) Mayr, H.; Ofial, A. R. *Pure Appl. Chem.* **2005**, *77*, 1807–1821. (c) Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584–595.

(21) (a) Yoh, S.-D.; Cheong, D.-Y.; Lee, C.-H.; Kim, S.-H.; Park, J.-H.; Fujio, M.; Tsuno, Y. *J. Phys. Org. Chem.* **2001**, *14*, 123–130. (b) Kim, S. H.; You, S.-D.; Lim, C.; Mishima, M.; Fujio, M.; Tsuno, Y. *J. Phys. Org. Chem.* **1998**, *11*, 254–260.

SCHEME 3. Relative Reactivities of Different Amines toward the Benzhydrylium Ion $(mfa)_2CH^+$ and Benzyl Bromide in CH_3CN at 20 °C



	1g	1h	1a	1e	1f	1a
k_{rel} $(mfa)_2CH^+$	1.0	0.51	0.70 [a]	2.4×10^4	5.0×10^2 [b]	<< 0.7
k_{rel} $(PhCH_2Br)$	1.0		$<< 6.2 \times 10^1$	3.7×10^4	3.6×10^2	6.2×10^1 [c]

[a]Value in CH_2Cl_2 divided by 3, as for **1c** (from Table 1). [b]Calculated by eq 1 from *E*, *N*, and *s*. [c]Value in DMSO divided by 2.7, as for **1e** (from Table 2).

rigorously exclude a faster, highly reversible electrophilic attack of benzhydrylium ions at the N_{sp3} center of **1a** and **1b**. The observed monoexponential decays of the benzhydrylium absorbances in the reactions of $Ar_2CH^+BF_4^-$ with an excess of **1a** or **1b** (pseudo-first-order conditions) allow us, however, to exclude the appearance of noticeable concentrations of intermediate ammonium ions, where the diarylmethyl group is located at the N_{sp3} center. The observed rate constants for the reactions of **1a,b** with Ar_2CH^+ can, therefore, unequivocally be assigned to the reactions at the N_{sp2} center.

Comparison of the nucleophilic reactivities of **1e-g** toward benzhydrylium ions and benzyl bromide shows common features (Scheme 3). Quinuclidine (**1e**) is 4 orders of magnitude more reactive than **1g** toward both types of electrophiles, and the attack of both electrophiles is 10^2-fold retarded by the naphthylmethyl group in **1f**. The additional hydroxy group in the cinchona alkaloids **1a,b** reduces the reactivities toward the sterically less demanding benzyl group much less (by a factor of 6) than toward the diarylmethylium ions ($> 10^3$).

Computational Analysis

To rationalize why benzyl bromide reacts selectively at the N_{sp3} center of cinchona alkaloids while benzhydrylium ions react selectively at the N_{sp2} center, we have calculated the benzhydryl cation and benzyl cation affinities of quinine and its building blocks at the MP2(FC)/6-31+G(2d,p)//B3LYP/6-31G(d) level.

As illustrated by the reaction enthalpies ΔH_{298} in Figure 3, the substituent effects on the quinoline ring affect its

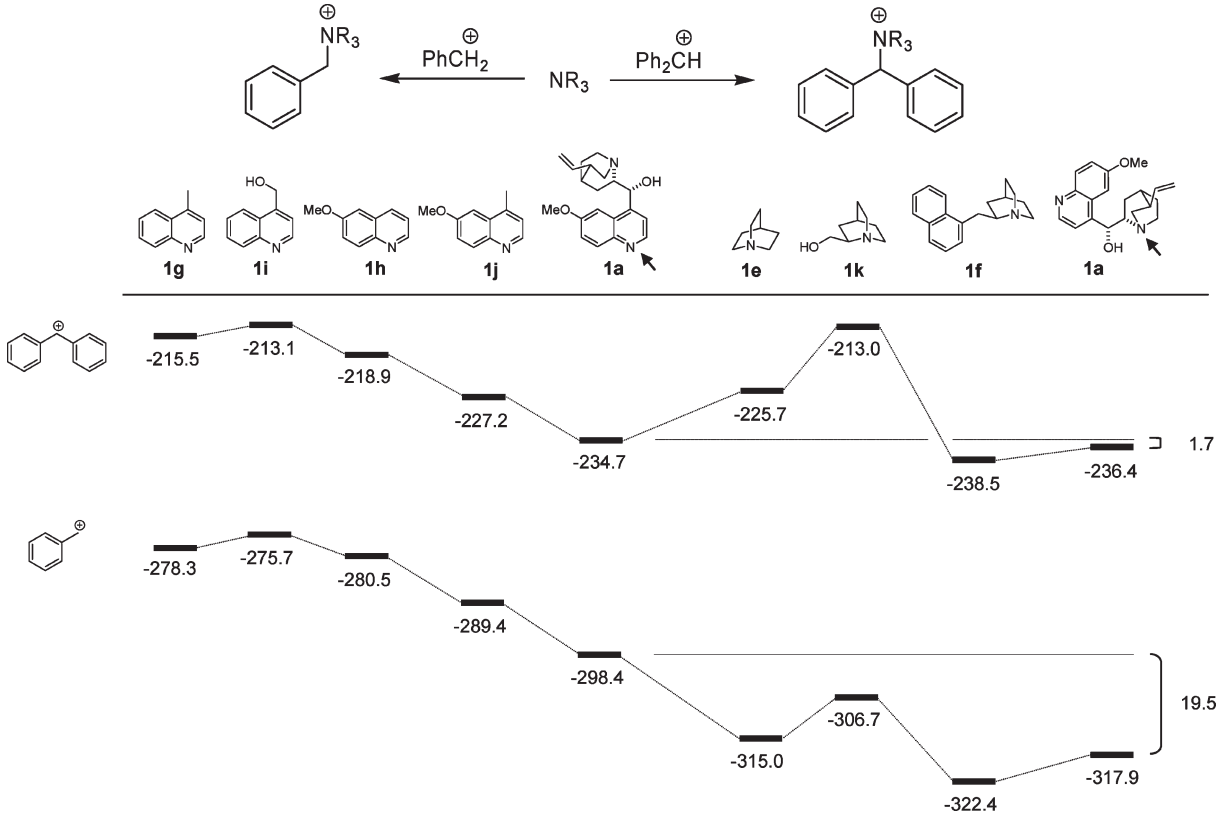


FIGURE 3. Comparison of gas-phase benzyl and benzhydryl cation affinities ΔH_{298} (kJ mol^{-1}) of quinine **1a** and several substructures [MP2(FC)/6-31+G(2d,p)//B3LYP/6-31G(d)].

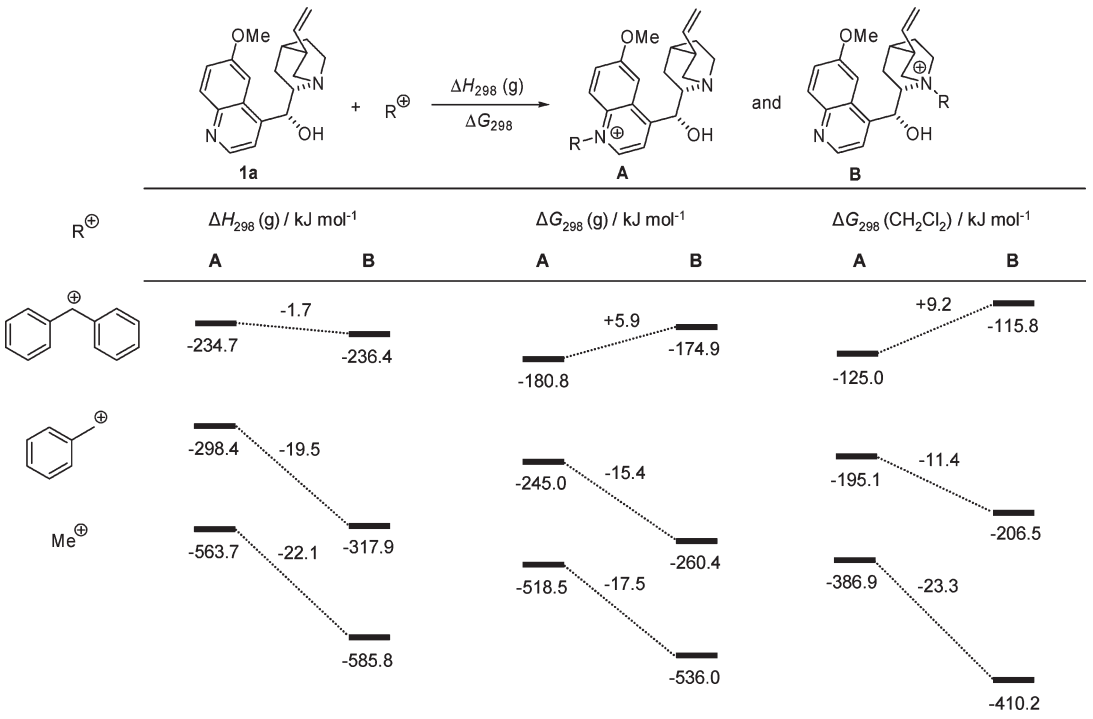
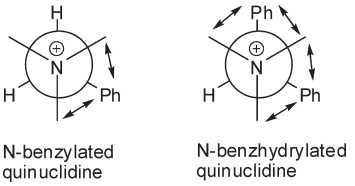


FIGURE 4. Benzhydryl, benzyl, and methyl cation affinities of the different nitrogen atoms of quinine (**1a**) [MP2(FC)/6-31+G(2d,p)//B3LYP/6-31G(d)].

benzhydryl cation and benzyl cation affinities almost equally. Replacement of CH_3 in lepidine (**1g**) by CH_2OH (→ **1i**) reduces the carbocation affinities by 2.5 ± 0.1 kJ mol^{-1}, whereas replacement of the 4-CH_3 group in **1g** by 6-OCH_3 (→ **1h**) raises the cation affinities by 2.8 ± 0.6 kJ mol^{-1}. Introduction of the 6-methoxy group into lepidine (**1g** → **1j**) increases the cation affinities by 11.4 ± 0.3 kJ mol^{-1}, and benzhydrylation or benzylation of the N_{sp2} center of quinine (**1a**) is 19.6 ± 0.5 kJ mol^{-1} more exothermic than that of lepidine (**1g**).

In contrast to the similar trends of the Ph_2CH^+ and $PhCH_2^+$ affinities of the differently substituted quinolines, large differences were calculated for the relative benzhydrylation and benzylation enthalpies of the quinuclidines. While the benzylation of quinuclidine (**1e**) is 37 kJ mol^{-1} more exothermic than the benzylation of lepidine (**1g**), this difference shrinks to 10 kJ mol^{-1} for benzhydrylation, which can be explained by two additional *gauche* interactions.



The lower carbocation affinity of 2-hydroxymethylquinuclidine **1k** (compared with quinuclidine **1e**) can be assigned to the loss of an intramolecular hydrogen bridge by the quaternization. Surprisingly, the introduction of side chains into **1e** to give **1a** or **1f** increases the affinity toward benzhydryl cations more than toward benzyl cations.

Eventually, Figure 4 (left) shows that ΔH_{298}(g) is almost identical for the benzhydrylation of both nitrogens of quinine (**1a**), while ΔH_{298}(g) for benzylation and methylation are considerably more negative for attack at the N_{sp3}- than at the N_{sp2}-center. When ΔG_{298}(g) values are compared, a shift in favor of N_{sp2} alkylation is observed (Figure 4, middle), which is enhanced when solvation is included (Figure 4, right). As a result, the preferred attack of benzyl bromide at N_{sp3} and of benzhydryl cations at N_{sp2} are in line with the relative thermodynamic stabilities of the reaction products. From these results, one can extrapolate that thermodynamic effects will direct sterically demanding electrophiles to the N_{sp2} center of the cinchona alkaloids, while small electrophiles are directed to the N_{sp3} center.

Intrinsic Barriers

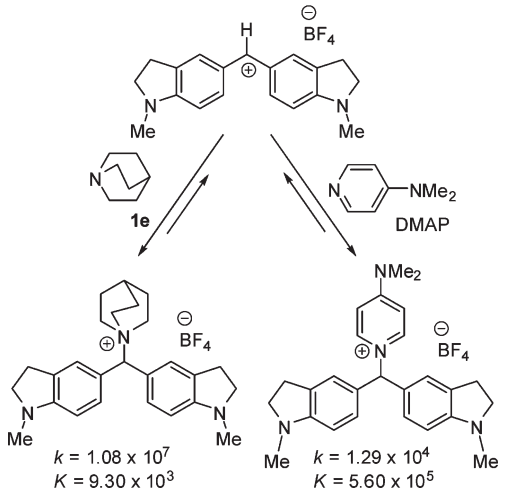
Relative reactivities are, however, not exclusively controlled by the relative stabilities of the products. The Marcus equation (eq 3) expresses the activation free enthalpy of a reaction ($\Delta G^{\ddagger}$) by a combination of the reaction free enthalpy (ΔG^0) and the intrinsic barrier ($\Delta G_0^{\ddagger}$). The latter term ($\Delta G_0^{\ddagger}$) corresponds to the activation free enthalpy ($\Delta G^{\ddagger}$) of a reaction without thermodynamic driving force (i.e., for $\Delta G^0 = 0$).[22]

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger} + 0.5\Delta G^0 + [(\Delta G^0)^2/16\Delta G_0^{\ddagger}] \qquad (3)$$

In previous work, we have shown that quinuclidine is a much stronger nucleophile than DMAP, although the Lewis basicities, i.e., the equilibrium constants for the generation of the ammonium ions, are the other way around (Scheme 4).[18]

(22) (a) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891–899. (b) Albery, W. J. *Annu. Rev. Phys. Chem.* **1980**, *31*, 227–263.

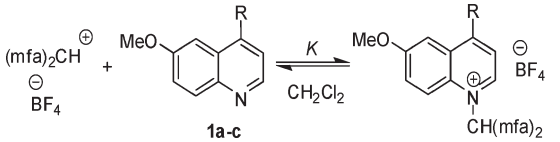
SCHEME 4. Comparison of Second-Order Rate Constants k (M^{-1} s^{-1}) and Equilibrium Constants K (M^{-1}) for Reactions of Quinuclidine and DMAP with $(ind)_2CH^+BF_4^-$ in CH_3CN at 20 °C (from ref 18)



The fact that quinuclidine (**1e**) reacts 10^3 times faster with benzhydrylium ions than DMAP and also departs 50,000 times faster from the benzhydrylium fragment than DMAP has been assigned to the lower intrinsic barrier $\Delta G_0^{\ddagger}$ for the reaction of quinuclidine ($\Delta G_0^{\ddagger} = 43$ kJ mol^{-1}) compared to the corresponding reaction of DMAP ($\Delta G_0^{\ddagger} = 65$ kJ mol^{-1}).[23] Presumably, a large portion of the higher reorganization energy ($\lambda = 4\Delta G_0^{\ddagger}$) in the reaction with DMAP comes from the reorganization of solvent molecules during the formation of the pyridinium ions.

To examine whether differences in intrinsic barriers also affect the different nucleophilicities of the two nitrogen centers in **1a**, we have now determined the intrinsic barriers for the reactions of benzhydrylium ions with some cinchona alkaloids.

The combinations of $(mfa)_2CH^+$ with **1a**−**c** in CH_2Cl_2 (eq 4) do not proceed quantitatively, and the corresponding equilibrium constants have been determined by UV−vis spectroscopy. Assuming a proportionality between the absorbances and the concentrations of the benzhydrylium ions (Lambert−Beer law), the equilibrium constants for reaction 4 can be expressed by the absorbances of the benzhydrylium ions before (A_0) and after (A) the addition of the amines **1a**−**c** (eq 5).



(4)

$$K = \frac{[(mfa)_2CH\text{-}NR_3^+]}{[(mfa)_2CH^+][\mathbf{1}]} = \frac{A_0 - A}{A[\mathbf{1}]} \qquad (5)$$

The equilibrium constants K (Table 3) and rate constants k (Table 1) were then converted into ΔG^0 and $\Delta G^{\ddagger}$, respectively, and inserted into the Marcus equation (eq 3) to give the intrinsic barriers ($\Delta G_0^{\ddagger}$) listed in Table 3.

TABLE 3. Equilibrium Constants (K), Reaction Free Energies (ΔG^0), Activation Free Energies ($\Delta G^{\ddagger}$), and Intrinsic Barriers ($\Delta G_0^{\ddagger}$) for the Reactions of the Benzhydrylium Ion $(mfa)_2CH^+$ with Amines 1a−c in CH_2Cl_2 at 20°C

amine	K/M^{-1}	ΔG^0/kJ mol^{-1} [a]	$\Delta G^{\ddagger}$/kJ mol^{-1} [b]	$\Delta G_0^{\ddagger}$/kJ mol^{-1}
1a	1.55×10^4	−23.5	44.0	55.1
1b	1.79×10^4	−23.9	43.8	55.1
1c	4.98×10^3	−20.7	44.2	54.1

[a] $\Delta G^0 = -RT \ln K$. [b] From k in Table 1, using the Eyring equation.

With $\Delta G_0^{\ddagger} \approx 55$ kJ mol^{-1}, the intrinsic barriers for the reactions of $(mfa)_2CH^+$ with **1a**, **1b**, and **1c** in CH_2Cl_2 are of similar magnitude as the intrinsic barriers for the reactions of pyridine and of *para*-substituted pyridines with benzhydrylium ions in the same solvent.[24] Because the intrinsic barriers for the reactions of benzhydrylium ions with quinuclidine have previously been reported to be approximately 20 kJ mol^{-1} smaller than those for the corresponding reactions with pyridines,[18] we can conclude that a similar difference holds for the electrophilic attack at the two different nucleophilic sites of the cinchona alkaloids. As a consequence, electrophilic attack at the N_{sp3} center can be expected if the thermodynamic stabilities of the two different products are similar.

Conclusion

In previous work we have demonstrated that the N and s parameters of amines, which have been derived from reactions with benzhydrylium ions, can be used to calculate rate constants for their reactions with ordinary Michael acceptors[25] and to predict their relative reactivities toward methyl iodide.[26] For that reason, it can be assumed that the kinetic data derived in this work and the resulting conclusions are also relevant for the reactions of cinchona alkaloids with other types of C-electrophiles.

Quinuclidinium ions arising from N_{sp3} attack of primary alkylating agents at cinchona alkaloids are more stable than the isomeric quinolinium ions arising from the corresponding N_{sp2} attack. In contrast, quinolinium ions are more stable than the isomeric quinuclidinium ions when sterically more demanding alkylating agents are used. Because more reorganization energy is needed for the electrophilic attack at the N_{sp2}- than at the N_{sp3}-center, kinetically controlled quinuclidine alkylation cannot only be expected when the N_{sp3} attack is the thermodynamically favored but also when the N_{sp2} attack is slightly favored by thermodynamics, *i*.e., when the less negative ΔG^0 term for N_{sp3} attack of eq 3 is overcompensated by the smaller intrinsic barrier $\Delta G_0^{\ddagger}$.

Experimental Section

Materials. Commercially available acetonitrile (HPLC gradient grade) and DMSO (H_2O content < 50 ppm) were used

(23) In line with these observations, pyridines have generally been found to be weaker nucleofuges in aminolysis reactions of esters compared with isobasic trialkylamines: (a) Castro, E. A.; Andujar, M.; Toro, A.; Santos, J. G. *J. Org. Chem.* **2003**, *68*, 3608–3613. (b) Castro, E. A.; Aliaga, M.; Campodonico, P.; Santos, J. G. *J. Org. Chem.* **2002**, *67*, 8911–8916. (c) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **1999**, *64*, 8298–8301.

(24) (a) Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr, H. *Chem.—Eur. J.* **2007**, *13*, 336–345.

(25) (a) Seeliger, F.; Berger, S. T. A.; Remennikov, G. Y.; Polborn, K.; Mayr, H. *J. Org. Chem.* **2007**, *72*, 9170–9180. (b) Kaumanns, O.; Mayr, H. *J. Org. Chem.* **2008**, *73*, 2738–2745. (c) Berger, S. T. A.; Seeliger, F. H.; Hofbauer, F.; Mayr, H. *Org. Biomol. Chem.* **2007**, *5*, 3020–3026. (d) Baidya, M.; Mayr, H. *Chem. Commun.* **2008**, 1792–1794.

(26) Phan, T. B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3869–3874.

without further purification. CH_2Cl_2 was freshly distilled over CaH_2. Compounds **1c**, **1f**, and benzhydryl chloride were synthesized according to literature procedures.[27] The benzhydrylium tetrafluoroborates were prepared as described before.[19b] All other chemicals were purchased from commercial sources and (if necessary) purified by recrystallization or distillation prior to use.

Kinetics. The reactions of amines with the colored benzhydrylium ions (Ar_2CH^+) were followed photometrically at the absorption maxima of Ar_2CH^+ by UV−vis spectroscopy using stopped flow techniques as described previously.[19,20] The pseudo-first-order rate constants k_{obs} were obtained by least-squares fitting of the absorbances to the monoexponential function $A_t = A_0 \exp(-k_{obs}t) + C$. The reactions of amines with benzyl bromide were followed by conductimetry. The first-order rate constants k_{obs} were obtained by least-squares fitting of the conductance data to the single exponential equation as mentioned in the text before. The temperature of the solutions during all kinetic studies was kept constant at 20 °C using a circulating bath thermostat.

Determination of Equilibrium Constants. Equilibrium constants were determined by UV−vis spectroscopy as follows: To solutions of the benzhydrylium tetrafluoroborate $(mfa)_2CH^+BF_4^-$ in CH_2Cl_2 were added small amounts of stock solutions of the amines **1a**−**c**, and the absorbances of $(mfa)_2CH^+BF_4^-$ were monitored at λ_{max} (593 nm) before (A_0) and immediately after (A) the addition of amines. This procedure was carried out with five to six different concentrations of the amines **1a**−**c**. The temperature was kept constant at 20 °C using a circulating bath thermostat.

Computational Details. The protocol for searching the conformational space of the, in part, very flexible systems and for calculating reaction enthalpies follows closely that used in recent studies of carbocation affinities of neutral N- and P-based nucleophiles.[28] This protocol involves a combination of geometry optimizations using the MM3 force field as implemented in the Tinker program package[29] with geometry optimizations and frequency calculations at the B3LYP/6-31G(d) level of theory and finally single point calculations at the MP2(FC)/6-31+G(2d,p) level. To account for the effects of solvation in apolar organic solvents, solvation free energies in dichloromethane have been calculated for all conformers located in the gas phase through single point calculations at the PCM/UAHF/RHF/6-31G(d) level of theory.[30] All quantum mechanical calculations have been performed using the *Gaussian 03* program package.[31]

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (Ma673/21-2) and the Fonds der Chemischen Industrie for financial support. Valuable suggestions by Dr. Armin R. Ofial are gratefully acknowledged.

Supporting Information Available: NMR spectroscopic characterization of the products, details of the equilibrium and rate measurements, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

(27) (a) For the synthesis of **1c**: Pettit, G. R.; Gupta, S. K. *J. Chem. Soc. C* **1968**, 1208–1213. (b) For the synthesis of **1f**: see ref 13a. (c) For the synthesis of benzhydryl chloride: Denegri, B.; Streiter, A.; Juric, S.; Ofial, A. R.; Kronja, O.; Mayr, H. *Chem.—Eur. J.* **2006**, *12*, 1648–1656.

(28) (a) Wei, Y.; Sastry, G. N.; Zipse, H. *Org. Lett.* **2008**, *10*, 5413–5417. (b) Wei, Y.; Sastry, G. N.; Zipse, H. *J. Am. Chem. Soc.* **2008**, *130*, 3473–3477. (c) Wei, Y.; Singer, T.; Mayr, H.; Sastry, G. N.; Zipse, H. *J. Comput. Chem.* **2008**, *29*, 291–297.

(29) Ponder, J. W. *TINKER*, 4.2 ed.; **2004**; http://dasher.wustl.edu/tinker/.

(30) (a) Cances, M. T.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3041. (b) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *106*, 5151–5158. (c) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253–260. (d) Amovilli, C.; Barone, V.; Cammi, R.; Cances, E.; Cossi, M.; Mennucci, B.; Pomelli, C. S.; Tomasi, J. *Adv. Quantum Chem.* **1998**, *32*, 227–261. (e) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43–54.

(31) Frisch, M. J. et al.; *Gaussian 03, revision D.01*; Gaussian, Inc.: Wallingford, CT, **2004**.