Chromatographic Enantiomer Separation and Chiroptical Properties of 1-Acyl-2-aryl-1,2,3,4-tetrahydropyridines and Some Analogues

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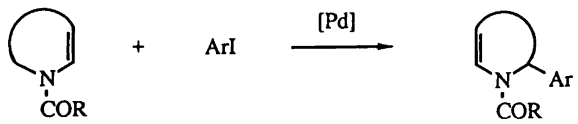
Ten 1-methoxycarbonyl-2-aryl-1,2,3,4-tetrahydropyridines (**1a–j**), two 1-formyl analogues (**2a, b**), 1-formyl-5-phenyl-2-pyrroline (**3**), a 1,2,5,6-tetrahydro analogue of **1** (**4**), and a tricyclic anhydride related to **1** with a rigid structure (**5**) have been quantitatively resolved into enantiomers by liquid chromatography on swollen microcrystalline triacetylcellulose (TAC). The CD spectra of the pure enantiomers have been recorded. Based on geometries obtained by empirical force-field calculations the rotational strengths of the strong transisitions have been calculated by a semi-empirical method and absolute configurations have been assigned to 11 of the 15 compounds. The enantiomers of the carbamates **1** of *R* configuration were found to be less strongly retained by TAC than the *S* enantiomers, whereas the order is the reverse for the formamides **2** and **3**. The capacity and selectivity factors, the latter varying between 1.13 and 23.1, are found to be strongly influenced by the position and nature of the substituents in the aromatic rings.

Nitrogen heterocycles, arylated in the 2-position, have the N–CH(Ar)– partial structure in common with many interesting alkaloids.[1] Two of us have recently reported a palladium-catalyzed arylation of cyclic enamides.[2] A characteristic feature of this reaction is the creation of a stereogenic center and the concomitant isomerization of the double bond, furnishing a new enamide function, accessible in principle for further functionalizations at either the α- or the β-position[3,4] (Scheme 1).



Scheme 1.

Enantiomer separation by chromatography on chiral stationary phases (CSPs) has developed greatly in recent years,[5] and attempts to understand the mechanisms underlying the selectivity have among other things, been based on studies of series of suitably substituted related compounds in attempts to establish quantitative structure–retention relationships (QSRR).[6] The 2-aryltetrahydropyridine derivatives **1–2** (Scheme 2) form such a series, and in this work we report on their enantiomer resolution by chromatography on microcrystalline triacetylcellulose (TAC). For comparison, compounds **3**, **4** and **5** are also included in the study. To be able to draw conclusions about the retention mechanism from the capacity and selectivity factors of the compounds studied, it is desirable to know their conformations and absolute configurations. We have tried to achieve these goals by means of empirical force-field calculations (MMP2-85) and by analysis of the circular dichroism (CD) spectra.

Experimental

Instruments. The chromatographic equipment has been described previously.[7] CD spectra were recorded on a JASCO Model J-500A spectropolarimeter and UV spectra on a Cary Model 2290 spectrophotometer. A Varian 3300 gas chromatograph, equipped with a 2 m glass column of 5 % OV 17 on Chromosorb W, was used for GLC analyses. NMR spectra were recorded with a Varian XL-300 NMR spectrometer.

Materials. The preparation of compounds **1–5** (Scheme 2) is reported elsewhere.[2] The identity of the compounds was verified by ^{1}H NMR (300 MHz) and mass spectroscopy, and by elemental analysis. The purity of the material was checked by GLC.

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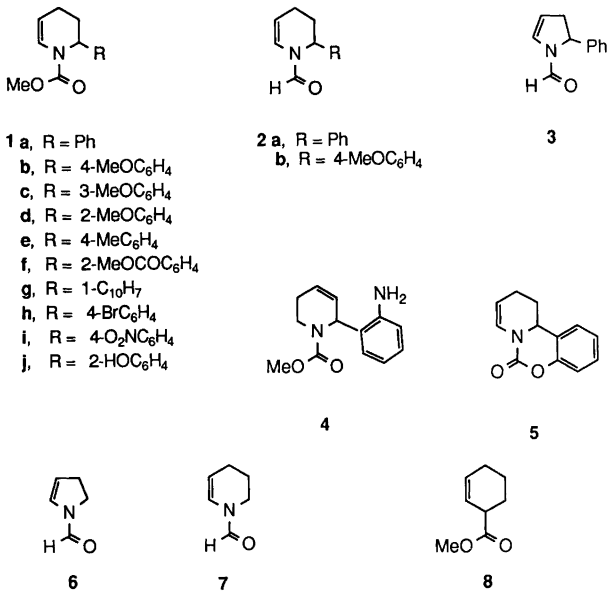


Scheme 2.

Chromatography. All the compounds were resolved on two TAC columns (600×10 mm I.D.) in series, connected to a switching valve (Rheodyne 7010). Ethanol–water (96:4) was used as the mobile phase at a flow rate of 1 ml min^{-1}. The samples (5–10 mg) were dissolved in ethanol (1 ml) and linjected with a loop injector (Rheodyne 7025). For most of the compounds, optically pure fractions were obtained in one operation, but for a few of them with low selectivity factors and giving low column efficiency, it was necessary to recycle selected fractions. The CD spectra (Table 1) were recorded directly on the eluted and collected fractions, and the concentrations were monitored by UV spectroscopy. The optical purity was checked by comparison of the CD spectra of each pair of enantiomers. Mirror image spectra were obtained, which also verified that no chemical changes occurred during the chromatographic separation. Compound **1h** was resolved in larger amount by injection of 50–70 mg samples in several runs. The dead volume of the columns was determined by injection of 1,3,5-tri-*tert*-butylbenzene, asumed not to be adsorbed on TAC.[8]

The capacity factors k_1' and k_2' for the first and second eluted enantiomers (E_1 and E_2) and the selectivity factors α (Table 2) were calculated by means of eqns. (1) and (2),

$$k_i' = (t_i - t_0)/t_0 \quad (1)$$

$$\alpha = k_2'/k_1' \quad (2)$$

where t_i and t_0 are the retention times of enantiomer and non-retained reference respectively.[5]

A chromatogram of **1a** is shown in Fig. 1.

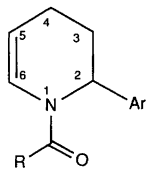
Calculations. The force-field calculations were performed with the MMP2-85 force field.[9,10] This lacks a few of the parameters required for compounds **1–5**, and the missing constants have been estimated by analogy with those known for similar bond system. Calculations with a selection of constants distributed above and below those finally chosen show that minimum-energy geometries and the energy differences between different conformers are rather insensitive to the values of these constants.

The CNDO/S calculations were performed with a program[11] which, for the present systems, is equivalent to the original Del Bene–Jaffé program,[12] employing a configuration interaction between a maximum of 99 singly excited configurations.

The calculations of rotational strengths and CD spectra were performed with a semiempirical matrix program devised by Schellman *et al.*,[13,14] which requires as input transition energies, direction and strengths of transition moments, and transition charge densities. The CD spectra are obtained from the calculated rotational strengths assuming Gaussian bandshape with bandwidths obtained from the UV spectra.

Results and discussion

Force-field calculations. The calculations on compounds **1** and **2** predict that the tetrahydropyridine atoms N-1, C-2, C-4, C-5 and C-6 and the H–C=O or O–C=O groups are nearly coplanar, with only C-3 outside the plane. The substituent on C-2 may be equatorial or axial,[15] and the carbonyl group may be *E* or *Z* oriented with respect to C-6. As follows from the results presented in Table 2, the *E* and *Z* forms have very similar energies. The assignment of *E* and *Z* forms is based on the ^1H chemical shift of H-6 (lower field for the *E* form).



1, 2

Calculations on the 2-phenyl derivatives **1a** and **2a** predict very similar energies for the axial and equatorial forms (Fig. 2). Evidently both *E* and *Z* rotamers of axial and equatorial conformers must be considered in the analysis of the CD spectra.

The ^1H resonance of H-2 appears in the spectra of all compounds **1** and **2** as a somewhat broadened and unsymmetrical triplet with a splitting of 4–5 Hz. The force-field calculations predict the H-2–H-3 dihedral angles to be ca. 180 and *ca.* 55° in the equatorial form and *ca.* 70 and *ca.* 45° in the axial form. The vicinal coupling constants predicted for these angles by calculations according to Haasnoot *et al.*[16] are 11.5, 4.5, 2.3 and 5.7 Hz respectively. The experimental coupling constants are population-weighted averages of those of the individual conformers, and a calcu-

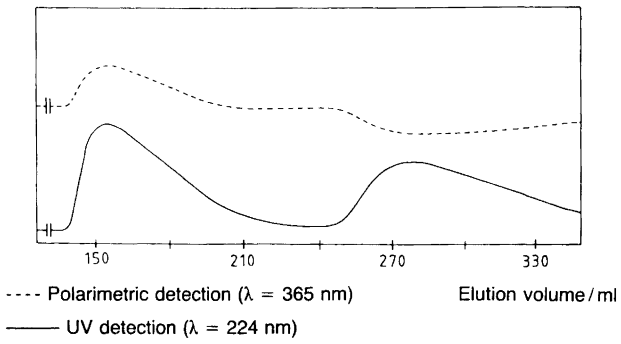


Fig. 1. Chromatogram of **1a**.

lation with the predicted values points to an equilibrium mixture with an excess of the axial form.

The situation is even more complex for the compounds containing phenyl groups substituted in positions other than *para,* and for the 1-naphthyl derivative **1g**. For these compounds, four minimum-energy conformations were found with respect to the 2-substituent, denoted equatorial *endo*, equatorial *exo*, axial *endo*, and axial *exo* (Fig. 3), and in general two or three forms are predicted to have low and similar energies. The tricyclic compound **5**, on the other hand, is a rigid molecule, for which only one energy minimum is predicted.

Calculations on *N*-formyl-5-phenyl-2-pyrroline (**3**), starting from several input geometries, led to only one energy minimum for the *E* and one for the *Z* form. In these, all ring atoms are almost in the plane of the formyl group, with the C-5–H and C-5–Ph bonds nearly eclipsed with C-4–H bonds. The dihedral angles between the C-5–Ph and C-4–H bonds are calculated to be ± 110.0 and ∓ 15.3° for the *E* and ± 105.1 and ∓ 20.3° for the *Z* form.

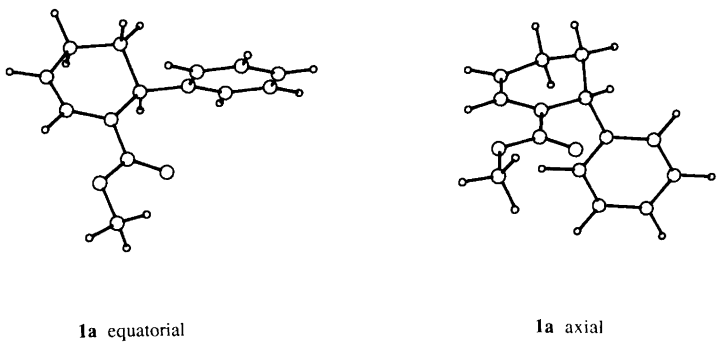
UV and CD spectra and absolute configurations. The strong bands in the CD spectra can be expected to result from interactions between transitions in two chirally disposed planar chromophores: the *N*-vinylformamide/*N*-vinylcarbamate and the 2-aryl chromophores. The former group is characterized by a strong $\pi \rightarrow \pi^*$ band at 234–236 nm for the formamides **6** and **7** and at 220 nm for the carbamate **8**, and a weak $n \rightarrow \pi^*$ transition at *ca.* 270 nm (Table 1). The energies and polarizations of the transitions in the aryl groups depend on the substituents.

The UV spectra of compounds **1–3** and **5** appear as superpositions of those of the two chromophores [Fig. 4(a)]. The CD spectra of most of the compounds with 2-phenyl groups display more or less distinct pairs of close-lying oppositely signed bands (couplets) centered at 220–230 nm [Fig. 4(b)]. These probably have their origin in coupling between the benzene ^1L_a transition[17] and the vinylamide $\pi \rightarrow \pi^*$ transition, and if the directions of the corresponding transition moments were known, it would be possible to establish the absolute configuration of an enantiomer from the sign of the couplet by use of the coupled oscillator technique.[18]

To find the direction of the transition moment of the lowest $\pi \rightarrow \pi^*$ transition of the vinylamide chromophore, CNDO/S calculations were performed for the simple *E* and *Z* forms of *N*-vinylformamide and methyl *N*-vinylcarbamate. For the *E* forms, the transition moments were found to be practically parallel with the C=C bond, whereas for the *E* forms they deviate by *ca.* 15° in the direction of the carbonyl oxygen atom. The transition charge density is almost entirely located on the carbonyl oxygen and vinyl carbon atoms.

The semiempirical technique devised by Schellman *et al.*[13,14] for the theoretical calculation of CD spectra (see the Experimental) was found to be quite successful for the calculation of the CD spectra of chiral dimers of coumarin,[19] and we now report on its use for the calculation of the CD spectra resulting from the interaction between the *N*-vinylamide $\pi \rightarrow \pi^*$ transition and the transitions in the aromatic substituents in **1–3** and **5**.

The CD spectra of most of the compounds also display a weak band with fine structure in the region 250–285 nm, originating in the benzene ^1L_b transition (ca. 300 nm without fine structure for the *p*-nitro compound **1i**). These transitions have also been included in the calculations, since agreement in sign and order of magnitude between experimental and calculated rotational strengths for more than one transition increases the credibility of the pre-



1a equatorial **1a** axial

Fig. 2. Calculated minimum-energy conformations of axial and equatorial forms of **1a** (*E*).

Table 1. UV and CD spectra of compounds **1–5**. Solvent ethanol.

Compound	UV: λ_{max}/nm (ε)	CD: λ_{max}/nm (Δε)[a]
1a	267 (320), 263 (370), 256 (480), 212 (20200)	267 (+0.16), 260.5 (+0.23), 237.5 (−4.0), 214 (+21.5)
1b	282 (1770), 275 (2000), 222 (27400)	283.5 (+0.38), 277 (+0.48), 271 (+0.38), 269 (+0.34), 234 (−12.9), 219.5 (+24.0), 205.5 (+17.7), 203.5 (+18.8)
1c	279 (1980), 272 (2220), 218 (26300)	275 (−0.04), 237.5 (−3.9), 211.5 (+17.3)
1d	278 (3070), 270 (3290), 218 (24400)	277.5 (−0.91), 270 (−0.95), 238.5 (+7.7), 225 (+7.4), 212 (−39.4)
1e	272 (510), 264 (590), 258 (570), 217 (22900)	273 (+0.19), 265.5 (+0.16), 259.0 (+0.10), 235.5 (−4.0), 217.0 (+20.4)
1f	280 (1320), 221 (23600)	286.5 (−1.02), 233 (+10.8), 214.5 (−20.7)
1g	313 (470), 293 (4880), 288 (5130), 281 (7250), 271 (6250), 262 (4500), 223 (93400)	314 (−0.06), 303 (−0.30), 294 (−1.31), 283 (−2.35), 273.5 (−1.85), 262.5 (−0.72), 250 (−0.81), 231 (+19.0), 221 (−48.5)
1h	260 (4970), 218 (27200)	240.5 (−4.35), 219.5 (+23.7)
1i	268 (7900), 216 (17900), 204 (15300)	303 (−1.46), 250 (sh, +3.0), 224.5 (+11.9)
1j	280 (2150), 275 (2500), 219 (21100)	276 (−0.48), 239.5 (+2.32), 224.5 (+2.32), 210 (−14.5)
2a	288 (910), 232 (10200), 204 (14700)	257.5 (+1.43), 251 (+11.3), 232 (+10.4) (negative end absorption)
2b	282 (1450), 274 (2000), 226 (19100)	283.5 (+1.06), 276.5 (+1.47), 269 (+1.36), 236 (+13.1), 223 (−2.6), 199 (−23)
3	305 (350), 236 (5650), 204 (12900)	269 (−0.84), 262.5 (−1.24), 230 (−4.25), 207 (+2.8)
4	292 (2440), 242 (6700), 204 (34100)	290 (+1.47), 239 (+9.36), 206 (−40.5)
5	274 (1150), 266 (1220), 232 (5600), 206 (sh, 19700)	274 (+1.98), 267 (+2.72), 261 (+2.42), 239 (+5.3), 218 (−8.0), 213 (−6.7), 200 (−30.7)
6	274 (sh, 2400), 236 (10000)	
7	272 (sh, 2000), 234 (10800)	
8	270 (590), 220 (16200)	

[a]First eluted enantiomer (E_1).

dictions. The calculations were first performed for the *R* enantiomer of **1a**, using geometries from the force-field calculations. The ^1L_a transition was oriented along benzene C1–C4 bond, the ^1L_b transition perpendicular in the ring plane, and the transition moments of the vinylamide $\pi \rightarrow \pi^*$ and the benzene transitions were adjusted to reproduce the experimental UV spectrum. The calculations were performed for the *E* and *Z* rotamers of the axial and equatorial forms. All four conformers gave negative couplets of similar strength (Δε ca. ± 4), which reflects the fact that the relative orientations of the transitions moments are rather similar in the four cases.

The rotational strengths of the ^1L_b transitions were calculated to be negative and weak for the two *E* forms and positive and stronger for the two *Z* forms. Experimentally, weak positive ^1L_b band systems are found in the CD spectra of the E_1 enantiomer of **1a**, **1b**, and **1e**, but since the positions of the *E*–*Z* equilibria in ethanol are unknown, this cannot be used to evaluate absolute configurations. The value of the ^1L_b bands for assignments is also limited by the shallow energy minimum to torsion about the C-2–C_{Ar} bond, which gives a large spread of relative orientations of the ^1L_b and enamide $\pi \rightarrow \pi^*$ transition moments.

Similar calculations were performed for **1b**, **1e**, **1h**, **1i**, **2a**, and **2b** after suitable adjustment of the transition energies and transition moment to obtain agreement with the experimental UV spectrum. In all cases the same result was obtained, i.e. a negative couplet corresponds to the *R* configuration. The CD spectra of all these compounds can be interpreted as containing the couplet under consideration, although the short-wavelength part is often somewhat deformed, probably owing to involvement of higher energy transitions in the two chromophores. Similar calculations for the 2-pyrroline derivative **3** gave the opposite result; a positive couplet for the *R* configuration of both the *E* and the *Z* form.

The tricyclic compound **5** should be a good model for a calculation. The aromatic chromophore has some similarity with that found in the coumarin dimers,[18] although in **5** cross conjugation with a vinylamino group increases the interaction between the ether oxygen atom and the aromatic ring. CNDO/S calculations indicate that the ^1L_a and

Table 2. Chromatographic data, absolute configurations, and fractional populations of the *E* form (p_{anti}, in $CDCl_3$) for **1–5**.

Compound	k'_1	k'_2	α	θ[a]	*R/S*[b]	p_E
1a	2.1	4.6	2.2	+	*R*	0.50
1b	1.2	7.4	6.4	+	*R*	0.50
1c	3.7	10.4	2.8	+	*R*	0.50
1d	1.2	9.8	8.3	–	–[c]	0.50
1e	0.8	18.5	23.1	+	*R*	0.50
1f	1.1	23.8	22.4	+	–[c]	0.46
1g	2.7	5.4	2.0	–	*R*	0.46
1h	0.9	12.5	13.8	+	*R*	0.54
1i	1.0	1.3	1.3	+	*R*	0.54
1j	0.2	0.3	1.7	–	–[c]	0.00
2a	2.7	4.8	1.8	+	*S*	0.60
2b	1.2	9.9	8.3	+	*S*	
3	1.4	1.5	1.1	–	*S*	0.60
4	0.8	1.1	1.3	–	–[c]	–
5	1.2	1.5	1.3	+	*R*	–

[a]Sign of α_{365} of first eluted enantiomer (E_1). [b]Absolute configuration of E_1. [c]Absolute configuration not derived.

^1L_b transition moments are stronger than for the coumarin dimers and more closely parallel (^1L_a) and perpendicular (^1L_b) to the O–C_{Ar} bond. The calculated couplet (positive for the *R* configuration) agrees well with the experimental one (calc. $\Delta\varepsilon$ = +5.0, −6.0; exp. $\Delta\varepsilon$ = +5.3, −8.0), and the ^1L_b transition also comes out with correct positive sign although is of too low intensity (calc. $\Delta\varepsilon$ = +1.0, exp. $\Delta\varepsilon$ = +2.7).

The CD spectrum of the E_1 enantiomer of the 1-naphthyl compound **1g** shows a strong positive couplet ($\Delta\varepsilon$ = +19, −48) centered at 227 nm, probably due to interaction between the $\pi \rightarrow \pi^*$ transition in the *N*-vinylcarbamate chromophore and the ^1B_b transition polarized along the long axis of the naphthalene ring.[20,21] A strong negative band with fine structure centered at 283 nm and a corresponding band in the UV spectrum can be ascribed to the naphthalene ^1L_a transition polarized along the short axis. Force-field calculations on the axial and equatorial *exo* and *endo* forms led to the prediction that only the axial *endo* form is so high in energy (10.9 kJ mol^{-1} above the nearest one) that it can be safely neglected, whereas the other three must be considered. The calculated CD spectra showed the expected couplets, albeit a very weak one for the axial *exo* form. The equatorial *endo* form was predicted to have a negligibly weak ^1L_a transition, whereas the equatorial *exo* form gave a strong positive couplet and a negative ^1L_a band with intensities (^1L_a −4.5, couplet ± 80) which were even higher than the experimental ones. This form should give the major contribution to the CD spectrum even if it constitutes *ca.* half of the conformer mixture; the other conformers could not give rise to the observed spectrum. Therefore, the E_1 enantiomer of **1g** can be assigned to the *R* configuration.

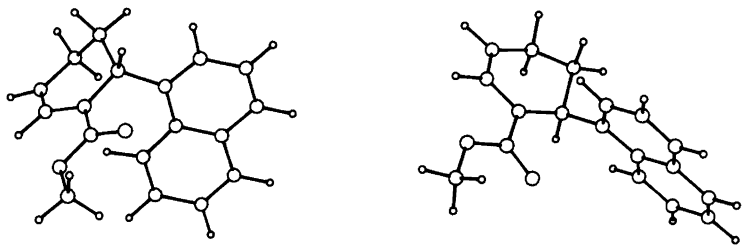
Similar calculations for the *R* forms of the *ortho*-methoxybenzyl derivative **1d** gave less conclusive results. A positive couplet was calculated for the axial *exo* form and negative ones for the other four. For all forms the same sign was predicted for the couplet and for the ^1L_b transition. Since the CD spectrum of the E_1 enantiomer of **1d** shows a positive couplet and a negative ^1L_b band system, it can only be rationalized as a superposition of spectra of two or more forms, and since no major contributor can be identified, as it could for **1g**, no assignment of the absolute configuration of **1d** is possible.

Similar calculations for the *meta* analogue **1c** predict a negative ^1L_a–enamide $\pi \rightarrow \pi^*$ couplet for all *R* forms, very weak for the axial *exo* form but stronger for the others. Very weak ^1L_b transitions were calculated and also found experimentally.

No CD calculations were performed for **1f**, **1j** or **4** because of the complicated conformational situation. The three chromophores in **4** are also less suited to calculation.

No distinct CD bands attributable to the carbonyl $n \rightarrow \pi^*$ transition were observed. The geometries are such that the magnetic transition moments of the $n \rightarrow \pi^*$ transitions and the electric moments of the aromatic ^1L_a transitions are far from parallel in all conformers, and the calculations predict low $n \rightarrow \pi^*$ rotational strengths, except for **5**, for which a somewhat higher positive rotational strength was calculated.

Discussion of capacity and selectivity factors. Remarkably high selectivity factors (α, Table 2) were observed in the separation of some enantiomeric pairs, and the effect of the



1g axial endo **1g** equatorial exo

Fig. 3. Calculated minimum energy conformations of the axial endo and equatorial exo forms of **1g** (*anti*).

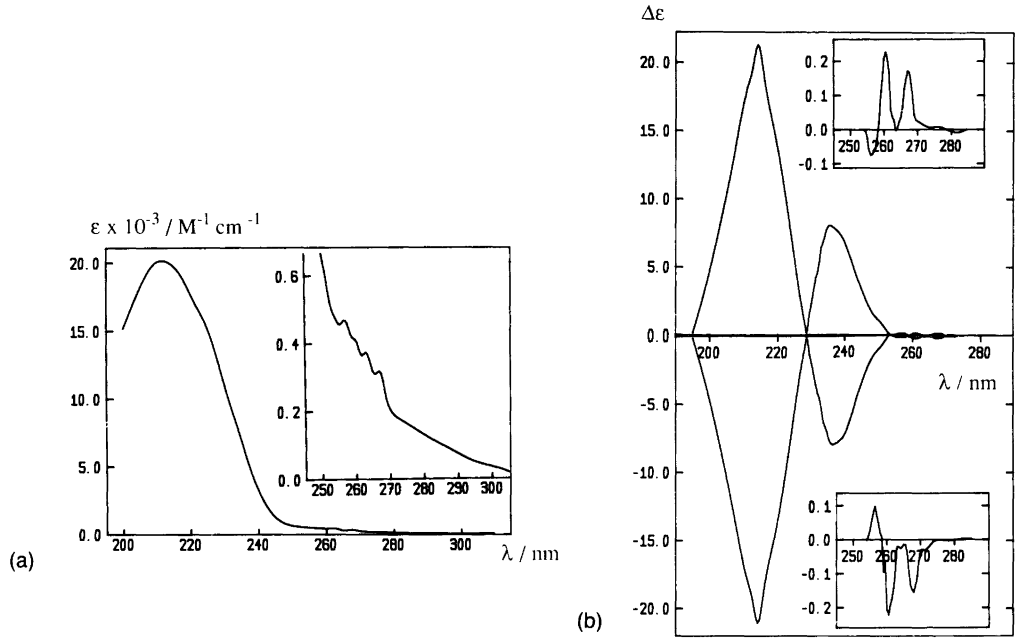


Fig. 4. (a) UV spectrum of **1a** in ethanol; (b) CD spectra of **1a** in ethanol, *R* and *S* forms.

substituent in the aromatic group on the selectivity is notable. However, a general effect of the absolute configuration was also observed. The first eluted enantiomer of the carbamates **1a–c**, **1e**, **1g**, **1h** and **1i** as well as the cyclic carbamate **5** has the *R* configuration. For **1d**, **1f** and **1j** the absolute configurations could not be assigned. However, change of the *N*-substituent from CH_3OCO to CHO reverses the order; the *S* enantiomers of **2a**, **2b** and **3** are eluted first.

The effect of the substituent in the benzene ring in the carbamates **1** may be due to a direct steric and/or electrostatic interaction between the substituent and the active sites on the CSP, or it may be ascribed to the influence of the substituent on the electron distribution in the benzene ring. Wolf *et al.*[22] have studied the chromatographic resolution of a series of compounds with some structural similarity to **1** (cyclohexane, oxane, and dioxane derivatives with a phenyl group at the asymmetric carbon atom). The capacity factor k_2' was correlated with the conformational mobility and with the electrostatic potential of the molecules, and it was found that k_2' increases with increasing negative charge at the asymmetric carbon atom. In compounds **1** the charge at C2 must be related to the charge at the adjacent aromatic carbon atom, which may be correlated with the corresponding ^{13}C chemical shift. An analysis of k_2' in terms of the ^{13}C substituent increments ($\Delta\delta$) in C_6H_5X[23] gives some indication of a similar charge effect, since k_2' is low (1.34) for X = *p*-NO_2 ($\Delta\delta$ +6.0), and high for X = *o*- and *p*-OCH_3 (k_2' 9.75 and 7.44, $\Delta\delta$ −14.7 and −8.1). However, X = *m*-OCH_3 ($\Delta\delta$ +0.9) gives an even higher k_2' value, and the high k_2' values for X = *p*-Br, *p*-CH_3, and *o*-CO_2CH_3 are in complete disagreement with the charge effect. Evidently, at least direct interaction of these substituents with the active sites on the CSP plays a dominant role.

Lipkowitz *et al.*[24] have made a theoretical model study of the formation of diastereomeric complexes between *R*- and *S*-solutes and a CSP. Their conclusions are that the enantioselectivity depends on the conformations of both solute and CSP, and also that relatively high-energy solute conformations may be important in determining the elution order. This complicates the analysis of the substituent effects, since different conformations in two solutes under consideration may be responsible for the larger part of the free energy of interaction with the CSP.

Very low capacity and selectivity factors are observed for the hydroxy compound **1j** and the amino compound **4**. This may be ascribed to hydrogen bonding between the analyte and the mobile phase, which generally results in low capacity factors.[7,25] The low α value found for the cyclic carbamate **5** are in disagreement with the view that rigid molecules, in general, give higher selectivity than flexible ones.[26] The 1-naphthyl compound **1g** has higher capacity factors than the phenyl analogue **1a**, which is in agreement with the observation of Hesse and Hagel[27] that naphthalene is more strongly retained than benzene on TAC. It is also worth observing the E_1 forms of the compounds with unsubstituted 2-phenyl group (**1a**, **2a**, **3**) are more strongly retained than all other E_1 forms except that of **1c**.

The influence of the *E–Z* isomerism on the selectivity has not been studied. In chloroform-*d* solution the *E–Z* ratio varies between 0.6:0.4 and 0.46:0.54. The barrier to *E–Z* interconversion is ca. 77 kJ mol^{-1} for *N*-vinylformamides[28] and probably somewhat lower for the analogous carbamates.[29] This corresponds to half-lives of 3 s or less. It is likely that the *E* and *Z* forms interact differently with TAC.

and some sites may bind preferentially the *E* forms and others the *Z* forms. Therefore the *E–Z* equilibrium ratio, although rapidly established, may be important for the selectivity. It may be worthwhile to study the ratio by NMR spectroscopy in ethanol-d_6 solution, but for the moment we have refrained from this, considering the very similar populations of the two forms in chloroform-*d* solution for all compounds except **1j**.

Conclusions. The 2-aryltetrahydropyridine derivatives **1**, **2**, **4** and **5** and the analogue **3** are, in general, suitable for enantiomer separation by chromatography on TAC. The elution order of the enantiomers seems largely to be governed by the absolute configuration. The large variations in selectivity are probably mainly determined by direct interaction of substituents in the aryl groups with the active sites on the TAC surface.

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