Conformational Behavior of Cinchonidine in Different Solvents: A Combined NMR and ab Initio Investigation

Thomas Bürgi and Alfons Baiker*

Contribution from the Laboratory of Technical Chemistry, ETH Zentrum, CH-8092 Zürich, Switzerland

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Abstract: The conformation of cinchonidine in solution has been investigated by NMR techniques as well as theoretically. Three conformers of cinchonidine are shown to be substantially populated at room temperature, Closed(1), Closed(2), and Open(3), with the latter being the most stable in apolar solvents. The stability of the closed conformers relative to that of Open(3), however, increases with solvent polarity. In polar solvents the three conformers have similar energy. The relationship between relative energies and the dielectric constant of the solvent is not linear but resembles the form of an Onsager function. Ab initio and density functional reaction field calculations using cavity shapes determined by an isodensity surface are in good agreement with experiment for solvents which do not show strong specific interaction with cinchonidine. The role of the conformational behavior of cinchonidine is illustrated using the example of the platinum-catalyzed enantioselective hydrogenation of ketopantolactone in different solvents.

Introduction

Cinchona alkaloids are widely used in asymmetric synthesis both in homogeneous[1,2] and heterogeneous[3−5] reactions. Addition of catalytic amounts of alkaloid to the reaction mixture leads to preferential reaction or formation of one enantiomer. At the origin of this enantioselectivity lies a specific interaction of the alkaloid with the reactant molecule, leading to energetic favoring of one diastereomeric complex over the other. It seems obvious that this specific interaction strongly depends on the conformation of the alkaloid itself, and to get a detailed picture of the reaction mechanism on a molecular level the conformation of the alkaloid has to be investigated. In the most dramatic scenario the conformation determines the chirality of the product if different conformers of the alkaloid favor the outcome of product with opposite chirality. For the 1,3−hydron transfer reaction catalyzed by dihydroquinidine,[6] for example, it has been demonstrated that the solvent affects the chirality of the product through its influence on the conformation of dihydroquinidine.

Also in heterogeneous catalysis, examples are known where the conformation of cinchona alkaloids is crucial. In the heterogeneous enantioselective hydrogenation of ketopantolactone over cinchonidine-modified Pt, for example, previous investigations indicate that one conformer of cinchonidine plays a dominant role for the enantiodifferentiation.[4] Specifically, systematic modification of cinchonidine suggests that in the transition state the interaction with the ketopantolactone takes place through the quinuclidine N, likely through hydrogen bonding. Furthermore, in the transition state the reactant requires access to activated hydrogen from the Pt surface. Molecular modeling calculations indicate that these two requirements are only simultaneously fulfilled if cinchonidine adopts a specific conformation.[7] The importance of the conformation of cinchonidine for homogeneous as well as heterogeneous asymmetric catalysis prompted us to investigate the solvent-dependent conformational behavior using a combined NMR and ab initio reaction field approach.

The conformation of several cinchona alkaloids and derivatives has been the subject of some experimental work in the past.[6,8−12] The most extensive study was performed by Dijkstra and co-workers [8−10] using mostly nuclear Overhauser enhancement spectroscopy (NOESY). This is also the only study reported so far for (dihydro)cinchonidine. It was concluded that 90% of dihydrocinchonidine adopts conformation Open(3) in the solvents investigated. On the theoretical side many investigations report on the conformation of cinchona alkaloids.[7,8,10,11,13,14] However, all of the reported studies either used empirical potentials, semiempirical methods, or ab initio methods with small basis sets, leading to considerable uncertainty in the relative energies of the conformers. None of the reported studies incorporates solvent effects.

Methods

(a) NMR Experiments. NMR spectra were recorded on Bruker DPX 200, DPX 300, and AMX 500 spectrometers. Information on the conformation was obtained from nuclear Overhauser enhancement

(1) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*; VCH Publishers: Weinheim, 1993.
(2) Wynberg, H. *Topics in Stereochemistry*; Wiley: New York, 1986; Vol. 16.
(3) Blaser, H. U.; Mueller, M. *Stud. Surf. Sci. Catal.* **1991**, *59*, 73−92.
(4) Baiker, A. *J. Mol. Catal. A: Chem.* **1997**, *115*, 473−493.
(5) Baiker, A.; Blaser, H. U. *Handbook of Heterogeneous Catalysis*; VCH Publishers: Weinheim, 1997; Vol. 5; pp 2422−2436.
(6) Aune, M.; Gogoll, A.; Matsson, O. *J. Org. Chem.* **1995**, *60*, 1356−1364.
(7) Schürch, M.; Schwalm, O.; Mallat, T.; Weber, J.; Baiker, A. *J. Catal.* **1997**, *169*, 275−286. Schürch, M.; Künzle, N.; Mallat, T.; Weber, J.; Baiker, A. *J. Catal.* **1998**, *176*, 569−571.
(8) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069−8076.
(9) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 195−204.
(10) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *J. Org. Chem.* **1990**, *55*, 6121−6131.
(11) Berg, U.; Aune, M.; Matsson, O. *Tetrahedron Lett.* **1995**, *36*, 2137−2140.
(12) Sai, T.; Takao, N.; Sugiura, M. *Magn. Reson. Chem.* **1992**, *30*, 1041−1046.
(13) Oleksyn, B. J.; Suszko-Purzycka, A.; Dive, G.; Lamotte-Brasseur, J. *J. Pharm. Sci.* **1992**, *81*, 122−127.
(14) Marrer, S. *Pharm. Acta Helv.* **1989**, *64*, 338−344.

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spectroscopy (NOESY),[15] low-temperature NMR experiments, and vicinal coupling constants. Signal assignment was assisted through correlation spectroscopy (COSY). Spectra were measured at 20 °C, unless otherwise noted. Only dilute solutions of cinchonidine (14 mM) were used to determine coupling constants in order to suppress autoaggregation.[16] For NOESY, concentrations were 34 mM. Typical NOESY spectra were obtained for spectral width of 12 × 12 ppm, using acquisition, relaxation, and mixing times of 0.57, 2.0, and 0.8 s, respectively. Cinchonidine (98% Fluka) was used as received, and methoxycinchonidine was prepared using standard procedures.

(b) Calculations. All calculations were performed using GAUSSIAN94[17] on a HP/Convex Exemplar SPP2000/X-32 and a HP model 735 workstation. Minimum-energy structures were computed at the Hartree−Fock (HF) level using a standard 6-31G** basis set (440 basis functions) by complete optimization of the $3N - 6 = 126$ internal degrees of freedom. To investigate the influence of diffuse basis functions, single-point calculations were performed using a 6-31+G* basis set. The effect of correlation was tested using a density functional hybrid method introduced by Becke[18] where the nonlocal correlation is provided by the LYP expression[19] (B3LYP keyword in GAUSSIAN94).

Solvent effects were investigated by performing single-point calculations at the gas-phase optimized structure using a self-consistent reaction field method recently implemented[17] which is conceptually related to the well-known Onsager reaction field model.[20] Briefly, the solute is accommodated in a cavity surrounded by a continuous dielectric medium. In contrast to the Onsager model where only dipolar interactions are considered, the dipole expansion is carried out to infinite order.[21] The cavity is adapted to the shape of the molecule rather than being a sphere as in the simple Onsager model. This is naturally achieved by choosing an isodensity surface as the cavity boundary. A value of 0.0004 au was chosen as the isodensity level, resulting in a cavity volume very close to the value derived from the molar volume. Mutual coupling between cavity and electron density is accounted for self-consistently by explicitly considering the solvation energy in each SCF step (scipcm option in GAUSSIAN94).[22]

ΔG was calculated using the standard statistical mechanical expressions for an ideal gas in the canonical ensemble. For this, gas phase vibrational energies were calculated using the AM1 semiempirical method. The energy contribution to create the cavity was neglected. The cavity volume and the solvent-accessible surface area are very similar for the different conformers, and hence the energy to create the cavity cancels when only relative energies are to be considered. The entropy was not corrected for solute concentration, since the cinchonidine concentration is very low and since this correction term is expected to be similar for the different conformers, thus canceling when considering relative energies.[23]

Results

(a) Calculations: Geometry and Relative Energy of Cinchonidine Conformers. Cinchonidine (Figure 1) shows a rich conformational behavior. The most important degrees of freedom are the two torsional angles τ_1: $C_3-C_4-C_9-C_8$ and τ_2: $C_4-C_9-C_8-N$ which determine the relative orientation of the quinoline and quinuclidine moieties. Other degrees of freedom are the orientation of the O−H and the vinyl group and the conformation of the quinuclidine ring (left- or right-handed screw).[8] The conformers with the hydroxyl H pointing away from the quinuclidine ring are calculated to be more stable with some, for our purposes, however, unimportant exceptions (see later). The quinuclidine ring turned out to adopt a left-handed screw conformation as was found for dihydroquinine,[8] and the C=C double bond of the vinyl group was in cis arrangement with the $C-H_{17}$ bond (Figure 1), in accordance with the crystal structure of cinchonidine.[24]

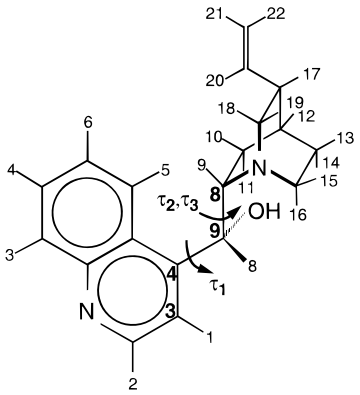

Figure 1. Cinchonidine atom numbering and definition of τ_1, τ_2, and τ_3 dihedral angles.

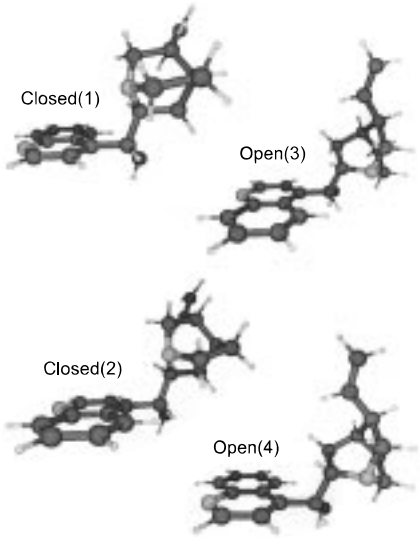

Figure 2. Ball-and-stick plot of the four most stable conformers of cinchonidine. Geometries are fully optimized at the HF level using a 6-31G** basis set.

In the two-dimensional conformational subspace of τ_1 and τ_2, six minima corresponding to six conformers exist on the potential energy surface (PES).[25] The structure of all six conformers was fully optimized on the HF 6-31G** PES. Figure 2 shows the ball-and-stick plots of the four most stable conformers which are labeled as in previous work.[7] For closed conformers the lone pair of the quinuclidine N points toward the quinoline ring. Table 1 gives the dihedral angles as defined

(15) States, D. J.; Haberkorn, R. A.; Ruben, D. J. *J. Magn. Reson.* **1982**, *48*, 286−292.
(16) Uccello-Barretta, G.; Bari, L. D.; Salvadori, P. *Magn. Reson. Chem.* **1992**, *30*, 1054−1063.
(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. GAUSSIAN94 (revision E.1); Gaussian, Inc., Pittsburgh, PA, 1995.
(18) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(19) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(20) Onsager, L. *J. Am. Chem. Soc.* **1936**, *58*, 1486−1493.
(21) Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098−16104.
(22) Foresman, J. B.; Frisch, A. *Exploring Chemistry with Electronic Structure Methods.*; 2nd ed.; Gaussian Inc.: Pittsburgh, 1996.
(23) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 1645−1652.
(24) Oleksyn, B. J. *Acta Crystallogr.* **1982**, *B38*, 1832−1834.
(25) Carrol, F. I.; Abraham, P.; Gaetano, K.; Mascarella, S. W.; Wohl, R. A.; Lind, J.; Petzoldt, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, *1*, 3017−3026.

Table 1. Calculated Dihedral Angles (deg) for Several Conformers of Cinchonidine[a]

	Closed(1)	Closed(2)	Open(3)	Open(4)	Open(5)	Open(6)
τ_1	−107.0	80.4	101.4	−89.3	85.7	−98.7
τ_2	57.5	65.3	153.6	150.1	−48.6	−54.9
τ_3	−176.8	−172.5	−78.3	−77.5	76.2	74.0

[a] τ_1: $C_3-C_4-C_9-C_8$, τ_2: $C_4-C_9-C_8-N$, τ_3: $H_9-C_8-C_9-H_8$ (see Figure 1). Complete optimization is Performed at the ab initio Hartree−Fock level using a standard 6-31G** basis set.

Table 2. Calculated Electronic Energy ΔE_{elec}, Gibbs Free Energy ΔG and Dipole Moment (D) for Several Cinchonidine Conformers[a]

		Closed(1)	Closed(2)	Open(3)	Open(4)
HF 6-31G**	ΔE_{elec}	1.43	2.14	0.00	3.33
	ΔG	1.17	1.32	0.00	3.35
	μ	2.70	2.81	1.74	1.84
HF 6-31+G*	ΔE_{elec}	1.11	1.84	0.00	3.29
	ΔG	0.85	1.02	0.00	3.31
	μ	2.88	2.98	1.85	1.97
B3LYP 6-31+G*	ΔE_{elec}	1.27	1.85	0.00	2.78
	ΔG	1.01	1.03	0.00	2.80
	μ	2.61	2.89	1.84	1.97

[a] All energies are in kcal/mol and relative to the most stable conformer Open(3). The electronic energy is calculated at the ab initio HF level using a 6-31G** and 6-31+G* basis set, respectively, and at the density functional level (B3LYP) using a 6-31+G* basis set. Thermal corrections are based on vibrational energies calculated using the AM1 semi-empirical method (see text). The temperature is set to 298 K.

in Figure 1. The angles are in qualitative agreement with the ones reported earlier using the MM2 force field and ab initio HF 3-21G method.[7] We note, however, that the torsional angles change up to 34° when going from MM2 to ab initio HF 6-31G**. The six conformers can be grouped according to the dihedral angles τ_1 and τ_2. For stable conformations τ_1 adopts values of either $-100 \pm 10°$ or $90 \pm 10°$. Closed(1), Open(4), and Open(6) belong to the first group. For these conformers, the O−H group is pointing toward H_5. For the other three conformers, the O−H group is directed toward H_1. In τ_2 three minima are located at $60 \pm 5°$ (closed conformers), $150 \pm 5°$ (Open(3) and (4)), and $-50 \pm 5°$ (Open(5) and (6)).

Table 2 gives the calculated gas-phase electronic (ΔE_{elec}) and Gibbs free energy (ΔG) of the four most stable conformers relative to conformer Open(3). Conformer Open(3) is the most stable followed by Closed(1), Closed(2), and Open(4). Conformers Open(5) and Open(6) ($\Delta E_{elec} = 6.78$ and 5.94 kcal/mol, respectively, for HF 6-31G**) are too high up in energy to play a significant role at room temperature. It is for these two conformers that upward orientation of the O−H group leads to slight stabilization due to a weak intramolecular hydrogen bond. Note that only the corresponding conformers 1−3 have been observed in NOESY experiments for some quinine and quinidine derivatives.[10] Table 2 also shows that inclusion of diffuse basis functions and changing from HF to density functional theory has only small effects on the gas-phase relative energies.

Solvent Dependence. Table 3 gives the relative energy in media with dielectric constants ϵ_r of 1.0 (gas phase), 2.0 (cyclohexane), 4.8 (chloroform), 20.7 (acetone), and 78.5 (water) at different levels of theory and Figure 3 shows a plot of the relative energy as a function of ϵ_r. The solvent has a considerable effect on the relative stability of the conformers. Closed(1) and (2) are strongly stabilized relative to Open(3) when going from $\epsilon_r = 1.0$ (gas phase) to $\epsilon_r = 78.5$, whereas conformer Open(4) is hardly stabilized. Inclusion of diffuse basis functions has no prominent effect. When density functional theory is used, the stabilization of the closed conformers relative to Open(3) is slightly less prominent when going from gas phase to polar solvents, amounting to about 0.7 kcal/mol.

Table 3 also gives the populations of cinchonidine conformers at room temperature calculated from the ΔG values. In apolar media conformer Open(3) prevails, in accordance with the results reported by Dijkstra and co-workers.[8] In polar media, however, the closed conformers are almost equally stable, according to our calculations. The values in Table 3 will have to be compared to those obtained by NMR experiments as described in the next section.

(b) NMR Experiments: Signal Assignment. As an example, we describe the assignment of the ^1H NMR spectrum for cinchonidine in d_6-acetone (spectrum available in Supporting Information). The aromatic protons H_1 and H_2 appear as doublets at δ 7.60 and 8.84, respectively. H_5 appears as a doublet at δ 8.28 with an ortho coupling to H_6 at δ 7.56 which appears as a multiplet owing to an additional ortho coupling to H_4 at δ 7.71. H_4 is also ortho coupled to H_3, appearing as a doublet at δ 8.05. The vinyl protons H_{20}, H_{21}, and H_{22}, respectively, appear as multiplets at δ 5.89, 4.91, and 4.97, respectively. H_8 which is easily identified by its NOE with H_5 and H_1, respectively, appears as doublet at δ 5.50. COSY identifies H_9 at δ 3.20 through its coupling with H_8. For H_9 COSY shows only two strong cross-peaks, one with H_8 and one with two protons at δ 1.78. This signal is therefore assigned to H_{10} and H_{11} which is supported by a NOE between H_9 and H_{10}. H_{20} shows a COSY cross-peak and a weak NOE with a signal at δ 2.23 which is assigned to H_{17}. This proton shows additional cross-peaks in COSY with signals at δ 1.78, 2.51, and 2.93 which are associated with H_{12}, H_{18}, and H_{19}. H_{19} at δ 2.93 is identified by its strongest NOE with H_{17}, and the assignment of H_{18} at δ 2.51 is supported by a NOE with H_9. H_8 shows a NOE with one of the remaining signals at δ 3.33 which can only be H_{16} since none of the remaining protons $H_{13}-H_{15}$ can be in close proximity with H_8. H_{16} shows a very strong NOE with a signal at δ 2.51, which is therefore assigned to its geminal proton H_{15}, and a weaker NOE with H_{14} at δ 1.73. The remaining signal at δ 1.49 is therefore assigned to H_{13}. This assignment is supported by the observed NOE of H_{13} with H_{14}, H_{15}, and H_{17}, respectively. The O−H proton is associated with a broad signal at δ 2.78, showing a NOE with H_8.

Identification of Conformers. For the identification of conformers interring NOEs between the quinoline and quinuclidine protons and NOEs involving H_8 and H_9 are most useful. Table 4 shows a selection of interproton distances for the three most stable conformers. In acetone NOEs were detected between H_1 and H_{16}, H_{11}, H_9, and H_8, respectively, and between H_5 and H_{16}, H_9 and H_8, respectively, among others. The H_1 and H_8 NOESY traces are available in the Supporting Information. The observed NOE between H_1 and H_{16} is indicative for conformer Closed(1) (see Table 4) which is supported by the NOE between H_1 and H_8. The strong NOE between H_5 and H_8 suggests the presence of conformer Closed(2) and/or Open(3). The presence of Open(3) is confirmed by the NOE between H_1 and H_{11}, while NOEs between H_1 and H_9 and between H_5 and H_{16} show that conformer Closed(2) is also present. We could not observe a NOE between H_5 and H_{11} which would be indicative of conformer Open(4). Hence, NOESY experiments suggest the presence of conformers Closed(1), Closed(2), and Open(3) in acetone, which is in qualitative agreement with the calculations presented above. The fraction of conformer Closed(1) in acetone can be estimated by comparing the NOE signals of H_8 with H_1

Table 3. Calculated Relative Energy ΔE_{elec} and Gibbs Free Energy ΔG (kcal/mol) of Different Conformers of Cinchonidine as a Function of Dielectric Constant ϵ_r of the Solvent[a]

		Closed(1)			Closed(2)			Open(3)			Open(4)	
	ϵ_r	ΔE	ΔG	P	ΔE	ΔG	P	ΔE	ΔG	P	ΔE	ΔG
HF 6-31G**	1.0	1.43	1.17	11	2.14	1.32	9	0.00	0.00	80	3.33	3.35
	2.0	1.16	0.90	16	1.91	1.09	12	0.00	0.00	73	3.25	3.27
	4.8	0.82	0.56	23	1.60	0.78	16	0.00	0.00	60	3.17	3.19
	20.7	0.46	0.20	33	1.26	0.44	22	0.00	0.00	46	3.11	3.13
	78.5	0.35	0.09	35	1.16	0.34	23	0.00	0.00	41	3.09	3.11
HF 6-31+G*	1.0	1.11	0.85	17	1.84	1.02	13	0.00	0.00	70	3.29	3.31
	2.0	0.80	0.54	24	1.55	0.73	17	0.00	0.00	59	3.19	3.21
	4.8	0.43	0.17	33	1.18	0.36	24	0.00	0.00	43	3.09	3.11
	20.7	0.04	−0.22	42	0.81	−0.01	29	0.00	0.00	29	3.03	3.05
	78.5	−0.08	−0.34	44	0.69	−0.13	31	0.00	0.00	25	3.01	3.03
B3LYP 6-31+G*	1.0	1.27	1.01	13	1.85	1.03	13	0.00	0.00	74	2.79	2.81
	2.0	1.08	0.82	17	1.64	0.82	17	0.00	0.00	66	2.72	2.74
	4.8	0.85	0.59	21	1.42	0.60	21	0.00	0.00	58	2.66	2.68
	20.7	0.62	0.36	26	1.18	0.36	26	0.00	0.00	48	2.62	2.64
	78.5	0.55	0.29	27	1.11	0.29	27	0.00	0.00	45	2.61	2.63

[a] All energies are calculated at the optimized ab initio HF/6-31G** gas-phase geometry. Vibrational energies and thermal corrections are calculated at the AM1 semi-empirical level (298 K). Solvation effects are incorporated using a reaction field model (see text). Also given are the derived population P (%) for the three most stable conformers, neglecting the small contribution from conformer Open(4).

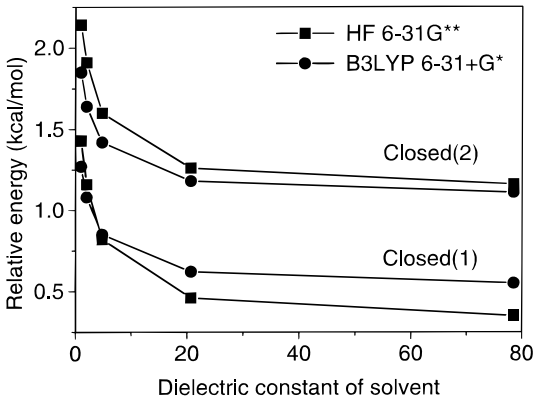

Figure 3. Plot of the electronic energy ΔE_{elec} (kcal/mol) of conformers Closed(1) and Closed(2) relative to Open(3) as a function of dielectric constant. Calculations are performed at the HF 6-31G** and B3LYP 6-31+G* level using a reaction field model (see text). Lines are just to guide the eye. The HF 6-31+G* result is omitted for clarity.

Table 4. Selected Interproton Distances (Å) for the Three Most Stable Conformers of Cinchonidine Derived from Fully Optimized Structures Calculated at the HF 6-31G** Level

	Closed(1)	Closed(2)	Open(3)
H_1-H_{16}	2.76	5.36	4.78
H_1-H_{11}	4.67	4.72	2.79
H_1-H_9	4.28	2.65	4.00
H_1-H_8	2.25	3.67	3.63
H_5-H_{16}	5.36	2.25	4.54
H_5-H_{11}	4.36	4.37	4.94
H_5-H_9	2.31	4.27	2.46
H_5-H_8	3.82	2.09	2.15

and H_5. The H_8-H_1 NOE signal is proportional to the population of conformer Closed(1), whereas the H_8-H_5 NOE signal is approximately proportional to the sum of Closed(2) and Open-(3). Integrating the cross-peak volumes gives a ratio of 1:2.6 for the former relative to the latter. Accounting for the slightly larger interproton distance for Closed(1) by scaling with the sixth power of the relative distances (Table 4) gives a fraction of conformer Closed(1) of $^1/_3$, as predicted by the calculations (Table 3, $\epsilon_r = 20.7$).

The result of a low-temperature NMR experiment, which substantiates the existence of conformer Closed(1) and gives some useful information concerning the interconversion barrier between conformer Closed(1) and Closed(2), is shown in Figure 4. Three ^{1}H NMR spectra of methoxycinchonidine (a synthetic variant of cinchonidine where the O−H group is replaced by a $O-CH_3$ group) in a mixture of $CDCl_3/CD_2Cl_2$ at 293, 223, and 183 K are depicted. At 293 K only one spectrum is observed

Table 5. Vicinal $^3J_{H_8H_9}$ Coupling Constants for Cinchonidine and Derived Population of Conformer Open(3) in Different Solvents[a]

solvent	ϵ_r	$^3J_{H_8H_9}$	$P_{Open(3)}$	P_{Closed}
benzene	2.28	5.0	0.58	0.42
toluene	2.34	4.1	0.70	0.30
ethyl ether	4.3	4.0	0.71	0.29
tetrahydrofurane	7.6	4.7	0.62	0.38
acetone	20.7	6.4	0.40	0.60
dimethylformamide	36.7	7.0	0.33	0.67
dimethyl sulfoxide	40.0	7.5	0.27	0.73
water	78.5	7.2	0.30	0.70
ethanol	24.3	3.5	0.77	0.23

[a] For Open(3) $^3J_{H_8H_9}$ is calculated as 1.7 Hz. For Closed(1) and Closed(2), respectively, $^3J_{H_8H_9}$ is calculated as 9.6 and 9.4 Hz. In the determination of P_{Closed} a value of 9.6 Hz was used. The accuracy of the measured coupling constants is about 0.1 Hz, except for the measurement in water where the uncertainty is a little higher because of bad solubility of cinchonidine.

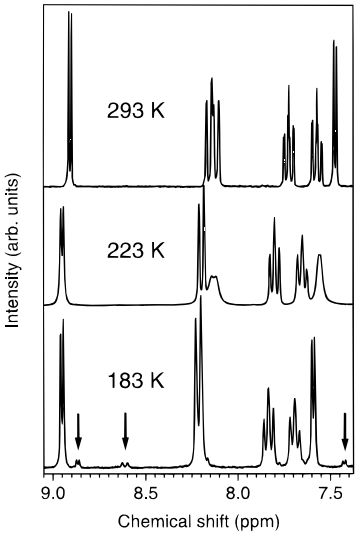

Figure 4. ^{1}H NMR spectra (300 MHz) of 14 mM methoxycinchonidine in a solution of $CDCl_3/CD_2Cl_2$ at 293, 223, and 183 K.

due to fast interconversion between the conformers on the NMR time scale. Lowering the temperature to 223 K leads to coalescence of some of the signals, and further lowering of the temperature results in decoalescence again. Below 223 K a second set of lines is observed (arrows in Figure 4) with an intensity at $T = 183$ K of 6−7% with respect to the main set, corresponding to ΔG (183 K) = 1 kcal/mol. At these low temperatures the interchange between one conformer and the others is so slow that this one conformer exhibits a separate spectrum. Using the broadening of the methoxy signal (not shown), a rate constant for the transition from the minor to the major conformer is estimated as 215 s^{-1}.[26] Using an Eyring equation[27] one can derive $\Delta G^{\ddagger}$(223 K, minor-major) = 10.7 kcal/mol. Such a high barrier is, according to molecular mechanics calculations,[7] only compatible with the interconversion of conformer Closed(1) to Closed(2) or Open(3), i.e., with a torsion along τ_1. The analogous barrier for dihydroquinidine was determined to be 8.3 kcal/mol.[6] Interconversion between conformers Closed(2) and Open(3) is expected to be hindered by 3−4 kcal/mol, which is a barrier too low for separate NMR spectra to be observed at 183 K. We therefore conclude that the separate signals in the 183 K spectrum in Figure 4 labeled with arrows belong to conformer Closed(1) while the major signals are associated with both Closed(2) and Open(3), which still interconvert fast on the NMR time scale. We also note that while the vicinal coupling constant $^3J_{H_8H_9}$ is 3.7 Hz at 293 K it cannot be resolved below 223 K for the major H_8 signal which shows that the minor signal belongs to a closed conformer (see below).

It is not straightforward to obtain populations of the different conformers from NOESY experiments quantitatively by measuring the volume of the cross-peak signals. Uncertainties in the knowledge of interatomic distances and especially their thermal averages for all of the conformers and different time constants can be crucial to the analysis. We therefore chose to obtain quantitative numbers for the populations of the different conformers of cinchonidine by measuring the $^3J_{H_8H_9}$ coupling constant as described below.

Quantification. At room temperature the measured coupling constant $^3J_{H_8H_9(exp)}$ is averaged over the populations $P_{(i)}$ of the different conformers in solution $^3J_{H_8H_9(exp)} = \sum P_{(i)}\ ^3J_{H_8H_9(i)}$. Using the calculated dihedral angles τ_3 for the different conformers (Table 1) and by applying a Karplus equation[28] modified for substituent effects we obtained the coupling constants $^3J_{H_8H_9(i)}$ for the different conformers. The equations proposed by Gandour and co-workers[29] and by Altona and co-workers[30] were applied, yielding very similar results. The method described here is limited to the determination of only two conformers from one experimental value (one coupling constant), despite the fact that NOESY experiments show three conformers to be present. Luckily, however, we note that τ_3 is very similar for the two closed conformers, differing by only 4° (Table 1). We can therefore determine the population of conformer Open(3) and the *sum* of the populations of the closed conformers. In Table 5 the measured coupling constants together with the resulting populations are given for different solvents and in Figure 5 the values for conformer Open(3) $P_{Open(3)}$ are compared to the ones derived from the ab initio calculations.

Discussion

Conformation of Cinchonidine and Its Solvent Dependence. Both NMR results and ab initio reaction field calculations show that, in apolar solvents, conformer Open(3) is the most stable. At all levels of theory applied here the fraction of conformer Open(3) at room temperature is calculated to be about 60−70% for $\epsilon_r = 2$ (Table 3), in excellent agreement with the NMR results (Table 5). The relative stability of the conformers is largely determined by the mutual repulsive interaction between the quinoline, quinuclidine, and O−H parts of the molecule such as the Pauli repulsion between the oxygen atom and H_5 and H_1, respectively. For conformers Closed(1) and Open(4) the O···H_5 distance is shorter than the O···H_1 distance for conformers Closed(2) and Open(3) by about 0.15 Å, leading to a destabilization of the former two conformers. This is supported by comparing the relative (Gibbs free) energies for cinchonidine given in Table 2 with the corresponding energies for deoxycinchonidine (see Supporting Information). In deoxycinchonidine a H atom replaces the O−H group, resulting in less repulsion with H_1 and H_5, respectively. This leads to a stabilization of conformer Closed(1) relative to Open(3) of about 0.7 kcal/mol when going from cinchonidine to deoxycinchonidine. Although Open(3) is still the most stable conformer, Closed(1) has come much closer in energy. Indeed, for deoxycinchonidine in benzene Dijkstra and co-workers[10] found conformer Closed(1) in considerable amounts (40%) besides Open(3).

ΔG and ΔE_{elec} are quite similar for the cinchonidine conformers except for conformer Closed(2) where the relative ΔG value is significantly lower than that for ΔE_{elec} (Table 2). A similar trend is found for deoxycinchonidine (see Supporting Information). This effect can be understood when considering the *shape* of the PES in τ_1 and τ_2. A two-dimensional PES map for τ_1 and τ_2 calculated using the MM2 force field has been reported recently.[7] The potential minimum corresponding to conformer Closed(2) is the most "shallow" one. This leads to lower frequencies for the two vibrational modes associated with the τ_1 and τ_2 degrees of freedom for conformer Closed(2) as compared to Open(3). This reflects itself in an increased vibrational partition function for Closed(2) relative to Open(3) and hence in a stabilization of the former relative to the latter when going from ΔE_{elec} to ΔG.

Table 3 shows that polar solvents stabilize the closed conformers relative to Open(3), whereas Open(4) is hardly stabilized. The most important quantity for the solvation interaction is the dipole moment of the solute molecule which depends on its conformation. The stabilization should therefore correlate with the dipole moment of the conformers. Table 2 shows that this is indeed the case. Conformers Closed(1) and (2) have a dipole moment larger than those of Open(3) and Open(4), whereas the dipole moment of the latter two is similar. The stabilization of the closed conformers relative to Open(3) when going from the gas phase to polar solvents is calculated to be 1.0−1.2 kcal/mol at the HF approximation (Table 3).

Another interesting point is the *form* of the curve ΔE_{elec} vs ϵ_r shown in Figure 3. The relative energies change most at low dielectric constants. The Onsager model of solvation,[20] for which analytical formula can be given, predicts the solvation energy to be proportional to the Onsager function $(\epsilon_r - 1)/(2\epsilon_r + 1)$. Indeed the curves shown in Figure 3 strongly resemble the Onsager function. Plotting ΔE_{elec} versus the Onsager function

(26) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982.
(27) Glasstone, S.; Laidler, K. J.; Eyring, H. *The Theory of Rate Processes*; McGraw-Hill: New York, 1941.
(28) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11−15.
(29) Colucci, W. J.; Jungk, S. J.; Gandour, R. D. *Magn. Reson. Chem.* **1985**, *23*, 335−343.
(30) Haasnoot, C. A. G.; Leeuw, F. A. A. M. d.; Altona, C. *Tetrahedron* **1979**, *36*, 2783−2792.

(not shown) does not yield a perfectly straight line, however, which is due to incorporation of higher order electrostatic terms, nonspherical cavity shapes, and backpolarization of the solvent by its reaction field in the applied model. A similar relation to the Onsager function was found for the energy differences between isomers of furfuraldehyde.[21]

The presented reaction field calculations were all performed using the gas-phase optimized structures, thus neglecting changes of the individual conformer structures induced by solvation. The validity of this assumption was checked. Conformers Open(3) and Closed(1) were fully optimized, incorporating the reaction field for $\epsilon_r = 20.7$. In both cases the resulting additional stabilization was small (about 0.2 kcal/mol). These additional stabilization energies even cancel when considering only relative energies. Only minor structural changes were observed by incorporating the reaction field during optimization. The dihedral angles $\tau_1 - \tau_3$ changed by less than 5 degrees. While solvation has a considerable effect on the relative stability of the conformers their individual structure is largely unaffected.

Figure 5 shows the good agreement between experiment and calculation, especially the dependence of $P_{Open(3)}$ on the dielectric constant ϵ_r is reproduced well by the calculations. At large dielectric constants, the HF 6-31G** and the density functional 6-31+G* calculations somewhat overestimate the stability of conformer Open(3), predicting a population of about 0.45 whereas the experiment gives a value closer to 0.3. This discrepancy corresponds to a difference in ΔG of about 0.3 kcal/mol between the experiment and the calculations which can be considered as excellent. For the HF 6-31+G* calculation, the $P_{Open(3)}$ values are even closer in agreement with the experiment. The achieved agreement between experiment and ab initio calculations has its price. Previously reported[7] relative gas-phase energies for the different conformers indicate that a smaller and considerably less computer time-consuming 3-21G basis set does not yield the accuracy reported here.

It has also to be noted that applying a Karplus equation with substituent correction might introduce a systematic error in the determination of the mean torsional angle and the population of conformers thereof. From the work of Gandour and coworkers[29] it is concluded that, for a given dihedral angle, the $^3J_{H_8H_9}$ coupling constant can be predicted with an error of 0.77 Hz (one standard deviation). This transfers to a systematic error in $P_{Open(3)}$ of about 0.1 for the experimentally determined values. Since we always consider the same molecule (cinchonidine) and only change the solvent in the present study, this systematic error affects all the experimentally determined values for $P_{Open(3)}$ in the same way. We note that the calculated values for $P_{Open(3)}$ almost fall within this systematic error in the experimental determination of $P_{Open(3)}$.

The relatively large scatter of the experimental $P_{Open(3)}$ values around the theoretically predicted shape of $P_{Open(3)}$ versus ϵ_r probably reflects specific interactions of cinchonidine with the various solvents which are beyond the applied reaction field model. The calculations discussed above can very well describe the nonspecific interaction of the solvent with the solute (cinchonidine). These interactions have their origin in the polarization of the solvent due to the electrostatic potential associated with the solute and the backpolarization of the solute due to the polarization of the solvent. Specific interactions can also affect the conformation. In the case of cinchonidine, hydrogen bonding of the solvent to the quinuclidine N shows an effect on the conformation. Figure 5 shows that in ethanol the population of conformer Open(3) is much higher than would be expected on the basis of its dielectric constant. We ascribe

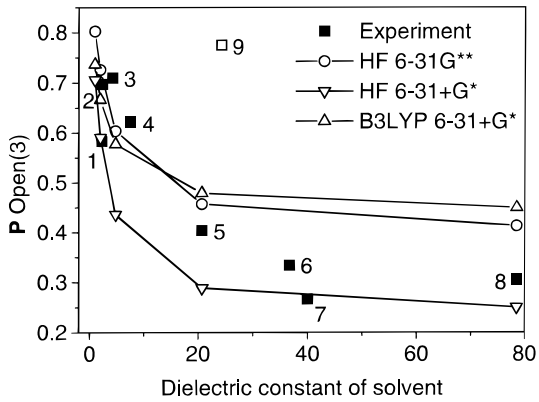

Figure 5. Plot of the population of conformer Open(3) ($P_{Open(3)}$) versus the dielectric constant of the solvent. Experimental values are determined from $^3J_{H_8H_9}$ coupling constants using a modified Karplus equation (see text). The solvents are (1) benzene, (2) toluene, (3) ethyl ether, (4) tetrahydrofurane, (5) acetone, (6) dimethylformamide, (7) dimethyl sulfoxide, (8) water, (9) ethanol. The calculated values are derived from ΔG values obtained from a reaction field model in combination with HF and density functional calculations (for details see text). The lines are just to guide the eye.

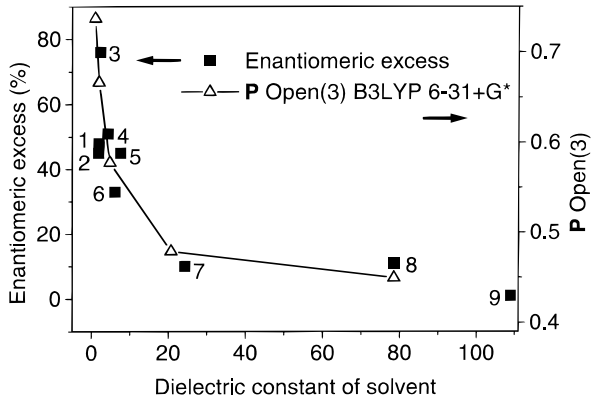

Figure 6. Combined plot of the enantiomeric excess achieved in the hydrogenation of ketopantolactone over cinchonidine-modified Pt[7] (left axis) and the population of conformer Open(3) as calculated by density functional theory in combination with a reaction field model ($P_{Open(3)}$, right axis) versus the dielectric constant of the solvent. The axis scale is arbitrarily chosen. The solvents are (1) cyclohexane, (2) hexane, (3) toluene, (4) diethyl ether, (5) tetrahydrofurane, (6) acetic acid, (7) ethanol, (8) water, (9) formamide.

this effect to hydrogen bonding of ethanol to the quinuclidine N which stabilizes Open(3) relative to the closed conformers. In conformer Open(3) ethanol is unhindered to bind to the quinuclidine N, whereas in the closed conformers the interaction is hindered as a result of repulsion with the quinoline moiety. This hindrance is less pronounced for smaller solvent molecules such as water.

An Example for the Importance of the Solvent-Dependent Conformational Behavior of Cinchonidine. The present work clearly demonstrates the effect of solvent polarity on the conformation of cinchonidine. The conformation of cinchonidine is one important factor determining the geometry and energetics of the relevant transition-state complexes in some asymmetric reactions. Solvent polarity is therefore anticipated to affect these reactions through its influence on the cinchonidine conformation. This point is illustrated with an example investigated in our own laboratory.[7] Figure 6 shows a plot of the enantiomeric excess ee (%) = $100|[R] - [S]|/([R] + [S])$ achieved in the enantioselective hydrogenation of ketopantolactone over cinchonidine-modified Pt as a function of the dielectric constant

ϵ_r of the solvent used. [R] and [S] are the concentrations of R and S products, respectively, in the product solution. The ee decreases with increasing dielectric constant, but the relationship between the two is highly nonlinear. Superimposed in the same plot is the population of conformer Open(3) obtained from density functional calculations in combination with a reaction field model, as discussed above. The two axes for ee and $P_{Open(3)}$ are arbitrarily chosen. It is obvious from Figure 6 that ee and $P_{Open(3)}$ show the same trend with respect to the dielectric constant of the solvent. Note that a similar behavior is found in the case of hydrogenation of ethylpyruvate over cinchonidine-modified Pt.[31] A change in solvent certainly has several effects on the reaction. The solubility of the reactants, their mass transport properties, and the adsorption behavior on the Pt active sites are directly affected by the solvent. None of the above-mentioned factors, however, can explain the observed dependence of ee on solvent polarity, whereas the conformational behavior of cinchonidine offers a rational explanation for the observed solvent effect. The relation between ee and the population of conformer Open(3) presented in Figure 6 is in complete agreement with the suggestion that Open(3) is the crucial conformer involved in the enantiodifferentiating transition state.[4]

We have found that apart from the solvent several other factors influence ee and the fraction of conformer Open(3) in solution in the same way. Addition of small amounts of water to apolar solvents results in a prominent decrease in ee.[32] Addition of a small amount of water to toluene (about 1μL/600μL) also resulted in an increase of $^3J_{H_8H_9}$ from 4.1 to 4.9 Hz, corresponding to a decrease of the population of conformer Open(3) of about 10%. Lowering the temperature favors Open-(3) over the other conformers since it is the most stable one and similarly results in higher ee.[7,33,34] Protonation of cinchonidine at the quinuclidine N increases ee[32,35] and induces a transition to conformer Open(3) revealed by a drastic decrease in $^3J_{H_8H_9}$ and the loss of the cross-peak between H_1 and H_8 in the NOESY spectra. The observed changes in $^3J_{H_8H_9}$ and the NOESY spectra could also result from a prominent structural change of the individual conformers upon protonation rather than the stabilization of conformer Open(3). Structure optimizations using ab initio methods, however, show that protonated cinchonidine conformers very much resemble the free base and that the relative stability of conformer Open(3) is increased upon protonation.[36] Finally, by replacing cinchonidine by deoxycinchonidine, our calculations (see Supporting Information) and NMR investigations[10] indicate a significant destabilization of conformer Open(3) relative to Closed(1) which is accompanied by a loss of ee from 79% to 44% in the enantioselective hydrogenation of ethyl pyruvate.

It has to be pointed out that ee is determined by the relative energies of the competing transition states. For the discussed heterogeneous reaction the conformation of cinchonidine within these transition states is important, i.e., the conformation of cinchonidine adsorbed on the Pt surface and interacting with the reactants. A rigorous treatment thus requires rather detailed structural information of the adsorbed layer. Further work needs to be conducted in this direction to unravel the similarities of the conformation of cinchonidine in solution investigated in the present work and the conformation on the Pt surface which ultimately influences ee.

Conclusions

Both NMR experiments and ab initio calculations show that Open(3) is the most stable conformer of cinchonidine in apolar solvents. When going to polar solvents two other conformers, Closed(1) and Closed(2), are strongly stabilized relative to Open-(3). The stabilization of the closed conformers is mainly due to their larger dipole moment as compared to Open(3). In polar solvents the fraction of cinchonidine adopting a closed conformation is more than 50% at room temperature. Ab initio and density functional methods using medium-sized basis sets in combination with a reaction field model are in good agreement with the experiment for solvents which do not exhibit strong specific interactions with cinchonidine. The calculations very well reproduce the solvent-dependent relative energies. The agreement between the experiment and the calculations is within about 0.3 kcal/mol.

The importance of the solvent-dependent cinchonidine conformation is illustrated by the hydrogenation of activated carbonyl compounds over cinchonidine-modified Pt. The achieved enantiomeric excess shows the same solvent dependence as the fraction of conformer Open(3) in solution, suggesting that this conformer plays a crucial role for the enantiodifferentiation.

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Supporting Information Available: ^{1}H NMR spectrum (500 MHz) of cinchonidine in acetone. Traces of the 300 MHz NOESY spectrum of cinchonidine in acetone. Calculated relative energies of deoxycinchonidine conformers (4 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(31) Minder, B.; Mallat, T.; Skrabal, P.; Baiker, A. *Catal. Lett.* **1994**, *29*, 115−124.
(32) Künzle, N.; Mallat, T.; Bürgi, T.; Baiker, A., unpublished results.
(33) Blaser, H. U.; Jalett, H. P.; Monti, D. M.; Reber, J. F.; Wehrli, J. T. *Stud. Surf. Sci. Catal.* **1988**, *41*, 153−163.
(34) Meheux, P. A.; Ibbotson, A.; Wells, P. B. *J. Catal.* **1991**, *128*, 387−396.
(35) Blaser, H. U.; Jalett, H. P.; Wiehl, J. *J. Mol. Catal.* **1991**, *68*, 215−222.
(36) Bürgi T.; Baiker, A., unpublished results.