Conformational isomerism of α-ketoesters. A FTIR and *ab initio* study

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The conformational behaviour of several α-ketoesters was investigated using solution FTIR in combination with *ab initio* calculations. The α-ketoesters show marked differences in the O=C–C=O torsional potential energy surface depending on the substituent at the α-keto group. In general the torsional potential is characterised by broad minima corresponding to s-*cis* and s-*trans* conformations and low interconversion barriers. The s-*trans* conformation is more stable but the fraction of s-*cis* is considerable at room temperature and increases with solvent polarity due to the higher dipole moment of the latter. Hydrogen bonding with alcoholic solvents also leads to a stabilisation of the s-*cis* conformer. The interaction of ethyl pyruvate with R_3N^+–H is much stronger when ethyl pyruvate adopts an s-*cis* conformation due to strong ion–dipole interaction. This type of interaction between ethyl pyruvate and protonated cinchonidine is considered to be crucial for the enantio-differentiation in the heterogeneous enantioselective hydrogenation of ethyl pyruvate over cinchonidine modified platinum in acidic media.

Introduction

α-Ketoacids and their derivatives, such as α-ketoesters are versatile intermediates in synthetic chemistry. The conformation of these compounds can influence the stereochemical outcome of pertinent reaction products. An example of this is the heterogeneous enantioselective hydrogenation of α-ketoesters over cinchona modified platinum catalysts. The mechanism of this reaction has been targeted by several groups.[1–4] The reaction is of practical interest, since high enantiomeric excess can be achieved using heterogeneous catalysts which offer inherent advantages for technical applications due to easier catalyst separation and handling. Key for the enantio-differentiation is a specific interaction between the modifier and the α-ketoester during its hydrogenation on the Pt surface. Structurally different modifiers have been synthesised in order to shed light on enantio-differentiation and modifier–substrate interaction.[5–9] A decisive role in the interaction is played by the quinuclidine-N of the modifier: *N*-alkylation leads to a complete loss of enantioselectivity.[4] On the other hand the OH group plays a minor role. Albeit different reaction mechanisms have been proposed,[1,3,4] current models suggest that the modifier interacts with the α-ketoester *via* a hydrogen bond.

The specific enantio-differentiating interaction between the cinchonidine modifier and the α-ketoester is likely to depend on the conformation of both molecules. Whereas the conformation of cinchona alkaloids and its solvent dependence have been addressed in some detail,[10–13] relatively little attention has been paid to the conformation of the α-ketoester so far. In the currently discussed models the conformation of the α-ketoester is either not addressed or the α-ketoester is assumed to be in its s-*trans* conformation. This uncertainty prompted us to study systematically the conformation of α-ketoesters and its dependence on intramolecular factors, as well as on solvent and hydrogen bonding. The studies provide evidence for the coexistence of rotational isomers in ethyl α-ketoesters (ethyl pyruvate in detail) at room temperature and demonstrate how the conformational equilibrium is affected by the solvent and hydrogen-bonding interactions. These aspects are crucial for a better understanding of the solvent dependence of enantio-differentiation in the hydrogenation of α-ketoesters over cinchona modified Pt and the proposal that hydrogen bonding is involved in the specific modifier–substrate interaction.

Although rotational isomerism (s-*cis v.s.* s-*trans*) is very well known for certain classes of organic compounds only the conformation of methyl pyruvate[14] and pyruvoyl halides[15,16] has received attention among the α-ketocarboxylic acid derivatives. An equilibrium between rotational isomers for some other ethyl α-ketoesters[17–19] has been postulated in an attempt to reveal the structures of 2-oxopropionic acid and phenylglyoxylic acid. Temperature dependence of the IR absorption band corresponding to the carbonyl stretching mode of ethyl pyruvate was reported by Yarkova *et al.*[20] Dipole moment measurements were also carried out.[17] Solvent dependence of the IR absorption of the carbonyl band was reported as a tool for investigating the rotational isomerism of *N,N′*-dimethyloxamide[21] and dimethyl oxalate.[22]

Materials and methods

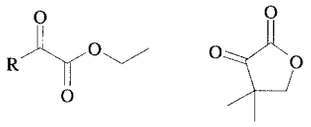
α-Ketoesters

The α-ketoesters used in this work and the corresponding acronyms are summarised in Scheme 1.

Ethyl pyruvate (EP, Aldrich 98%), ethyl trifluoropyruvate (ETFP, Lancaster Synthesis 97%), ethyl 3-methyl-2-oxobutyrate (EMOB, Acros 95%), ethyl 4-phenyl-2-oxobutyrate (EPOB, Aldrich >97%), ethyl phenylglyoxylate (EPG, Merck), ethyl 3-bromopyruvate (EBP, Acros 80–85%), dihydro-4,4-dimethylfuran-2,3-dione (ketopantolactone, KPL, F. Hoffmann-La Roche >97%) were used as received.

Ethyl 2-oxobutyrate (EOB) was prepared by refluxing 2-oxobutanoic acid (5 g, 48 mmol) with ethanol (42 ml), benzene (20 ml), and toluene-*p*-sulfonic acid according to Nakamura.[23] IR (neat): 1730 (s, C=O), 1750 (sh, C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 4.32 (q, J = 7.1 Hz, 2H), 2.87 (q, J = 7.2, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H).

Diethyl 2-oxoglutarate (DEOG) was prepared by refluxing 2-oxopentanedioic acid (10 g, 49 mmol) with ethanol (50 ml), and conc. sulfuric acid (*ca.* 1 ml) according to Joshi.[24] IR (neat): 1731 (s, C=O), 1749 (sh, C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 4.34 (q, J = 7.1 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.16 (t, J = 6.5 Hz,



1 2 (KPL)

R	Acronym
Me	EP
Et	EOB
i-Pr	EMOB
Ph	EPG
C_2H_4Ph	EPOB
C_2H_4COOEt	DEOG
CH_2Cl	EBP
CF_3	ETFP

Scheme 1

2H), 2.66 (t, $J = 6.5$ Hz, 2H), 1.38 (t, $J = 7.1$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H).

Solvents

Carbon tetrachloride, dichloromethane, and tetrahydrofuran (all stored over molecular sieves), *n*-hexane, benzene (dried over $CaCl_2$), toluene, ethanol, methanol, and acetonitrile were used as solvents. To investigate the influence of hydrogen bonding in some experiments *p*-fluorophenol (PFP, Fluka ≥98%) was used as hydrogen-bond donor. Before use PFP was purified by sublimation and stored over P_2O_5.

FTIR analysis

Spectra were recorded on a Bruker IFS-66 spectrometer. A liquid cell with 1 mm path length and CaF_2 windows was used if not otherwise specified. Spectra were measured by averaging 200 scans at 4 cm^{-1} resolution. Band fitting was performed with the Bruker OPUS/IR 2.0 program by applying the Levenberg–Marquardt algorithm and mixed Lorentzian–Gaussian functions.

Ab initio calculations

Ab initio calculations were performed using the GAUSSIAN94 suite of programs.[25] A density functional hybrid method with Becke's 3 parameter functional[26] and the non-local correlation of Perdew and Wang[27] (B3PW91) was applied to calculate vibrational frequencies and dipole moments, after complete structure optimisations. Since diffuse basis functions are important for the calculation of dipole moments a 6-31++G(d,p) basis set was used. Solvent effects were included by using a self-consistent reaction field model (SCIPCM). Potential energy scans were performed at the Hartree Fock (HF) level using a 6-31G(d,p) basis set. At every point of the scan the remaining degrees of freedom were completely optimised. To calculate hydrogen-bonded complexes the HF method with a 6-31G(d,p) basis set was used. It has been shown that this combination yields good hydrogen-bond interaction energies, due to cancellation of basis set superposition error and correlation correction.[28]

Results and discussion

Structure of α-ketoesters

A series of α-ketoesters (Scheme 1) was investigated to elucidate the conformational isomerism of this class of compounds. α-Ketoesters can adopt s-*cis* and s-*trans* conformations, which can be interconverted by changing the dihedral angle

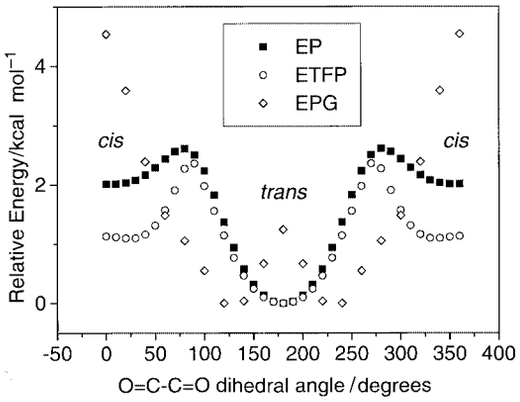


Fig. 1 Calculated potential energy surface along the O=C–C=O dihedral angle for EP, EPG and ETFP. Calculations were performed at the Hartree Fock level using a 6-31G(d,p) basis set. At each point all the remaining degrees of freedom were fully relaxed.

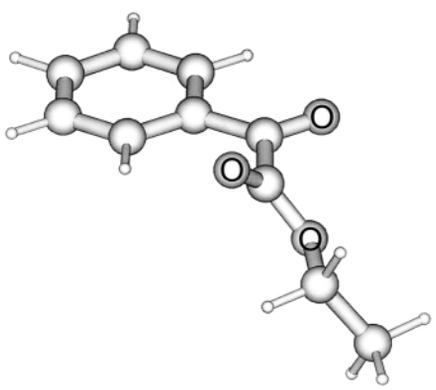


Fig. 2 Calculated minimum energy structure of EPG. Optimisation was performed at the DFT level (B3PW91) using a 6-31++G(d,p) basis set.

O=C–C=O. As will become clear, the potential energy surface (PES) along this dihedral angle is determined by at least three intramolecular factors: (i) steric hindrance (Pauli repulsion), (ii) electrostatic interaction between the polar carbonyl groups, and (iii) conjugation of the p-orbitals. These factors can be qualitatively discussed by comparing the PES along O=C–C=O for ethyl pyruvate (EP), ethyl trifluoropyruvate (ETFP) and ethyl phenylglyoxylate (EPG). The PES's shown in Fig. 1 were calculated at the HF level using a 6-31G(d,p) basis set. A qualitative similar PES for EP has recently been reported.[29] Stabilisation due to overlap of the p-orbitals is maximised when the two carbonyl groups are coplanar, *i.e.* in s-*cis* (0°) and s-*trans* (180°) conformations. At 90° and 270° the overlap between the p-orbitals at the two C atoms is minimal. In the s-*trans* conformation the local dipole moments of the carbonyl groups point in opposite directions, whereas in the s-*cis* conformation they form an angle of about 60° only, thus leading to destabilization. This is the main reason why most α-ketoesters preferentially adopt the s-*trans* conformation in the gas phase as can be seen in Fig. 1 for EP and ETFP. We note that for ETFP the s-*cis* conformation at 0° is in fact a maximum. The actual minima are found at torsional angles O=C–C=O of about ±24° (B3PW91). In contrast, for EPG the PES is dominated by steric repulsion between one hydrogen atom of the phenyl group and the O atoms of the ester carbonyl group. As a consequence both s-*cis* and s-*trans* conformations are maxima on the PES. The repulsion is more pronounced for the s-*cis* conformer. Note that the PES's are symmetric with respect to reflection at 0 and 180°. Thus the two minima for EPG correspond to equivalent, although not identical structures. In fact, the structures corresponding to the two minima are enantiomeric. The calculated minimum energy structure is depicted in Fig. 2.

Table 1 Calculated frequencies (cm^{-1}) and intensities (km mol^{-1}) for the ν(C=O) vibrations and dipole moments (D) for EP (s-*cis* and s-*trans*), ETFP (s-*cis* and s-*trans*), EPG and KPL. Calculations were performed at the DFT level (B3PW91) using a 6-31++G(d,p) basis set

Molecule	ν(C=O) frequencies	Description	Intensity	Dipole moment
s-*trans*-EP	1800	Sym. C=O	267	1.54
	1830	As. C=O	128	
s-*cis*-EP	1832	Sym. C=O	346	4.99
	1839	As. C=O	28	
s-*trans*-ETFP	1820	Ester C=O	264	3.69
	1871	Ketone C=O	81	
s-*cis*-ETFP	1840	Ester C=O	262	4.06
	1874	Ketone C=O	99	
EPG	1771	Ketone C=O	238	2.91
	1801	Ester C=O	235	
KPL	1869	Ketone C=O	116	5.84
	1884	Ester C=O	355	

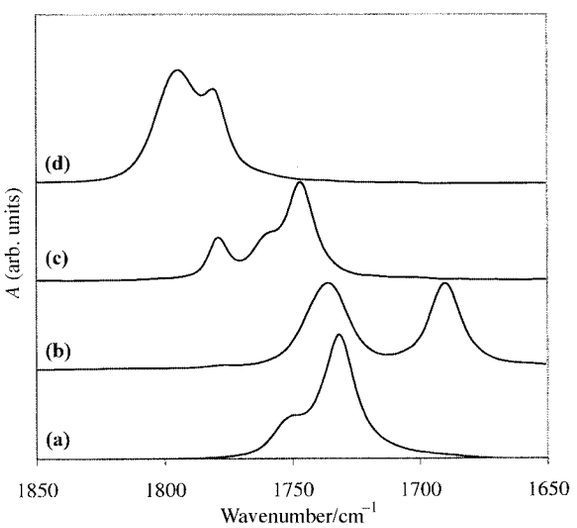


Fig. 3 IR spectra of a) EP, b) EPG, c) ETFP and d) KPL 0.02 M in CH_2Cl_2.

We also note that EP and ETFP are very flexible around the torsional angle O=C–C=O. On the one hand the minima are very broad. Hence at room temperature the vibrational motion corresponding to the O=C–C=O torsion probes an angle of ±40° for s-*trans* and ±60° for s-*cis*. On the other hand, the barrier between s-*cis* and s-*trans* is low in energy, leading to rapid interconversion.

Calculated dipole moments for EP, ETFP, EPG and ketopantolactone (KPL) are given in Table 1. Not surprisingly, the dipole moments are quite large for these carbonyl compounds. For comparison, the water molecule has a dipole moment of 1.85 D. More important is the fact that the s-*cis* and s-*trans* conformers of EP have very different dipole moments (4.99 *vs.* 1.54 D), as can be understood from the relative orientation of the two polar C=O groups. In contrast, for ETFP the CF_3 group is also very polar, leading to similar dipole moments for s-*cis* and s-*trans*.

Carbonyl spectra of α-ketoesters

Some of the α-ketoesters (Scheme 1) were investigated by IR spectroscopy. The spectra of the carbonyl region of EP, EPG, ETFP and KPL are shown in Fig. 3 and the calculated frequencies are given in Table 1. It becomes clear that the CH_3, CF_3 and C_6H_5 substituents at the α-keto group have a marked influence on the carbonyl spectra. For the remaining substrates ethyl 2-oxobutyrate (EOB), ethyl 3-methyl-2-oxobutyrate (EMOB), ethyl 4-phenyl-2-oxobutyrate (EPOB), diethyl 2-oxoglutarate (DEOG) and ethyl 3-bromopyruvate (EBP) the spectra are similar to that of EP.

Ethyl pyruvate shows a main signal at 1731 cm^{-1} (ν(C=O)) and a shoulder at 1751 cm^{-1} in CH_2Cl_2 (Fig. 3, trace a). For simplicity in our discussion the C=O bands at low and high frequency are referred to as A and B, respectively. Based on the calculations we assign the lower frequency band A to one of the carbonyl stretching vibrations ν(C=O) of the s-*trans* conformer. The higher frequency band is composed of the other ν(C=O) vibration of s-*trans* and the two carbonyl stretching vibrations of s-*cis* EP. The calculated frequencies are about 70 cm^{-1} too high. Some of this overestimation results from anharmonicity, which is neglected in a normal modes analysis. The splitting between the two carbonyl vibrations for s-*trans* is calculated to be 30 cm^{-1}, which compares to a measured splitting of 20 cm^{-1} in CH_2Cl_2 and 26 cm^{-1} in CCl_4 between the A and B bands. For EP the normal modes are linear combinations of local ester and ketone carbonyl stretching vibrations (delocalised modes). In such cases it is more appropriate to label the bands as symmetric (sym.) and antisymmetric (as.), respectively. For strongly delocalised C=O stretching modes of α-ketoesters one mode gives rise to intensive absorption, whereas the other one is very weak due to addition or subtraction of the local dynamic dipole moments (see for example the calculated intensity for s-*cis* EP in Table 1). The fact that the spectrum of EP in CCl_4 is composed of one strong and one comparably weak band is evidence for delocalised modes in s-*trans* EP (whereas the calculations would rather indicate local modes), and we can label the band at 1731 as the antisymmetric ν(C=O) of s-*trans* EP. For ETFP, EPG and KPL both experiment and calculations indicate local carbonyl stretching modes.

EPG (Fig. 3, trace b) shows two distinct bands at 1689 and 1736 cm^{-1} that were assigned to the benzoyl (A) and ester (B) groups.[17,18] The strong conjugation between the keto group and the aromatic ring leads to a pronounced frequency redshift and a clear separation of the two bands. The above assignment, the redshift and the clear separation of the two bands are well reproduced by the DFT calculations. In addition, the calculation predicts equal intensity for the two bands, which is in good agreement with the spectra. The appearance of only two bands is also consistent with the PES presented in Fig. 1: the two structures corresponding to the two equivalent minima on the PES give rise to identical spectra.

Furthermore, ETFP (Fig. 3, trace c) shows three absorptions in the carbonyl region at 1746 (A), 1760 (B) and 1779 cm^{-1} (C). The lowest frequency band A is assigned to the ester ν(C=O) of s-*trans*-ETFP, band B to the corresponding mode of s-*cis*-ETFP and band C to the ketone ν(C=O) of both s-*cis* and s-*trans*-ETFP.

In the spectrum of KPL the two bands observed in CH_2Cl_2 at 1780 (A) and 1795 cm^{-1} (B) cannot be associated with rotational isomers owing to the fixed s-*cis* conformation due to the ring. The band splitting ($\Delta\nu = 15$ cm^{-1}) and the intensity ratio are again in good agreement with the calculations.

Solvent dependence

Table 2 shows the effect of increasing the relative permittivity (ε_r) of the solvent on the ratio of the integrated absorption A/B and on the frequency of the A and B bands for EP. All values were obtained by curve fitting. The intensity of B increases and the A/B ratio decreases accordingly with increasing solvent polarity. Moreover, the frequency of B is affected more by the solvent than the frequency of A. The measurements in ethanol and methanol are complicated by the fact that EP forms a hemiketal[30] with these alcoholic solvents within 20–30 min. Indeed we found a strong change in the carbonyl stretching region and the appearance of new bands in the fingerprint region which are consistent with hemiketal formation.

Together with the assignment of band A to s-*trans* EP and B

to mainly s-*cis* EP (see above), the solvent dependence of the A/B intensity ratio clearly shows the coexistence of s-*trans* and s-*cis* conformers for EP at room temperature. s-*trans* is the predominant species. The fraction of s-*cis*, however, increases with solvent polarity. This is rationalised by the considerably larger dipole moment of the s-*cis* conformer (see Table 1). The dependence of the fraction of s-*cis* EP on ε_r (strong increase at low ε_r) is typical for solvent stabilisation of a conformer with higher dipole moment, as predicted by the Onsager model of solvation.[31]

We have attempted to estimate the fraction of s-*cis* from the measured intensity of the A and B bands, assuming that the A and B bands correspond exclusively to s-*trans* and s-*cis*, respectively, and that the sum of the intensity of the ν(C=O) bands is equal for s-*trans* and s-*cis*. The first assumption is justified by the measured IR spectrum of EP in CCl_4, which shows that for s-*trans* the two carbonyl modes are delocalised, leading to a very weak high frequency mode overlapping with the s-*cis* ν(C=O) modes. The second assumption is justified by comparing the calculated sum of the intensities for the ν(C=O) modes of s-*trans* and s-*cis* conformers for EP and ETFP, respectively (Table 1), which are close to equal. The analysis gives a fraction of s-*cis* EP of about 9% in CCl_4 and about 20% in acetonitrile. We have also calculated the relative stability of s-*cis* and s-*trans* in media of different polarity by means of DFT (B3PW91, 6-31++G(d,p)) in combination with a reaction field model. The calculated relative stability and the resulting fraction of s-*cis* EP are shown in Table 3. In CCl_4 ($\varepsilon_r = 2.2$) a fraction of 15% is predicted, whereas the fraction increases to 41% in acetonitrile ($\varepsilon_r = 37.5$).

Similarly to EP all the ethyl α-ketoesters shown in Scheme 1 were investigated in CCl_4 and CH_2Cl_2. With the exception of KPL, ETFP and EPG the behaviour was similar to that of EP, showing a marked decrease in the A/B ratio when increasing the solvent polarity, thus indicating the coexistence of s-*trans* and s-*cis* conformers. The results are summarised in Table 4.

The distinctly different behaviour of KPL, ETFP and EPG can be readily understood from the above information. KPL has a fixed s-*cis* conformation accounting for the insensitivity towards the solvent. ETFP shows only a slight solvent dependence (Tables 3 and 4). Although there are both s-*cis* and s-*trans* conformers present at room temperature, as indicated by the spectrum in Fig. 3 and by the calculated ΔE (Table 3), the fraction of both does not change drastically with solvent polarity. The two conformers have similar dipole moments, due to the polar CF_3 group, and are hence stabilised to a similar extent when going to polar solvents. Using the measured band intensity ratios (Table 4) and the calculated intensities (Table 1) the abundance of s-*cis*-ETFP is determined as about 21% in CCl_4 and 25% in CH_2Cl_2. This compares well with 28% and 30% as derived from the calculated relative stability of s-*cis* *versus* s-*trans* in solvents of relative permittivity 2.2 (CCl_4) and 8.9 (CH_2Cl_2) (see Table 3). In the case of EPG the calculations predict two equivalent structures (Fig. 1) with identical spectrum and dipole moment and thus no solvent dependence of the spectrum due to stabilisation of one conformer over the other is expected. The observed slight solvent dependence of

Table 2 Effect of solvent polarity on A/B ratio and IR frequencies of A and B bands

Solvent	ε [a]	ν_A/cm^{-1}	ν_B/cm^{-1}	A/B
Hexane	1.9	1735	1763	8.53
Carbon tetrachloride	2.2	1732	1758	9.44
Benzene	2.3	1731	1755	6.20
Toluene	2.4	1731	1756	4.84
Chloroform	4.8	1731	1751	6.59
Tetrahydrofuran	7.6	1731	1755	4.73
Dichloromethane	8.9	1731	1751	4.52
Acetonitrile	37.5	1733	1752	4.18

[a] Values from B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, *Vogel's textbook of practical organic chemistry*, 5th edn., Longman Scientific and Technical, Harlow, UK, 1989, p. 1442.

Table 3 Calculated relative energy $\Delta E = E$(s-*cis*) − E(s-*trans*) and fraction of s-*cis* conformer for EP and ETFP. Calculations were performed at the DFT level (B3PW91) using a 6-31++G(d,p) basis set in combination with a self consistent reaction field model. The relative permittivities correspond to *vacuum* (1.0), carbon tetrachloride (2.2), dichloromethane (8.9) and acetonitrile (37.5)

	Relative permittivity	ΔE/kcal mol^{-1}	% s-*cis*
EP	1.0	1.62	6.1
	2.2	1.03	15.0
	8.9	0.42	33.1
	37.5	0.22	41.0
ETFP	1.0	0.67	24.5
	2.2	0.56	28.2
	8.9	0.50	30.2
	37.5	0.50	30.2

Table 4 Solvent dependence of A/B ratio for some ethyl α-ketoesters

α-Ketoester	CCl_4/cm^{-1}	A/B	CH_2Cl_2/cm^{-1}	A/B	$\Delta\nu$/cm^{-1}
EP	1732	9.44	1731	4.52	1
	1758		1751 (sh.)[b]		7
EOB	1730	6.21	1728	2.77	2
	1756 (sh.)[b]		1745 (sh.)[b]		11
EMOB	1729	9.52	1727	3.76	2
	1751 (sh.)[b]		1743 (sh.)[b]		8
ETFP	1749	3.71	1746	2.96	3
	1763 (sh.)[b]		1760 (sh.)[b]		3
	1779		1779		0
EBP	1732	5.46	1732	2.18	0
	1762		1756		6
EPOB	1730	9.76	1729	2.79	1
	1756 (sh.)[b]		1746 (sh.)[b]		10
EPG	1693	1.37	1689	0.98	4
	1737		1736		1
DEOG	1733	6.59	1730	4.68	3
	1754 (sh.)[b]		1748 (sh.)[b]		6
KPL	1782[a] (sh.)[b]	0.65	1780	0.69	2
	1794[a]		1795		−1

[a] Acetonitrile. [b] (sh.): appearing as shoulder in the spectra.

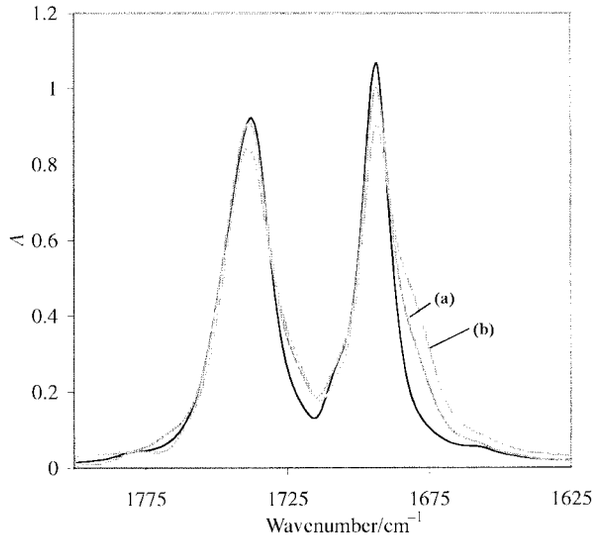


Fig. 4 IR spectra of EPG solutions with increasing amounts of PFP. Conditions: EPG 0.1 M, PFP 0.1 M (a), PFP 0.2 M (b); CCl_4; $d = 0.2$ mm.

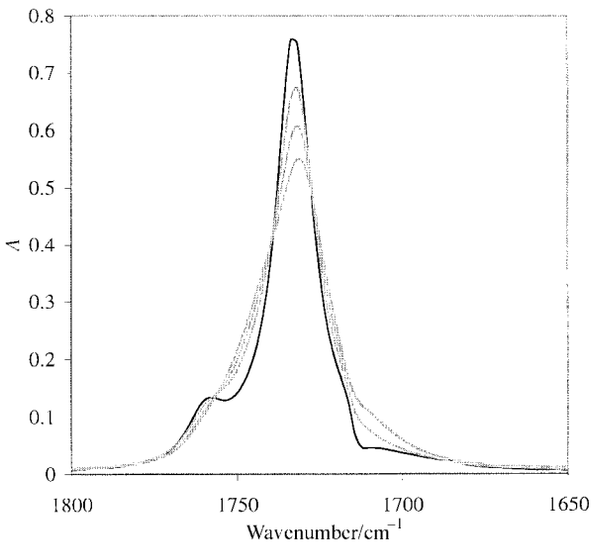


Fig. 5 IR spectra of EP solutions with increasing amounts of PFP. Conditions: EP 0.01 M; 0.15 M < PFP < 0.6 M; CCl_4.

the A/B band intensity ratio is ascribed to a small change of the equilibrium conformation.

Effect of hydrogen bonding

To investigate the influence of hydrogen bonding on the structure of the α-ketoesters *p*-fluorophenol (PFP) was chosen as the hydrogen-bond donor. PFP is a strong hydrogen bond donor owing to the high acidity of the proton. PFP was used recently to determine the basicity of several sets of proton acceptors.[32–36] We note that during measurements we could not observe hemiketal formation between PFP and the investigated α-ketoesters.

The clear separation of the ester and ketone *ν*(C=O) bands in EPG allowed us to investigate the hydrogen bond site. Fig. 4 shows that upon addition of PFP to a solution of EPG in CCl_4 two new signals appear at the low frequency side of the A (*ν*(C=O) of ketone) and B (*ν*(C=O) of ester) bands. The intensity of the new signals increases with PFP concentration, whereas the A and B bands become weaker. Curve fitting gives the position of the new bands as 1683 and 1720 cm^{-1}, which corresponds to a shift of 10 and 17 cm^{-1} with respect to the A and B band, respectively. We associate the new bands with the *ν*(C=O) modes of EPG hydrogen-bonded to PFP. Fig. 4 thus demonstrates that both the ketone and the ester group are involved in hydrogen bonding. Fig. 4 also shows that band A, which is associated with the ketone group, decreases more strongly than B upon addition of PFP and the corresponding new low frequency band due to hydrogen bonding increases more strongly for A than for B. Thus PFP prefers the ketone C=O over the ester C=O for hydrogen bonding.

The result of the analogous experiment with EP is shown in Fig. 5. EP is less diagnostic than EPG with respect to the determination of the hydrogen bond site, mainly because the ketone and ester carbonyl stretching modes are delocalised. Hence hydrogen bonding at either ketone or ester carbonyl will have an effect on both modes. Upon addition of PFP the main signal at 1732 cm^{-1}, which is associated with s-*trans* EP, strongly decreases and two shoulders at lower and higher frequencies appear with the shoulder at higher frequency being more pronounced. The signal associated with the s-*cis* conformer (1758 cm^{-1}) also decreases in intensity. Curve fitting centres the new bands at 1719 and 1740 cm^{-1} corresponding to a shift from the main bands A (s-*trans*) and B (s-*cis*) of 13 and 18 cm^{-1}, respectively. According to the assignment given above the new bands at 1719 and 1740 cm^{-1} are associated with hydrogen-bonded s-*trans* and s-*cis* EP, respectively.

The fact that most of the intensity disappearing at 1732 cm^{-1} appears at 1719 cm^{-1}, as can be seen from Fig. 5 and also from curve fitting, indicates that hydrogen bonding stabilises the s-*cis* conformation of EP. This would mean that the total (free *plus* hydrogen bonded) relative amount of s-*cis* *versus* s-*trans* conformer is increased upon addition of the alcohol. This stabilisation of the s-*cis* conformer upon hydrogen bonding is certainly in line with the observed solvent dependent conformational behaviour described above and underlines the role played by the large dipole moment of the s-*cis* conformer for the conformational behaviour of EP.

Implications for the mechanism of heterogeneous enantioselective hydrogenation of α-ketoesters

The results presented above are interesting in view of the continued effort to better understand the mechanism of the heterogeneous enantioselective hydrogenation of α-ketoesters over cinchonidine modified platinum catalysts. As already stated in the introduction, the conformation of the α-ketoester is likely to play an important role in the specific enantio-differentiating interaction between the cinchonidine modifier and the α-ketoester. As becomes clear from our results for ethyl pyruvate (EP), the most investigated reactant, both s-*trans* and s-*cis* conformers can be found in considerable amounts in solution. In polar solvents the fraction of s-*cis* is even comparable to s-*trans*. Hence the s-*cis* conformer should not be neglected in the discussion about the mechanism. Whether s-*cis* or s-*trans* is involved in the enantio-differentiation for the hydrogenation of EP or whether enantio-differentiation depends at all on the conformation at the carbonyl groups cannot be answered yet. In this respect it is interesting to note that KPL[37] and 1-ethyl-4,4-dimethylpyrrolidine-2,3,5-trione,[38,39] which have a fixed s-*cis* conformation can be hydrogenated with high enantiomeric excess (ee) reaching 91% under optimised conditions. The same is, however, true for EPG for which our results indicate that the s-*cis* conformation is relatively unfavourable.

The enantioselective hydrogenation of α-ketoesters shows a pronounced solvent dependence in some cases. Proposed reasons are the solubility of H_2 and the conformational behaviour of the modifier cinchonidine. We have recently shown that the ee achieved in the enantioselective hydrogenation of KPL shows the same solvent dependence as the fraction of a conformer termed Open(3) of cinchonidine in solution, suggesting that this conformer is involved in the enantio-differentiation and that the conformation of cinchonidine is the cause of the observed solvent dependence in this

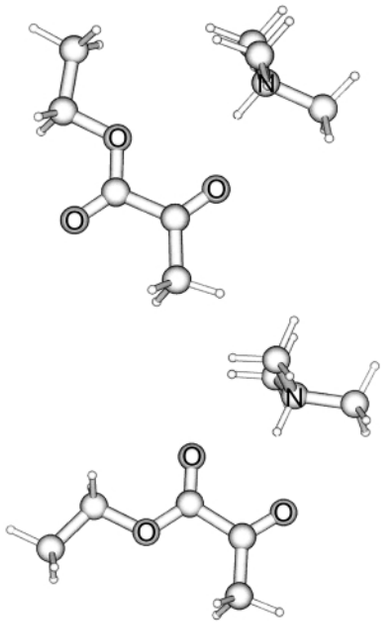


Fig. 6 Calculated structures for the complexes formed between trimethylammonium ion and EP. Upper part: s-*trans* EP, lower part: s-*cis* EP. The calculations were performed at the Hartree Fock level using a 6-31G(d,p) basis set. The complex with EP adopting the s-*cis* conformation is calculated to be 6.8 kcal mol^{-1} more stable.

case. The solvent has no large effect on the conformation of KPL (fixed s-*cis* conformation). The conformation of EPG is not largely affected by the solvent either, whereas the achieved ee shows a marked solvent dependence[40,41] similar to KPL. In contrast, the solvent dependence of ee achieved in the hydrogenation of EP and methyl pyruvate is much less pronounced.[3,41] In contrast to KPL and EPG, the solvent has a distinct effect on the conformation of EP, as shown above. This is an indication that the effects of the solvent dependent conformational behaviour of cinchonidine and EP on the achieved ee cancel to some extent. This in turn would suggest that s-*cis* is the favourable conformation for enantio-differentiation, since it is stabilised when increasing the solvent polarity.

We note, however, that in the enantioselective hydrogenation the solvent is only one factor, which determines the conformation of the α-ketoester. Other factors could easily determine the conformation since, as shown above, EP is very flexible around the O=C–C=O torsional angle and the energy difference between s-*cis* and s-*trans* is only small. Adsorption on the metal surface could have a prominent effect on the relative stability of s-*cis* and s-*trans* conformers. One part of the adsorption energy is the interaction of the molecule's dipole moment with its image charge. This dipole induced dipole interaction depends quadratically on the dipole moment and is hence expected to be considerably stronger for s-*cis* due to its much larger dipole moment.

Another factor which could determine the conformation of the α-ketoester is the interaction with the cinchonidine modifier itself. It has been proposed that in acidic media the modifier–EP interaction is determined by a hydrogen bond between the protonated quinuclidine N^+–H and the carbonyl group of the α-ketoester. Such an interaction is mainly determined by charge dipole interaction, which scales linearly with the dipole moment of EP. Hence, also the modifier–EP interaction would favour the s-*cis* conformer. To investigate this effect we have calculated the interaction of s-*trans* and s-*cis* EP with protonated trimethylamine as a model. Fig. 6 shows the structure of the stable s-*cis* and s-*trans* complexes as calculated at the HF level using a 6-31G(d,p) basis set. The complex with s-*cis* EP is calculated to be 6.8 kcal mol^{-1} more stable than the one with s-*trans* EP. Together with the calculated energy difference for the free molecule of about 2 kcal mol^{-1} in favour of s-*trans* EP the interaction energy for the s-*cis* complex is larger by almost 9 kcal mol^{-1}. This result illustrates the importance of the dipole moment of EP for this type of intermolecular interaction, which is thought to be the origin of enantio-differentiation.

Conclusion

IR spectroscopy and *ab initio* calculations were used to investigate the conformation around the O=C–C=O torsional angle of α-ketoesters. The potential energy surface around this torsional angle is characterised by a low potential barrier between the minima at 0° (s-*cis*) and 180° (s-*trans*) and large flexibility around the potential minima. At room temperature both s-*cis* and s-*trans* conformers can be found in considerable amounts. s-*trans* is the predominant conformer in apolar solvents. The fraction of s-*cis* increases with solvent polarity. This behaviour is rationalised by the much larger dipole moment for the s-*cis* conformer. Exceptions to this behaviour can be found when the dipole moments of s-*cis* and s-*trans* are similar due to other polar groups such as CF_3.

Alcoholic solvents form hydrogen bonds with the C=O groups of the α-ketoesters and stabilise the s-*cis* conformer. Our IR results on EPG show that both the α-keto and the ester group are forming hydrogen bonds with an alcohol. Hydrogen bonding involving the α-keto group is slightly preferred.

The large dipole moment difference between s-*cis* and s-*trans* EP also plays an important role for the intermolecular interaction of EP with ammonium ions. Such an interaction between EP and protonated cinchonidine was proposed for the enantio-selective hydrogenation of EP over cinchonidine modified Pt in acidic media. The biggest contribution to the interaction energy is the charge–dipole interaction, which strongly favours s-*cis* over s-*trans* EP.

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