Molecular interaction between cinchonidine and acetic acid studied by NMR, FTIR and *ab initio* methods

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Cinchona alkaloids play a major role as chiral auxiliaries in asymmetric catalysis. Acetic acid is known to be an excellent solvent in the enantioselective hydrogenation over chirally modified platinum metals. The crucial interaction between the chiral auxiliary and the solvent has been investigated using the cinchonidine–acetic acid pair. Solutions containing cinchonidine and acetic acid were studied by means of NMR and IR spectroscopy as well as by *ab initio* Hartree–Fock calculations. In the presence of the acid cinchonidine is protonated at the quinuclidine N and adopts an open conformation where the quinuclidine N points away from the quinoline moiety. In the most stable 1 : 1 and 2 : 1 acetic acid–cinchonidine complexes both the N–H^+ and O–H groups of cinchonidine are involved in hydrogen bonding. The most stable 1 : 1 complex is found to be cyclic. The relative arrangement of the N–H^+ and O–H groups of protonated cinchonidine is ideally suited to bind an acetate anion, and the interaction hardly affects the cinchonidine conformation. Several 2 : 1 acid–base complexes coexist in solution. The IR spectra give evidence for the existence of a 2 : 1 cyclic complex. Calculated structures, relative energies and vibrational frequencies are in good agreement with the experiment. The findings rationalise the importance of the O–H group of cinchonidine for the enantiodifferentiation in the enantioselective hydrogenation of α,β-unsaturated carboxylic acids over cinchonidine-modified Pd.

Introduction

Cinchona alkaloids are widely used chiral auxiliaries in homogeneous[1,2] as well as heterogeneous[3,4] asymmetric synthesis. In particular cinchonidine is an efficient chiral modifier used in the heterogeneous enantioselective hydrogenation of activated carbonyl compounds and α,β-unsaturated acids, over platinum and palladium metals, respectively. The interaction of cinchonidine with acetic acid is of interest for two reasons in this respect: First, acetic acid has been successfully used as the solvent for the enantioselective hydrogenation of activated carbonyl compounds. Several parameters such as, for example, catalyst pretreatment, hydrogen partial pressure and modifier concentration have been found to influence the enantiomeric excess (ee), but of particular importance is the solvent used. In the enantioselective hydrogenation of α-ketoesters,[5] for example, it has been found that the ee drops with solvent polarity. This has recently been rationalised by the solvent dependent conformational behaviour of cinchonidine.[6] Very high selectivities can be achieved in acetic acid. It has been argued that protonation of the quinuclidine N of cinchonidine favours the interaction with the carbonyl reactant.[7] The stabilisation of a favourable cinchonidine conformation due to protonation[6] or due to a specific interaction with acetic acid are other feasible explanations for the high enantioselectivities achieved in acetic acid.

Second, for the enantioselective hydrogenation of α,β-unsaturated carboxylic acids acetic acid can be used as a model to investigate the specific interaction with cinchonidine, which plays a fundamental role for the enantiodifferentiation. Borszeky *et al.*[8] postulated open 2 : 1 acid–base complexes to rationalise the catalytic results while Nitta and Shibata[9] favoured a 1 : 1 interaction between cinchonidine and the acid. In their model the acid is bound to cinchonidine *via* two hydrogen bonds involving the protonated quinuclidine N as well as the O–H group of cinchonidine. The importance of the cinchonidine–acid interaction for understanding the enantioselective hydrogenation of α,β-unsaturated acids prompted us to investigate the complexes formed between cinchonidine and acetic acid in some detail. Also in the homogeneous enantioselective decarboxylation of substituted malonic acids in the presence of cinchonidine and Cu(I)Cl the cinchonidine–acid interaction plays a crucial role.[2]

It is well known that in solution acids and bases can form 1 : 1 and 1 : 2 complexes of the general formula B···HA, $B^+H\cdots A^-$ and $B^+H(A^-\cdots HA)$.[10,11] These structures were evidenced by different analytical methods among which infrared spectroscopy has an important place. However, to our knowledge no direct spectroscopic study is available, that gives structural information on the cinchonidine–acetic acid complexes formed in solution. In the solid state cinchonidine carboxylic acid salts tend to form chains in which the acid is bound to two cinchonidine molecules by N–H···O and OH···O hydrogen bonds.[12,13]

We have used NMR spectroscopy to determine the conformation of cinchonidine within the acid–base complexes, while FTIR spectroscopy revealed the hydrogen bonding interactions between the acid and the base. *Ab initio* quantum chemical calculations were used to find the most stable structures and to predict the characteristic vibrational frequencies associated with them.

Theoretical methods

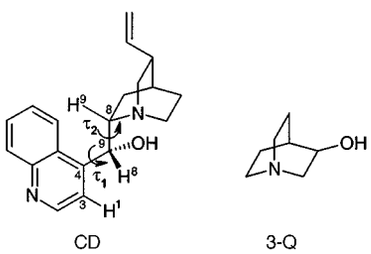
All calculations were performed using GAUSSIAN94.[14] Minimum-energy structures were computed at the Hartree–Fock (HF) level using 4-31G and 6-31+G* basis sets by complete optimization of all intra- and intermolecular degrees of freedom. No attempts were made to correct for basis set superposition error (BSSE) and electron correlation energy. For hydrogen-bonded systems the two corrections tend to cancel each other quite evenly when using medium sized basis sets such as 6-31+G*.[15] Vibrational frequencies were calculated using the 4-31G basis set and were scaled by 0.90195[16] in order to correct for anharmonicity and to account for the problem of restricted HF theory in describing dissociation.

Table 1 Relative electronic energies (kcal mol^{-1}) of singly protonated cinchonidine as a function of the relative permittivity ε_r of the solvent as calculated by *ab initio* HF theory using a 6-31+G* basis set in combination with a reaction field model

ε_r	Closed(1)	Closed(2)	Open(3)	Open(4)	Open(5)	Open(6)
1.0	0.25	0.99	0.00	3.16	0.68	2.60
2.0	0.65	1.61	0.00	2.91	1.27	3.44
4.8	1.11	2.14	0.00	2.89	2.11	4.45
20.7	1.50	2.52	0.00	3.10	2.98	5.38
78.5	1.56	2.57	0.00	3.16	3.22	5.67

Experimental

Acetic acid (Riedel-de-Haën, puris. grade 100%), cinchonidine (CD, Fluka >98% pure) and quinuclidin-3-ol (3-Q, Fluka, >98% pure) were used as received. Structural formulas of CD and 3-Q are represented in Scheme 1. Dichloromethane (Fluka)



Scheme 1 Structure of cinchonidine (CD) and quinuclidin-3-ol (3-Q).

was used as solvent for the IR experiments and was dried over 5 Å molecular sieves. NMR spectra were recorded on Bruker DPX 300 and AMX 500 spectrometers. Information on the conformation was obtained from nuclear Overhauser enhancement spectroscopy (NOESY) and $^3J_{H^8H^9}$ coupling constants. Signal assignment was assisted through correlation spectroscopy (COSY). Infrared spectra were measured on a Bruker IFS-66 spectrometer at a resolution of 4.0 cm^{-1} by recording 100 scans. All spectra were measured in a cell equipped with CaF_2 windows with a 0.16 cm path length. The spectrum of pure dichloromethane was used as the reference.

Theoretical results

Protonated cinchonidine (CD)

In order to discuss the interaction of CD with acetic acid the conformation of CD itself is of importance. The various conformers of CD (Scheme 1) have been classified according to their torsional angles C^3–C^4–C^9–C^8 (τ_1) and C^4–C^9–C^8–N (τ_2).[17] The solvent dependent conformational behavior of unprotonated CD (free base) in solution has recently been investigated by NMR experiments and *ab initio* reaction field calculations.[6] It has been shown that conformer Open(3) is the most stable. In polar solvents two other conformers, Closed(1) and Closed(2) are considerably populated. For Closed conformers the quinuclidine N points towards the quinoline ring whereas for Open conformers it points away from it. For conformers Open(3) and Closed(2) the O–H group is in the *trans* position whereas for Closed(1) it is in the *syn* position with respect to the quinoline moiety. In the presence of a weak acid such as acetic acid the quinuclidine N of CD is protonated.[18] In analogy to the above-mentioned study of the solvent dependent conformational behaviour of the free base[6] we have calculated the relative energy of several conformers of singly protonated CD as a function of solvent polarity using a self consistent reaction field approach (scipcm option in GAUSSIAN94). Table 1 summarises the results. Conformer Open(3) is the most stable followed by

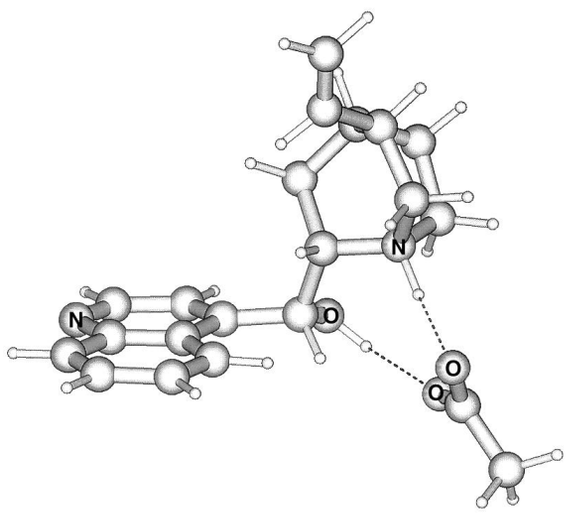


Fig. 1 Structure of cyclic 1:1 acetic acid–CD complex calculated at the HF level using a 6-31+G* basis set. Cinchonidine adopts the Open(3) conformation within this complex.

Closed(1), as was found for the free base. Similar to the free base the relative stability is mainly determined by mutual steric hindrance between the quinoline, quinuclidine and O–H parts of CD. In contrast to the free base, however, conformer Open(3) has a larger dipole moment (9.71 D) than Closed(1) (6.97 D). Open(3) is therefore predicted to be stabilised with respect to Closed(1) when increasing the solvent polarity (see Table 1). In medium polar solvents as used in the IR experiments (CH_2Cl_2, $\varepsilon_r = 9.08$) the calculations predict that singly protonated CD adopts almost exclusively conformation Open(3), which is in full accordance with the NMR experiments (see later). We point out that for protonated CD intramolecular hydrogen bonding N^+–H···O is possible for conformers Open(5) and Open(6), leading to a stabilisation. However, these conformers are still less stable than Open(3) and Closed(1) and we could not find any experimental evidence for their existence. In the following only conformer Open(3) is further investigated. For the calculations presented in Table 1 any effect of the counter ion is neglected. Nevertheless, the principal finding of the calculation, namely that conformer Open(3) is the most stable, is in accordance with the experiment (see later). In fact, the results presented below suggest that this conformation is even further stabilised by the interaction with acetic acid.

Acetic acid–CD 1:1

Using the Open(3) conformation the interaction of protonated CD with deprotonated acetic acid (acetate) was investigated next. The major interaction between the two is the coulomb attraction. One can therefore expect the carboxylate group of the acetate ion and the protonated quinuclidine N to be in close proximity. Fig. 1 shows the minimum energy structure we have found for the ion pair. Minimum energy structures where the deprotonated acid is bound by the N–H^+ but not by the O–H group were less stable by about 4.5 kcal mol^{-1} (4-31G). Table 2

Table 2 Selected torsional angles (degrees), hydrogen bond lengths (H ··· O distances in Å) and relative energy (kcal mol^{-1}) for CD, protonated CD (CDH^+) and acetic acid–cinchonidine complexes CDH^+A^- (1:1 complex) and CDH^+ (A^-HA) (2:1 complexes) calculated at the HF level using 4-31G and 6-31+G* basis sets. Electronic energies D_e and binding energies D_0 are relative to the separated neutral monomers

		$C^3C^4C^9C^8$ (τ_1)	$C^4C^9C^8N$ (τ_2)	C^8C^9OH	N–H_{CD} ··· O_A^-	O–H_{CD} ··· O_A^-	O–H_{AH} ··· O_A^-	$-D_e$	$-D_0$
4-31G	CD	100.2	154.0	168.3					
	CDH^+	98.5	170.5	183.0					
	CDH^+A^-, 1:1	104.9	173.8	106.2	1.49	1.74		18.6	16.3
	CDH^+ (A^-HA), 2:1, cycl.	104.1	158.5	147.6	1.59	1.76[a]	1.55	40.4	36.5
	CDH^+ (A^-HA), 2:1, Half 1	107.8	176.8	105.2	1.66	1.74	1.56	40.7	36.5
	CDH^+ (A^-HA), 2:1, Half 2	104.4	172.6	102.6	1.61	1.79	1.63	35.6	31.7
6-31+G*	CD	100.4	154.3	169.0					
	CDH^+	99.1	168.1	180.3					
	CDH^+A^-, 1:1	104.7	173.0	101.5	1.59	1.82		7.4	5.1
	CDH^+ (A^-HA), 2:1, cycl.	103.9	159.2	146.5	1.67	1.89[a]	1.68	22.9	19.0
	CDH^+ (A^-HA), 2:1, Half 1	107.4	175.4	101.3	1.72	1.81	1.70	23.0	18.8
	CDH^+ (A^-HA), 2:1, Half 2	104.2	172.5	99.3	1.67	1.87	1.76	19.9	16.0

[a] O–H_{CD} ··· O_{AH}.

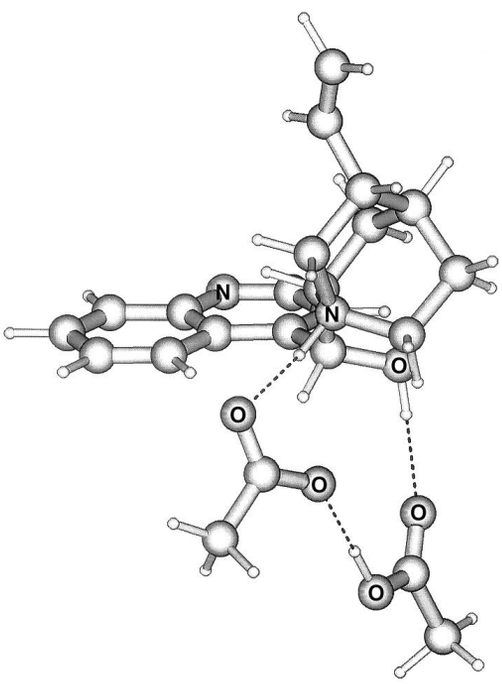


Fig. 2 Structure of 2:1 cyclic acetic acid–CD complex calculated at the HF level using a 6-31+G* basis set. Cinchonidine adopts the Open(3) conformation within this complex.

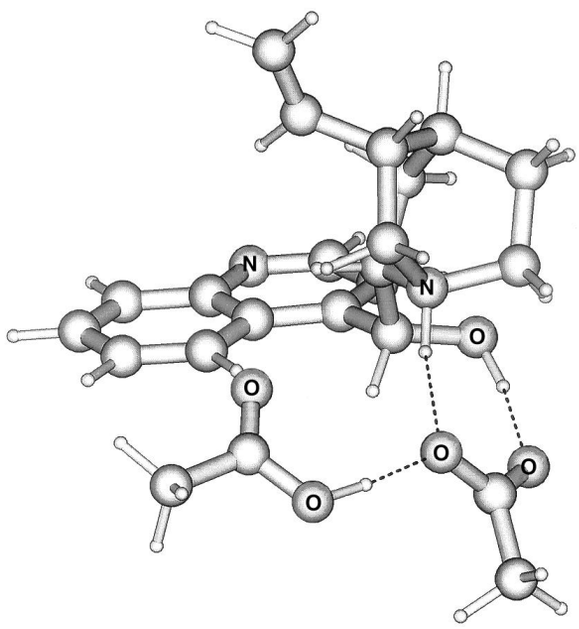


Fig. 3 Structure of 2:1 Half 1 acetic acid–CD complex calculated at the HF level using a 6-31+G* basis set.

gives some geometrical parameters and interaction energies for CD, protonated CD and acetic acid–CD 1:1 and 2:1 complexes. In the 1:1 complex the carboxy group of the acetate is hydrogen-bonded to the N–H^+ group, as expected, but also to the hydroxy group of CD. The conformation of CD within the ion-pair complex is very similar to the structure of the free base (Table 2). Upon protonation of the quinuclidine N τ_2 increases by about 15° whereas the presence of the acetate hardly has an effect on τ_1 and τ_2. This shows that conformation Open(3) is ideally suited to bind a carboxylic acid. The largest structural change upon complexation is observed for the O–H group, which is rotated by about 80°, due to the hydrogen-bonding interaction with the acetate.

Acetic acid–CD 2:1

Several minima were located for the 2:1 complex with the general formula $B^+H(A^- \cdots HA)$. One stable structure is the cyclic hydrogen-bonded arrangement shown in Fig. 2, where the protonated acid molecule is a H-bond acceptor for the O–H group of CD and a H-bond donor to the deprotonated acid. The second possible cyclic structure, where the positions of A^- and HA within the H-bonded arrangement are exchanged, is considerably less stable, probably mostly due to a weaker coulomb interaction resulting from the larger distance between the two charged species. The conformation of cinchonidine within the cyclic 2:1 complex is again very much like the conformation of the free base. With respect to the 1:1 complex the C^8C^9OH torsional angle increases by about 40° and is again closer to a more relaxed position (Table 2), which shows that in the cyclic 2:1 complex the hydrogen-bonded network is less stressed than in the 1:1 complex. The structures shown in Fig. 3 and 4 termed Half 1 and Half 2 can be thought of as 1:1 complexes with an additional acetic acid molecule bound to either one of the carboxylate oxygen atoms. This is also reflected by the torsional angles $C^3C^4C^9C^8$ and $C^4C^9C^8N$ (Table 2) which are similar for the 1:1 and the 2:1 Half 1 and Half 2 complexes. Half 1 is about as stable as the cyclic 2:1 complex, whereas Half 2 is

Table 3 Selected vibrational frequencies (cm^{-1}) of cinchonidine CD, acetic acid AH, acetic acid dimer AH_2, acetic acid–cinchonidine 1:1 complex CDH^+A^- and acetic acid–cinchonidine 2:1 complexes $CDH^+(A^-HA)$ (cyclic, Half 1 and Half 2) calculated at the *ab initio* Hartree–Fock level using a 4-31G basis set (frequencies are scaled by 0.90195)

	$(O–H)_{CD}$	$(N–H)_{CD}$	$(O–H)_{AC}$	$(C=O)_{AC}$	$(OCO^-)_{AC}$
CD	3596.3				
AH			3577.4	1752.5	
AH_2			3249.3	1699.0	
			3184.1[a]	1679.4[a]	
CDH^+A	3224.7	2188.9			1553.2
$CDH^+(A^-HA)$, cycl.	3382.0	2572.0	2796.9	1682.6	1536.4
$CDH^+(A^-HA)$, Half 1	3269.2	2734.4	2817.7	1679.0	1599.7
$CDH^+(A^-HA)$, Half 2	3310.6	2665.4	3017.7	1706.3	1543.0

[a] Only the higher frequency mode is IR active.

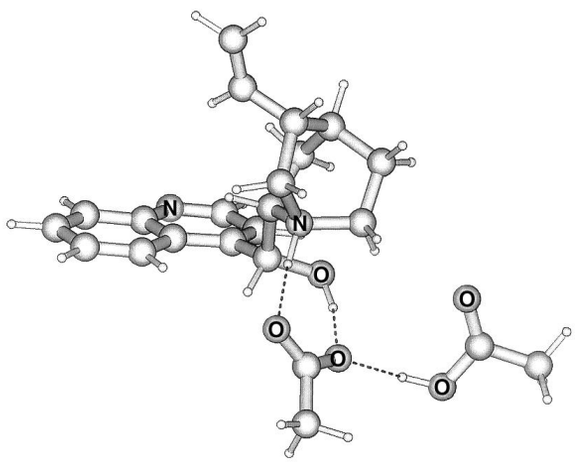


Fig. 4 Structure of 2:1 Half 2 acetic acid–CD complex calculated at the HF level using a 6-31+G* basis set.

less stable by about 3 kcal mol^{-1}. A 2:1 complex where the second acetic acid molecule is bound to the quinoline N is less stable by 7.7 kcal mol^{-1} (4-31G) than the complex shown in Fig. 2 and an open 2:1 complex, where the O–H of CD is not involved in hydrogen bonding, is less stable by about 5.5 kcal mol^{-1}. It is clear that the absolute energies given in Table 2 will be strongly affected by the solvation of the charged species. However, the relative energies for the 2:1 complexes are expected to be less affected. This has been confirmed by incorporating solvation effects by means of a reaction field. With a relative permittivity ε_r of 9.08 (CH_2Cl_2) for the dielectric medium the stabilization energy ($-D_e$) for the cyclic 2:1 complex is calculated as 18.0 kcal mol^{-1} instead of 22.9 kcal mol^{-1} for $\varepsilon_r = 1.0$ (Table 2, 6-31+G*). The relative energy of the three 2:1 complexes shown in Fig. 2, 3 and 4 calculated using a reaction field with $\varepsilon_r = 9.08$ is similar to the values in Table 2 ($\varepsilon_r = 1.0$). The cyclic 2:1 complex is the most stable, followed by Half 1 and Half 2, which are less stable by 0.2 and 2.3 kcal mol^{-1}, respectively. The binding energy (HF 6-31+G*) of the second acid molecule (D_e of 2:1 complex − D_e of 1:1 complex = −15.5 kcal mol^{-1}) is roughly the same as the binding energy calculated for the acetic acid dimer (−15.5 kcal mol^{-1}) at the same level of theory. From a purely energetic point of view Table 2 therefore suggests that 2:1 complex formation is more favourable than acid dimer formation because the binding energy *per* acid molecule is only 7.75 kcal mol^{-1} for acid dimer formation.

Table 3 gives a selection of the calculated vibrational frequencies for the different complexes. Within the cyclic 2:1 complex ν(O–H) of CD is considerably less shifted with respect to the monomeric species than ν(O–H) of the acid. From Table 2 it can be seen that the distance is largest for the H-bond involving the O–H group of CD. Both the frequency shift and the H-bond distance indicate that the H-bond involving the CD O–H is the weakest.

Spectroscopic results and discussion

NMR experiments

When adding acetic acid to CD in CD_2Cl_2 or d_6-acetone the ^1H NMR signals of CD exhibit a typical shift. The proton signals near the quinuclidine N are shifting the most. This shift shows a discontinuity at 1:1 acid–base ratio indicating that only the quinuclidine N is protonated by the weak acid at low acid–base ratios. Similar conclusions were drawn from ^{13}C chemical shift data.[18]

NMR experiments are ideally suited to determine the conformation of CD in solution.[19] For the free base the $^3J_{H^8H^9}$ coupling constant has been used to determine whether the conformation is open or closed.[6] An Open(3) or Open(4) conformation results in a small value of $^3J_{H^8H^9}$. For solutions of CD with acetic acid $^3J_{H^8H^9}$ is very small, often not resolvable, indicating that CD adopts conformer Open(3) or Open(4). NOESY experiments confirm this: only NOEs indicative for conformer Open(3) are observed. Specifically, when adding the acid the NOE between H^1 and H^8, which is indicative for conformer Closed(1), vanishes. This also eliminates the possibility that Open(4) is present in large quantities. No NOE between H^1 and H^9 is observed, which would be expected for conformer Closed(2). The above-described observations are not only made for CD–acetic acid solutions in CD_2Cl_2 but also in acetone and when using DCl instead of acetic acid. The observations do not change when the acid is added in considerable excess. The NMR experiments hence show that conformation Open(3) is predominant in acidic media, which is in full accordance with the calculations presented above and justifies our focus on this conformation for the CD–acetic acid complexes.

IR spectra

Fig. 5 and 6 show IR spectra for the ν(O–H) and ν(C=O) regions, respectively, when adding acetic acid to a 0.01 M solution of CD in dichloromethane. The IR spectrum of CD in dichloromethane shows a peak at 3598 cm^{-1} due to ν(O–H) of non-hydrogen-bonded O–H. A weak broad band above 3150 cm^{-1} can be attributed to the formation of intermolecular N···H–O hydrogen bonds between CD molecules (self association). The bands in the frequency range 1500–1650 cm^{-1} are associated with the aromatic system and the vinyl group of CD. When adding the acid to CD the intensity of ν(O–H) of CD at 3598 cm^{-1} decreases fast. ν(O–H) of the acid monomer at around 3500 cm^{-1} and a band at 3371 cm^{-1} start to grow when the acid is in excess. When adding the acid in large excess (not shown) the intensity of the ν(O–H) of the acid monomer further increases, whereas the intensity of the band at 3371 cm^{-1} remains constant. In the 3000–1800 cm^{-1} region (not shown) an increase in the baseline, characteristic for N–H$^+$···O hydrogen bond formation can be observed and only after the equivalence point the characteristic ν(O–H) band of hydrogen-bonded O–H of the acid dimer appears together with the typical bands due to Fermi resonances with combination bands and/or overtones.[20]

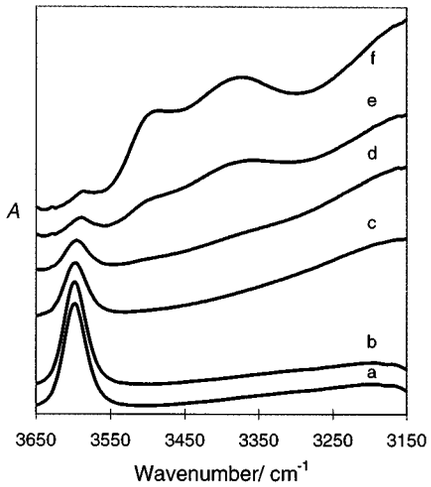


Fig. 5 IR spectra of CD–acetic acid solutions in CH_2Cl_2. ν(O–H) region. a) CD 0.01 M (constant in all spectra) and b) 10:1, c) 2:1, d) 1:1, e) 1:2, f) 1:4 base–acid ratios. Spectra are offset.

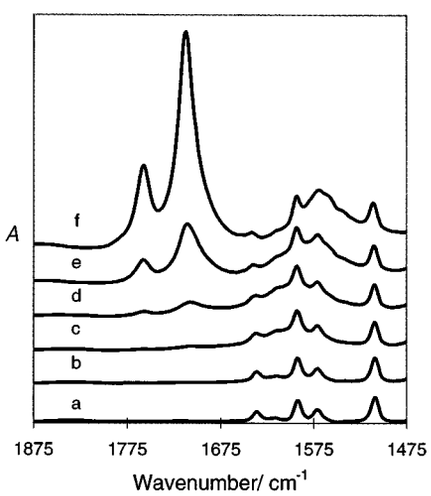


Fig. 6 IR spectra of CD acetic acid solutions in CH_2Cl_2. ν(C=O) region. a) CD 0.01 M (constant in all spectra) and b) 10:1, c) 2:1, d) 1:1, e) 1:2, f) 1:4 base–acid ratios. Spectra are offset.

In the carbonyl region (Fig. 6) the intensity of the ν(C=O) signals at 1758 and 1712 cm^{-1} increases quickly only after a 1:1 acid–base ratio is reached. The lower frequency band can be assigned to the hydrogen-bonded carbonyl group of the acid, whereas the higher frequency band arises from non-hydrogen-bonded C=O from free acetic acid molecules. Comparison of the band at 1712 cm^{-1} in Fig. 6 with a spectrum of acetic acid dimers in CH_2Cl_2 shows that the band at 1712 cm^{-1} is not only due to acetic acid dimers but is broadened at the low frequency tail. This indicates that other species are contributing to the overall intensity of the band. This carbonyl band slightly shifts towards higher frequencies due to a change in the relative abundance of the species contributing to it when the acid is added. The overall shift is only 8 cm^{-1}. Curve fitting of the feature at around 1712 cm^{-1} reveals that it is composed of at least two bands. The higher frequency component belongs to the acid dimer, which is in equilibrium with the monomer, whose ν(O–H) can be detected in the high frequency range at 3500 cm^{-1}.

A carboxylate band is seen at around 1590 cm^{-1} when adding the acid, as can be expected upon formation of an ion pair.[21] When the acid is added in excess a second band (more clearly visible in spectra where the cinchonidine bands are subtracted) is seen at 1560 cm^{-1}.

1:1 Acetic acid–CD complex. For acid–base ratios up to 1 the described observations show the formation of a 1:1 ion pair complex between CD and acetic acid. The disappearance of ν(O–H) of CD furthermore shows that CD binds the acid also *via* its free O–H forming a $N–H^+\cdots OCO^-\cdots H–O$ 1:1 cyclic complex as predicted by the *ab initio* calculations (Fig. 1). ν(O–H) of CD is shifted towards lower frequencies due to this hydrogen bonding with the carboxylate of the acid molecule. The frequency of this mode is calculated as 3224 cm^{-1} (Table 3). The broad band centred at around 3190 cm^{-1} in the spectra of acid–base ratio ≤ 1 (Fig. 5) can be attributed to ν(O–H) of the hydrogen-bonded hydroxy group of CD, since it is the only O–H group in the system at this acid–base ratio. At these low acid–base ratios acetic acid is deprotonated as can be seen from the almost absent carbonyl bands in Fig. 6.

For the 1:1 acid–base ion pair complex between acetic acid and CD in solution the combined information from the IR and NMR spectra and the *ab initio* calculations gives a detailed picture of its structure. The IR spectra (almost completely missing carbonyl bands up to 1:1 acid–base ratio) show that the equilibrium $CD + AH \rightleftharpoons CDH^+\cdots A^-$ lies far on the right side, *i.e.* the quinuclidine N is almost completely protonated at 1:1 acid–base ratio, whereas the quinoline N is not, in full accordance with the NMR ^1H shift data. The IR spectra clearly show that within the acid–base complex the CD O–H group is hydrogen-bonded to the carboxy group of the deprotonated acid. NOESY experiments give the conformation of CD within the acid–base complex as Open(3). The structure compatible with these two observations is also found to be the most stable in the *ab initio* calculations (Fig. 1). The calculations furthermore show that for conformation Open(3) the distance and orientation of the $N–H^+$ and O–H groups are ideal to bind a carboxy group *via* two hydrogen bonds $N–H^+\cdots O–C–O^-\cdots H–O$ without large conformational changes. This bidentate binding of the acid leads to an enhanced rigidity of the complex. Note that through this specific interaction conformer Open(3) is further stabilized with respect to the closed conformers, since for the latter such bidentate complexes are not possible due to an unfavorable arrangement of the $N–H^+$ and O–H groups. The relative stability of conformers of protonated CD given in Table 1 is therefore even further shifted in favor of conformer Open(3) in solutions containing carboxy acid.

Close inspection of the spectra shows that the free ν(O–H) band of CD does not completely vanish at 1:1 acid–CD ratio and that it can be observed even at high acid–CD ratios, although slightly shifted by about 10 cm^{-1} to lower frequency. This seems to indicate that the 1:1 complex shown in Fig. 1, although the most stable, is not the only one present in solution at room temperature. Other complexes with the open structure (not bonded to the O–H) coexist with the one shown in Fig. 1. Although the *ab initio* calculations indicate that open structures are energetically less stable than the one shown in Fig. 1, they are favored by the entropy term due to their larger flexibility. The slight shift of ν(O–H) to lower frequency is in accordance with the *ab initio* calculations, which predict a shift of 10 cm^{-1} to lower frequency for free O–H of protonated CD as compared to the free base (not shown in Table 1).

2:1 Acetic acid–CD complexes. With the acid in excess three features in the IR spectra indicate the existence of 2:1 acid–base complexes: i) the ν(O–H) signal at 3371 cm^{-1}, ii) the coexistence of two different carboxylate bands and iii) the coexistence of two different carbonyl bands. The band at 3371 cm^{-1} is almost absent for acid–base ratios < 1, its intensity increases for 1 < acid–base ratios < 2 and remains almost constant afterwards. This is a strong indication that the band is associated with a 2:1 acid–base complex. The high frequency is indicative for ν(O–H) of a weak hydrogen bond and can be assigned to ν(O–H) of CD. The frequency is in good agreement with the value calculated for the cyclic 2:1 acid–base complex

shown in Fig. 2 (Table 3) and with ν(O–H) frequencies for alcohols hydrogen-bonded to carbonyl groups.[22]

The frequency shift of the carboxy group above 1:1 acid–base ratio also indicates that further acid molecules interact with the 1:1 complex thus forming 2:1 $B^+H(A^- \cdots HA)$ complexes. This is also shown by the carbonyl signal, which is composed of at least two bands, best seen at acid–base ratios slightly higher than 1. The higher frequency ν(C=O) signal belongs to the acetic acid dimer. The lower frequency signal is assigned to ν(C=O) of a second molecule of acid interacting with the 1:1 complex thus accounting for the formation of 2:1 acid–base complexes as in the case of the trifluoroacetic acid–pyridines system.[10]

Although the IR spectra clearly indicate the formation of 2:1 acetic acid–CD complexes, the determination of their structure seems more complicated than for the 1:1 complex. The most useful information in this respect is the comparison of IR spectra shown in Fig. 5 and 6 with the calculated vibrational frequencies of the proposed structures shown in Fig. 2, 3 and 4. The calculated relative stability of the proposed 2:1 complexes is also useful. The observed ν(O–H) band at 3371 cm^{-1} is in excellent agreement with ν(O–H) calculated for the cyclic 2:1 complex at 3382 cm^{-1} (Table 3). For the Half 1 and Half 2 structures the calculated frequency for ν(O–H) is considerably lower than the experimental 3371 cm^{-1}, especially in the case of Half 1 (see Table 3). Based on this comparison we assign the band at 3371 cm^{-1} to ν(O–H) of the cyclic 2:1 complex. In the carboxy region a shift towards lower frequency is observed when adding the acid in excess. For the 1:1 complex the asymmetric carboxylate stretching vibration ν_{as}(O–C–O^-) is centred at 1590 cm^{-1} (calculated 1553 cm^{-1}, see Table 3). A second band at lower frequency appears when extra acid is added. A downwards shift of ν_{as}(O–C–O^-) is predicted by the calculations for the cyclic structure and Half 2, whereas for Half 1 an upwards shift by about 40 cm^{-1} is predicted. This indicates that Half 1 is not the major 2:1 species. The IR spectra show that the frequency of ν(C=O) within the 2:1 complex at about 1704 cm^{-1} is slightly lower than within the acid dimer (1712 cm^{-1}). The calculations predict such a shift for the cyclic 2:1 complex and Half 1, whereas the predicted shift is in the wrong direction for Half 2, indicating that Half 2 is not the major 2:1 species. In general, the calculated frequencies are in good agreement with the observed frequencies. For example ν(C=O) is observed at 1758 and 1712 cm^{-1} for acetic acid monomer and dimer whereas the calculations yield 1753 and 1699 cm^{-1}.

Taken all together, the comparisons between the experimental IR spectra and the calculated frequencies indicate that the major 2:1 complex is the cyclic structure shown in Fig. 2, in agreement with the calculations, which predict this structure to be the most stable together with Half 1. However, it seems clear that the cyclic structure is not the only 2:1 complex found at room temperature. The asymmetric carboxylate band ν_{as}(O–C–O^-), for example, shows at least two components. Furthermore, ν(O–H) of CD does not vanish completely even at high acid excess, indicating that an open 2:1 complex also exists.

IR spectra of quinuclidin-3-ol (3-Q)–acetic acid solutions. Replacement of CD by 3-Q (Scheme 1) helps to support some of the conclusions drawn above. 3-Q represents the part of CD which is actively involved in the CD–acetic acid complex, with the important difference that the O–H group is directly positioned on the quinuclidine moiety.

The difference between the spectra shown in Fig. 2 for CD and acetic acid and those for which 3-Q is used instead of CD is restricted only to some particular signals. When adding acetic acid to 3-Q the intensity of ν(O–H) of 3-Q at 3602 cm^{-1} does not decrease. This indicates that this group is not involved in hydrogen bonding when adding the acid. *Ab initio* calculations reveal that the relative position and orientation of the N–H^+ and O–H groups of 3-Q are such that formation of cyclic 1:1 complexes with the acid is impossible, in contrast to CD. The band at 3371 cm^{-1} observed in the CD case and assigned to the cyclic 2:1 complex is completely absent even when the acid is in high excess. This shows that also in the case of the 2:1 acid–base complex an open structure is preferred for 3-Q as has been found for example in the case of pyridines,[10] in stark contrast to the behaviour of CD. We ascribe this difference between 3-Q and CD to the different relative arrangement of the N–H^+ and O–H groups. As for CD ν_{as}(O–C–O^-) is shifted from 1606 to 1568 cm^{-1} after 1:1 acid–base ratio and the band is also composed of two components.

Implication on the model for enantiodifferentiation in the hydrogenation of α,β-unsaturated carboxylic acids

Nitta and co-workers found that in the enantioselective hydrogenation of α,β-unsaturated carboxylic acids over CD-modified Pd the substitution of the O–H group of CD by a O–CH_3 group has a large effect on enantiodifferentiation. In an *N*,*N*-dimethylformamide–water mixture (9:1) they observed an enantiomeric excess of 61% *S* when using cinchonidine, whereas 18% *R* was found when using *O*-methylhydrocinchonidine, showing that the O–H group is important for the enantiodifferentiation of this reaction.[9] The change of the absolute configuration of the product hints at the involvement of various possible structures in the transition state for hydrogenation, which seems likely, based on the present findings. Note that similar substitution of the O–H group has only a minor effect on the enantiodifferentiation of α-ketoesters over CD modified Pt. The above-reported findings demonstrate that the O–H group is involved in the CD–acetic acid interaction, and hence offer an explanation for the observed effect of the O–H group in the enantiodifferentiation of α,β-unsaturated carboxylic acids over CD modified Pd. Nitta and co-workers proposed an enantiodifferentiating transition state similar to the 1:1 complex shown in Fig. 1. However, it remains to be shown whether the enantiodifferentiating transition state is a 1:1 or 2:1 complex. With the present knowledge, it is impossible to decide which of the observed diastereomeric complexes (1:1, 2:1 cyclic, 2:1 Half 1, 2:1 Half 2) is decisive for enantiodifferentiation. At high acid–CD ratios (50:1 under reaction conditions) 2:1 complexes are favoured thermodynamically. Obviously the interaction of the complexes with the Pd surface has to be taken into account for final assessment. It is generally assumed that CD adsorbs *via* its π-system with the quinoline moiety oriented parallel to the Pd surface. This means that the complexes shown in Fig. 1 and 2 will have to distort in order to adsorb. In this respect the cyclic 2:1 complex seems to be more flexible than the 1:1 complex.

Summary

In the presence of acetic acid the quinuclidine N of CD is protonated. NOESY experiments show that CD adopts conformation Open(3) within the acid–base complexes. IR spectra demonstrate that at 1:1 acetic acid–CD ratio a 1:1 cyclic ion pair complex is predominantly formed, where both the N–H^+ and the O–H groups of CD are involved in hydrogen bonding (N–$H^+ \cdots OCO^- \cdots$ H–O). The calculations indicate that the geometrical arrangement of the N–H^+ and O–H groups of CD within conformation Open(3) are ideally suited to bind a carboxylate anion. A small fraction of open 1:1 complexes, where the O–H group of CD is not hydrogen-bonded is also present. With the acid in excess 2:1 complexes are formed. Comparison of the calculated vibrational frequencies with the experimental ones, especially ν(O–H), indicates that also for the 2:1 complex the cyclic structure is the major species in solution. However, other structures are also present. The *ab initio* Hartree–Fock calculations are in good agreement with the observations with respect to the stability of the complexes, conformation of CD within the complexes and vibrational frequencies. Comparisons

of the IR spectra of CD–acetic acid solutions with 3-Q–acetic acid solutions support the conclusions and corroborate the suggestion that the relative geometrical arrangement of the $N–H^+$ and O–H groups within the CD Open(3) conformation is a prerequisite for the formation of cyclic structures. The findings indicate the relevance of the O–H group of CD in the intermolecular complex formed in the enantioselective hydrogenation of α,β-unsaturated carboxylic acids over CD-modified Pd.

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