Influence of Intramolecular Hydrogen Bonds on the Acid Hydrolysis of Di(ethoxycarbonyl)pyridine *N*-Oxides

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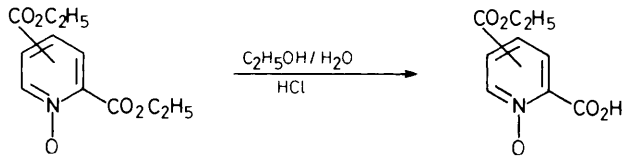
Acid hydrolysis of 2,4-, 2,5-, and 2,6-di(ethoxycarbonyl)pyridine *N*-oxides yields monoesters of picolinic acid *N*-oxides in high yield. Selective hydrolysis of the ethoxycarbonyl group at the 2-position is caused by intramolecular hydrogen-bond formed in the first step of the hydrolysis reaction. FTIR studies of $HAuCl_4$ salts of (4*R*)-2-ethoxycarbonylpyridine *N*-oxides show that a complex tautomeric equilibrium, depending on the substituent, exists in acetonitrile solution.

Intramolecular hydrogen bonds can be an important factor in determining both the reaction rate and mechanism. They may affect the reaction rate by taking part in the reaction itself or by altering the properties of a reactant. The reaction rate can change in either direction since the intramolecular hydrogen bond can either hinder or open an active centre. A study of a number of 2-(2-acetoxyphenyl)imidazole derivatives has shown that acidic hydrolysis of these compounds results in a 25–100-fold rate enhancement by comparison with analogous systems in which intramolecular hydrogen bond participation is not available.[1] On the other hand, a lower reaction rate in the chelated ester and a higher activation energy required to overcome this restraint are known to exist for the hydrolysis of the ethyl maleate ion.[2]

We have recently found that the susceptibility towards acid hydrolysis of ethoxycarbonyl groups in di(ethoxycarbonyl)-pyridine *N*-oxides is significantly different for groups at position 2 and for those at other positions. We suppose that the different reactivity of these groups is caused by an intramolecular hydrogen bond which occurs only between the *N*-oxide group and the ethoxycarbonyl group at position 2. To obtain more information about the influence of intramolecular hydrogen bonding on the reaction mechanism, esters of (4*R*)-picolinic acid *N*-oxides and their $HAuCl_4$ salts were studied by FTIR spectroscopy in acetonitrile solution.

Results and Discussion

Acid-catalysed hydrolysis of the di(ethoxycarbonyl)pyridine *N*-oxides (**1**)–(**3**) gives the ethoxycarbonylpicolinic acid *N*-oxides (**4**)–(**6**) in high yields (Table 1).



(**1**) 2,4-substituted
(**2**) 2,5-substituted
(**3**) 2,6-substituted

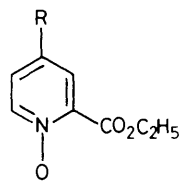
(**4**) 4-substituted
(**5**) 5-substituted
(**6**) 6-substituted

Analysis of the reaction products showed that compounds (**1**) and (**2**) gave only the corresponding monoacid; no dicarboxylic acid was formed. However, in the hydrolysis of compound (**3**), in addition to monoacid (**6**), we also found small amounts of dipicolinic acid *N*-oxide. Thus, the yield of monoacid (**6**) is somewhat lower by comparison with that of compounds (**4**) and (**5**). The above results demonstrate that the ethoxycarbonyl group at position 2 undergoes hydrolysis much faster than those at other positions. This is undoubtedly due to the intramolecular hydrogen bond formed between the protonated *N*-oxide group and the ethoxycarbonyl group at position 2.

The ^1H n.m.r. chemical shifts and coupling constants of the di- and mono-esters (**1**)–(**6**) are given in Table 2. The significant downfield shifts for the protons of carboxylic groups reflect the formation of intramolecular hydrogen bonds between the *N*-oxide and the carboxylic groups.

Intramolecular hydrogen bonds in picolinic acid *N*-oxides and their derivatives have extensively been studied by i.r. and n.m.r. spectroscopy.[3–10] It was found that the chemical shifts of intramolecular hydrogen-bonded protons correlate linearly with Hammett's substituent constant .[4,7,8] The new data obtained for compounds (**4**) and (**5**) show little deviation from the previously established straight line.

To understand better the influence of intramolecular hydrogen bonding on the acid-catalysed hydrolysis of di(ethoxycarbonyl)pyridine *N*-oxides, we have undertaken FTIR studies of (4*R*)-2-ethoxycarbonylpyridine *N*-oxides with electron-withdrawing and electron-releasing substituents in acetonitrile. For the three esters (**7**)–(**9**), where R = NO_2, H, and OEt, respectively, the corresponding $HAuCl_4$ salts (**10**)–(**12**) with acid:base ratio 1:1 were obtained. The FTIR



(**7**) R = NO
(**8**) R = H
(**9**) R = OEt

spectra of the free esters (**7**) and (**8**) and their protonated derivatives (**10**) and (**11**) in acetonitrile solution are shown in Figure 1.

The i.r. spectra of the $HAuCl_4$ salts of the esters show continuous absorption of a relatively low intensity in the region 3 300–600 cm^{-1}. The i.r. spectra indicate that the hydrogen bonds formed in these complexes show considerable proton polarizability.[11,12] However, the relatively low intensity of this continuum suggests that the proton is bonded by an intramolecular hydrogen bond in strongly conjugated systems, similar to those in picolinic acid *N*-oxides.[10,13]

The carbonyl-stretching vibration region of esters (**7**)–(**9**) and their protonated analogues (**10**)–(**12**) is shown in Figure 2.

Table 1. Melting points and i.r. data of mono- and di-(ethoxycarbonyl)pyridine *N*-oxides (**1**)–(**12**) in acetonitrile.

Compound	M.p./°C	Recrystallisation solvent	Yield (%)	$\nu_{C=O}$/cm^{-1}	$^{A}\nu_{C=O}$ [a]	$\nu_{N=O}$/cm^{-1}
(**1**) 2,4-Di(ethoxycarbonyl)pyridine *N*-oxide	Oil	—	96	1 745	53.5	1 258
(**2**) 2,5-Di(ethoxycarbonyl)pyridine *N*-oxide	Oil	—	93	1 744	53.9	1 261
(**3**) 2,6-Di(ethoxycarbonyl)pyridine *N*-oxide	Oil	—	94	1 744	53.3	1 259
(**4**) 4-Ethoxycarbonylpicolinic acid *N*-oxide	105	H_2O–EtOH (1:1)	92	1 733, 1 716	54.5	*b*
(**5**) 5-Ethoxycarbonylpicolinic acid *N*-oxide	131	H_2O–EtOH (1:1)	95	1 737, 1 704	54.9	*b*
(**6**) 6-Ethoxycarbonylpicolinic acid *N*-oxide	71	H_2O–EtOH (1:1)	80	1 749, 1 718	54.8	*b*
(**7**) 4-Nitropicolinic acid *N*-oxide ethyl ester	69	EtOH	83	1 749	27.8	1 268
(**8**) Picolinic acid *N*-oxide ethyl ester	Oil	—	88	1 744	29.2	1 252
(**9**) 4-Ethoxypicolinic acid *N*-oxide ethyl ester	89	EtOH	90	1 745	31.9	1 218
(**10**) $HAuCl_4$ salt of (**7**)	—	—	—	1 756, 1 723	11.7	*c*
(**11**) $HAuCl_4$ salt of (**8**)	—	—	—	1 755, 1 722	15.0	*c*
(**12**) $HAuCl_4$ salt of (**9**)	—	—	—	1 754, 1 721	19.7	*c*

[a] The integrated absorption intensities were calculated by means of the standard Brüker program. [b] Strongly coupled. [c] No band is observed.

Table 2. ^{1}H N.m.r. chemical shifts (ppm) and coupling constants/Hz for compounds (**1**)–(**6**).

Compound	2-CO_2H	2-OCH_2	2-CH_3	–OCH_2	–CH_3	H-3	H-4	H-5	H-6	$J_{3,4}$	$J_{3,5}$	$J_{3,6}$	$J_{5,6}$	$J_{4,6}$
(**1**)	—	4.44	1.41	4.45	1.43	8.20	—	7.91	8.25	—	2.4	0	7.8	—
(**2**)	—	4.43	1.41	4.48	1.43	7.62	7.84	—	8.78	8.2	—	0	—	1.2
(**3**)	—	4.46	1.41	4.46	1.41	7.61	7.29	7.61	—	8.4	2.5	—	—	—
(**4**)	16.84	—	—	4.46	1.44	8.94	—	8.16	8.43	—	2.2	0.6	7.5	—
(**5**)	17.52	—	—	4.49	1.45	8.51	8.20	—	8.91	8.1		0.8	—	2.0
(**6**)	16.97	—	—	4.52	1.45	8.51	7.80	7.80	—	7.6	3.2	—	—	—

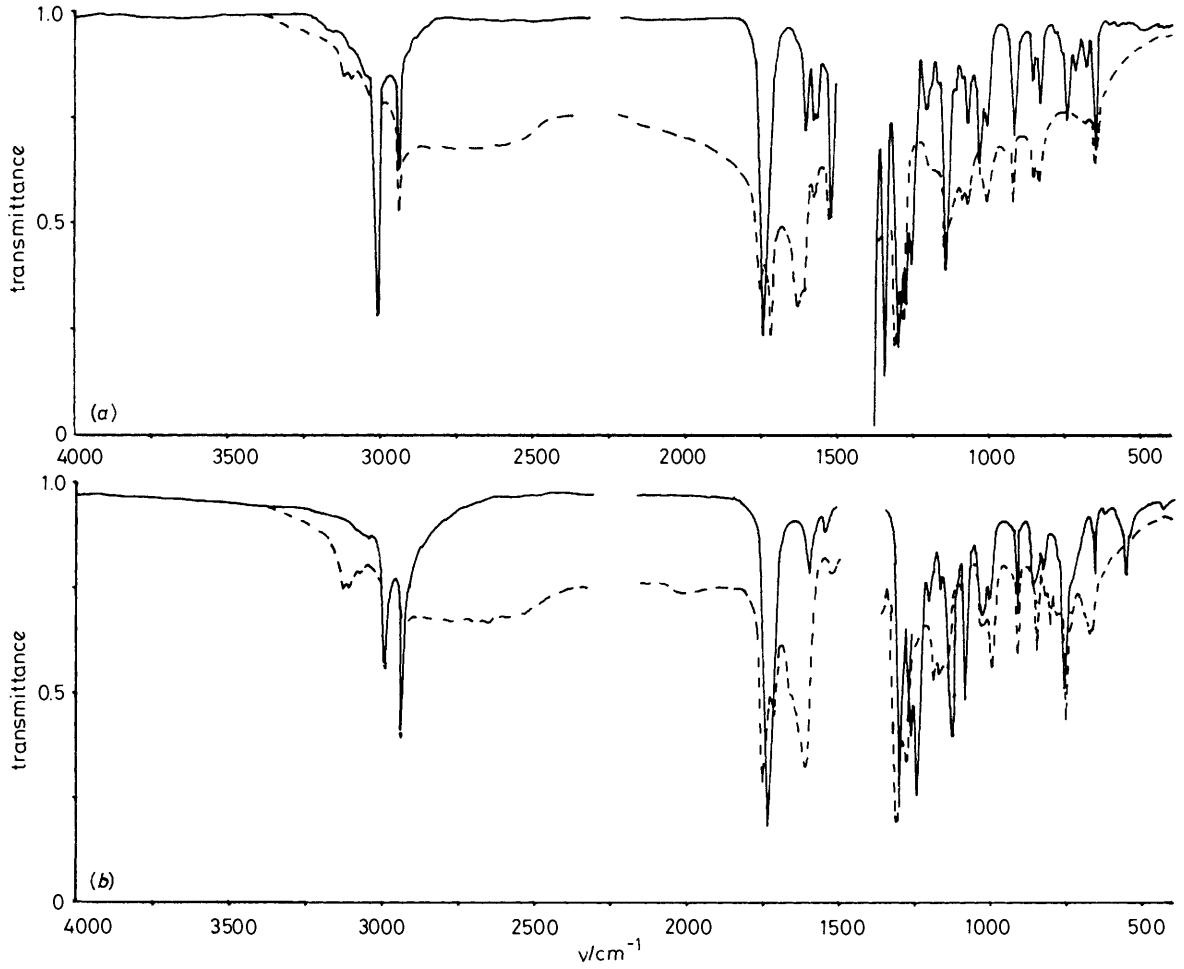


Figure 1. FTIR spectra of (——) ethyl esters and (– – –) their $HAuCl_4$ salts in acetonitrile in the region 4 000–400 cm^{-1}; (*a*) compound (**7**) and (*b*) compound (**8**).

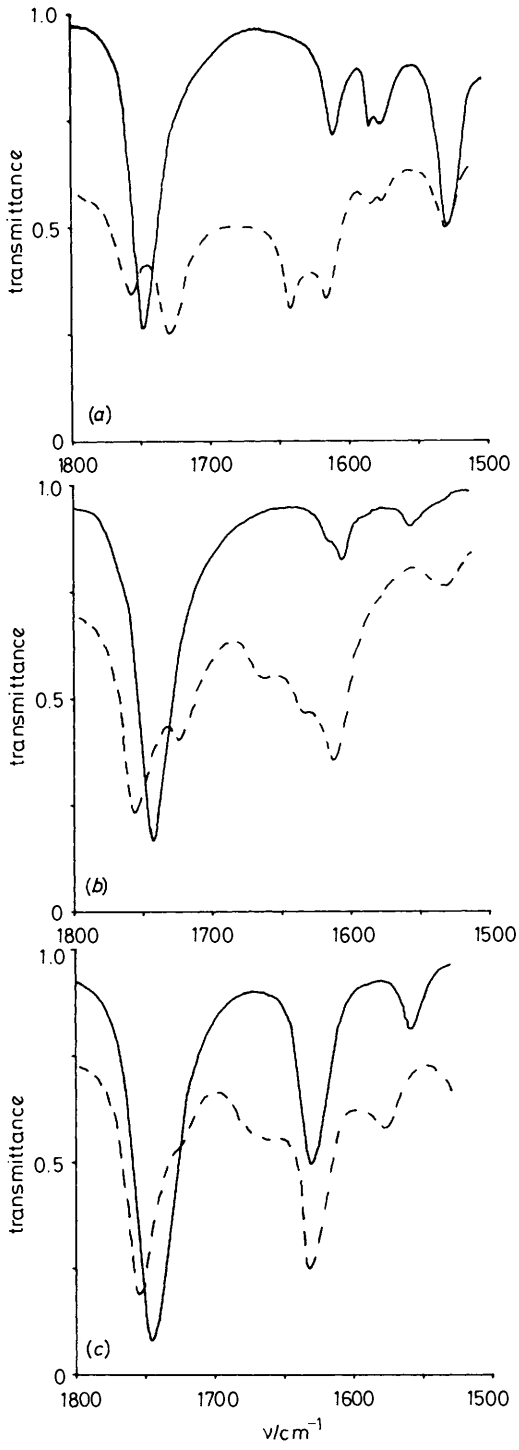
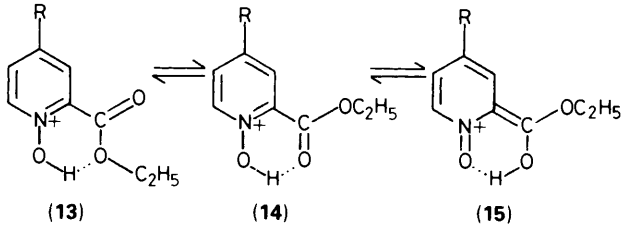


Figure 2. FTIR spectra of (——) ethyl esters and (– – –) their $HAuCl_4$ salts in acetonitrile in the range 1 800–1 500 cm^{-1}; (*a*) compound (**7**), (*b*) compound (**8**), and (*c*) compound (**9**).

All esters investigated display a single carbonyl stretching vibration band, $\nu_{C=O}$. For protonated esters the intensity of the carbonyl band strongly decreases, with a simultaneous splitting for a doublet. One of the doublet bands is shifted to higher frequencies and the second one to lower frequencies by comparison with the frequency of the carbonyl band of the free ester.

The total and partial intensities of both carbonyl bands depend on the substituent at position 4. This clearly indicates that at least two tautomeric forms, (**13**) and (**14**), can exist in solution.

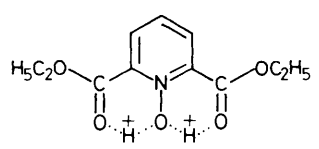


(**13**) (**14**) (**15**)

According to spectroscopic studies of *ortho*-substituted benzoic acids and esters,[14,15] the carbonyl band at higher frequencies can be assigned to structure (**13**), and that at lower frequencies to structure (**14**). The tautomeric form (**14**) may undergo proton transfer rapidly and easily to give a tautomeric form (**15**) without a carbonyl group. The significant decrease in the carbonyl band intensity, $\nu_{C=O}$, and higher intensity of the ring stretching vibrations, $\nu_{C=C}$ and $\nu_{C=N}$, in protonated esters, confirm the presence of the tautomeric form (**15**) in solution. Further proof is derived from a shift of the ν_{C-O-C} stretching vibrations at *ca.* 1 310 and 1 130 cm^{-1} towards higher frequencies and the appearance of a new band at *ca.* 1 000 cm^{-1}, that can be assigned to a ν_{C-O-H} stretching vibration (Figure 3). Additional evidence for participation of the tautomeric form (**15**) in the equilibrium mixture is provided by the disappearance of the stretching vibration band of the *N*-oxide group in protonated esters. This suggests that the *N*-oxide group changes bond order or that it is involved in a strong intramolecular hydrogen bond. However, this latter conclusion is common to all tautomeric forms.

The total intensity of the carbonyl band for protonated esters (**10**)–(**12**) comes from both tautomeric forms (**13**) and (**14**). In the case of the $HAuCl_4$ salt of 2-ethoxycarbonylpyridine *N*-oxide, (**11**), the total intensity of this band is almost two times smaller than that for the free ester, at 15.0 and 29.2, respectively (Table 1). For an ester with an electron-withdrawing substituent, *e.g.* R = NO_2, this difference is even greater, whereas for an ester with an electron-releasing substituent, *e.g.* R = OEt, the difference is smaller. This clearly indicates that the ratio of tautomeric forms depends on the substituents and that for electron-withdrawing substituents the tautomeric form (**15**) is dominant. Taking into account the charge distribution in the ester group, one can expect that the susceptibility of the ester carbon atom towards reaction with a nucleophilic molecule of water would be much greater for tautomeric forms (**13**) and (**14**) than for structure (**15**). Thus, electron-releasing substituents will facilitate the acid-catalysed hydrolysis of 2-ethoxycarbonylpyridine *N*-oxides. This conclusion is confirmed by kinetic studies on the acid-catalysed hydrolysis of substituted 2-ethoxycarbonyl pyridine *N*-oxides.[16]

Still more interesting is the hydrolysis of 2,6-di(ethoxycarbonyl)pyridine *N*-oxide (**6**), where two intramolecular hydrogen bonds can be formed in acidic solution (**16**), similar to those in dipicolinic acid *N*-oxides.[17]



(**16**)

However, the product analysis showed that only small amounts of dicarboxylic acid were formed during the hydrolysis process. This suggests that hydrolysis of one ethoxycarbonyl

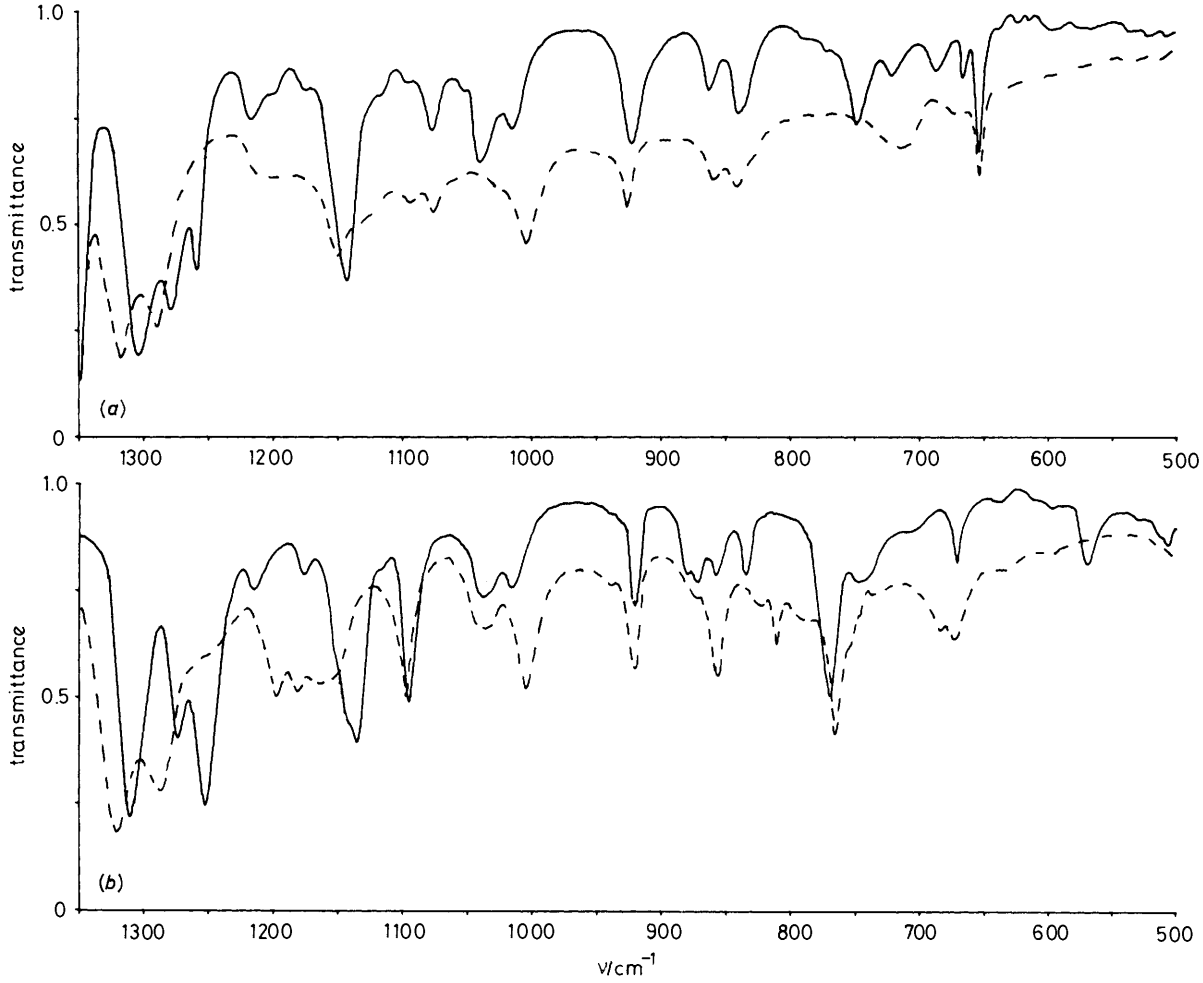


Figure 3. FTIR spectra of (——) ethyl esters and (– – –) their $HAuCl_4$ salts in acetonitrile in the range 1 350–500 cm^{-1}; (*a*) compound (**7**) and (*b*) compound (**8**).

group gives a monoacid with a strong intramolecular hydrogen bond between the second ethoxycarbonyl group and the *N*-oxide group. Thus, the electrophilicity of the second ethoxycarbonyl group is reduced, and consequently, 2,6-di(ethoxycarbonyl)pyridine *N*-oxide can be converted into the monoacid selectively.

Conclusions

Acid-catalysed hydrolysis of di(ethoxycarbonyl)pyridine *N*-oxides yields selectively the corresponding monoacid. The first step of the reaction, *i.e.*, protonation of the *N*-oxide group, leads to a complex tautomeric equilibrium which can be described by three structures with intramolecular hydrogen bonds. The relative ratio of the tautomeric forms depends on the substituents. The electron-withdrawing substituents shift the equilibrium towards form (**15**), which is less susceptible to nucleophilic attack by water, whereas the electron-releasing substituents favour the tautomeric forms (**13**) and (**14**).

Experimental

The preparation of pyridine *N*-oxide carboxylic acids is given in refs. 17–19. The new esters (**1**)–(**3**) were prepared according to the procedure given in ref. 20. Yields are listed in Table 1.

Compounds (**4**)–(**6**) were obtained as follows: di(ethoxycarbonyl)pyridine *N*-oxide (**1**)–(**3**) (1 g) was dissolved in an ethanol–water mixture (10 cm^{-3}; 1:1, v/v) and then conc. hydrochloric acid (0.1 cm^3) was added. The reaction mixture was heated for 12 h at 60 °C. After cooling, the resulting precipitates were filtered off and recrystallized. Yields and recrystallization solvents are given in Table 1.

The $HAuCl_4$ salts of esters (**7**)–(**9**) were prepared by mixing a solution of $HAuCl_4$ in acetonitrile (1 cm^3 of a 0.2 mol dm^{-3} solution) with a solution of the corresponding ester dissolved in acetonitrile (1 cm^3 of a 0.2 mol dm^{-3} solution). The resulting solutions (0.1 mol dm^{-3}) were used directly for i.r. measurements. All manipulations with the substances were performed in a carefully dried glove box.

The i.r. spectra were recorded in carefully dried acetonitrile solutions (0.1 mol dm^{-3}) with an FTIR spectrometer, model IFS 113v (Brüker, Karlsruhe, FRG) using a cell with Si windows (sample thickness 0.4 mm, detector DTGS, resolution 2 and number of scans 250).

The n.m.r. spectra were obtained for $CDCl_3$ solutions (0.1 mol dm^{-3}) with a JEOL FX90Q spectrometer calibrated with TMS as internal standard.

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