organic compounds

Tosyl esters of cinchonidine and cinchonine alkaloids: the structure–reactivity relationship in the hydrolysis to 9-epibases

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In the crystal structures of the diastereoisomers of O-tosylcinchonidine [(9R)-cinchon-9-yl 4-methylbenzenesulfonate], (I), and O-tosylcinchonine [(9S)-cinchon-9-yl 4-methylbenzenesulfonate], (II), both $C_{26}H_{28}N_2O_3S$, both molecules are in an *anti*-closed conformation and, in each case, the position of the aryl ring of the tosylate system is influenced by an intramolecular C—H···O hydrogen bond. The molecular packing in (I) is influenced by weak intermolecular C—H···O and C—H···π interactions. The crystal structure of (II) features C—H···π interactions and van der Waals forces only. The computational investigations using RHF/6–31G** *ab initio* and AM1 semi-empirical methods performed for (I) and (II) and their protonated species show that the conformational and energetic parameters of the molecules are correlated with differences in their reactivity in hydrolysis to the corresponding 9-epibases.

Comment

Studies on the difference in biological activity of natural *Cinchona* alkaloids with respect to their structural, stereochemical and physicochemical properties have attracted much attention owing to the pharmacological interest in these compounds (Verpoorte *et al.*, 1988). Recently, *Cinchona* alkaloids and their derivatives have been investigated as natural organocatalysts giving asymmetric induction in organic reactions with the formation of stereogenic centres (Song, 2009). Transformation of natural alkaloids into pharmacologically inactive 9-epibases is known to be a two-step process: formation of sulfonate esters followed by hydrolysis in a weak acid medium (Hoffman & Frackenpohl, 2004). The first step proceeds with retention and the second one with inversion of the carbinol atom configuration. It was found that hydrolysis of O-tosyl derivatives is a good method for

epimerization of C9 in the quinine, quinidine and cinchonidine cores, but is ineffective for cinchonine since its tosylate converts slowly and not selectively to the corresponding 9-epibase (Braje *et al.*, 2000). In order to link the differences in experimental reactivity in the hydrolysis to 9-epibases with structural and energetic parameters, X-ray investigations and theoretical calculations were undertaken using cinchonidine and cinchonine tosylates, (I) and (II), as model compounds.
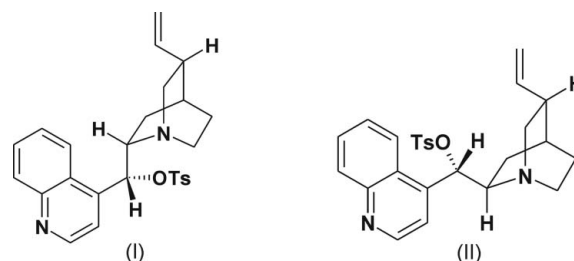
Structural analysis of the diastereoisomeric molecules (I) and (II) confirms the retention of the original, respective, *R* and *S* configurations at atom C9 in the crystals of both tosylates (Figs. 1 and 2, respectively). The geometry (bond lengths, angles and planarity) of the main *Cinchona* alkaloid skeleton is similar in (I) and (II) and the related parent structures of cinchonidine and cinchone molecules (Oleksyn, 1982; Oleksyn *et al.*, 1979). Both molecules adopt an *anti*-closed conformation, torsion angles φ_1 = N1—C8—C9—O1 = 166.6 (6) and −176.7 (4)°, φ_2 = N1—C8—C9—C24 = 48.4 (6) and −57.6 (6)°,
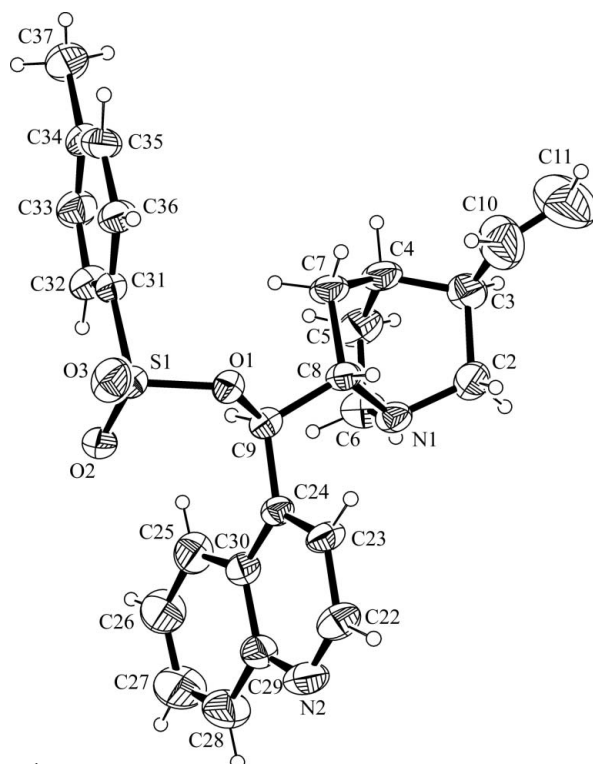

Figure 1
A view of (I) showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms are represented as small spheres of arbitrary radii.

$\varphi_3 = $ O1—C9—C24—C23 = −59.7 (4) and 50.9 (6)°, and $\varphi_4 = $ C8—C9—C24—C23 = 55.9 (5) and −65.7 (6)° in (I) and (II), respectively, which is characteristic, for example, for *O*-mesyl-quinidine (Braje *et al.*, 2000) and is in contrast to an *anti*-open conformation observed for the parent alkaloids. The four conformers, *viz. anti*-closed, *syn*-closed, *anti*-open and *syn*-open (Caner *et al.*, 2003), of the cinchonine-type molecule, showing the lowest energy, are presented in Fig. 3.

The orientation of the vinyl substituent in relation to the quinuclidine system is different in (I) and (II): the torsion angle C2—C3—C10—C11 describing this orientation is 105.4 (13)° in (I) and 175.0 (12)° in (II). The *gauche* conformation of the vinyl group in (I) may be caused by a weak intermolecular C10—H101···O3 hydrogen bond and a C11—H111···π interaction (Table 1). Similarly, the *trans* conformation of the vinyl group in (II) may be a result of the weak C11—H111···π(quinoline) intermolecular interaction (Table 2). The aryl ring of the tosyl group is inclined to the quinoline ring at angles of 20.24 (10) and 11.51 (13)° in (I) and (II), respectively, and its position is influenced by the C32—H321···O2 short intramolecular contact (Tables 1 and 2).

The hydrolysis of *O*-tosylated molecules proceeds with inversion of the C9 configuration as an S_N2 attack by the nucleophilic water molecule from the opposite site to the tosylate leaving group in the substrate requires it to be protonated at the quinuclidine N atom. This process is favoured when the substrate molecule can change from an *anti*-closed conformation, observed in the crystal, into a *syn*-open one which is optimal for the S_N2 attack in the aqueous weak acid medium. It can be assumed on the basis of known reactivity that the transition state may be formed more easily in the case of cinchonidine tosylate (I) than in the case of cinchonine tosylate (II). The theoretical calculations at the RHF SCF *ab initio* 6–31G** level (Bylaska *et al.*, 2006; Kendall *et al.*, 2000) show that the conformations of molecules (I) and (II) as observed in their crystals are not equi-energetic, with a difference in energy between the (I) and (II) conformations of $\Delta E = $ 2.57 kcal mol^{-1} (1 kcal mol^{-1} = 4.184 kJ mol^{-1}; single-point energy calculations). The energy minimization and full geometry optimization with initial geometries obtained from the X-ray analysis for molecules (I) and (II) yielded a smaller difference in energy of 0.85 kcal mol^{-1} between the conformations of molecule (I) ($\varphi_1 = -178.8°$, $\varphi_2 = 62.8°$, $\varphi_3 = -44.0°$ and $\varphi_4 = 72.1°$) and (II) ($\varphi_1 = 174.9°$, $\varphi_2 = -66.6°$, $\varphi_3 = 39.8°$ and $\varphi_4 = -76.8°$) than that reported for the single-point calculation. It is clear that these energy values do not prevent molecule (II) from changing from an unfavourable *anti*-closed conformation to a *syn*-open conformation as expected in the S_N2 hydrolysis reaction. The calculations performed for N1-protonated molecules in the *syn*-open conformation after energy minimization and geometry optimization [$\varphi_1 = -54.0$ and 48.9°, $\varphi_2 = 179.3$ and 176.4°, $\varphi_3 = 146.8$ and −144.6°, and $\varphi_4 = -87.2$ and 88.5° for (I) and (II), respectively] gave a difference in energy between the protonated (II) and (I) species of 0.39 kcal mol^{-1} and, moreover, a larger energetic profit of 1.84 kcal mol^{-1} after protonation of (I) compared with (II) with respect to the free *O*-tosylates in an *anti*-closed conformation. Therefore, the different reactivity of (I) and (II) towards the appropriate 9-epibases may be related to a change in energy during protonation on the N1 atom and a change in conformation from *anti*-closed to *syn*-open during the hydrolysis process. In
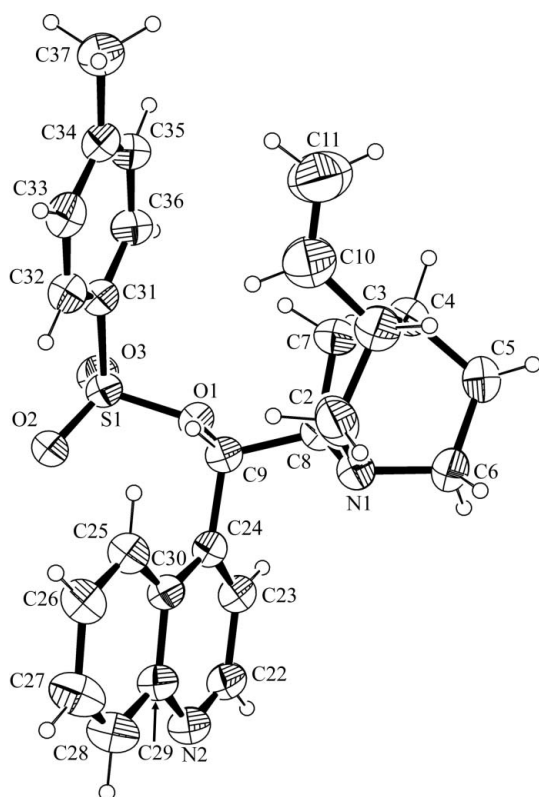

Figure 2
A view of (II) showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms are represented as small spheres of arbitrary radii.
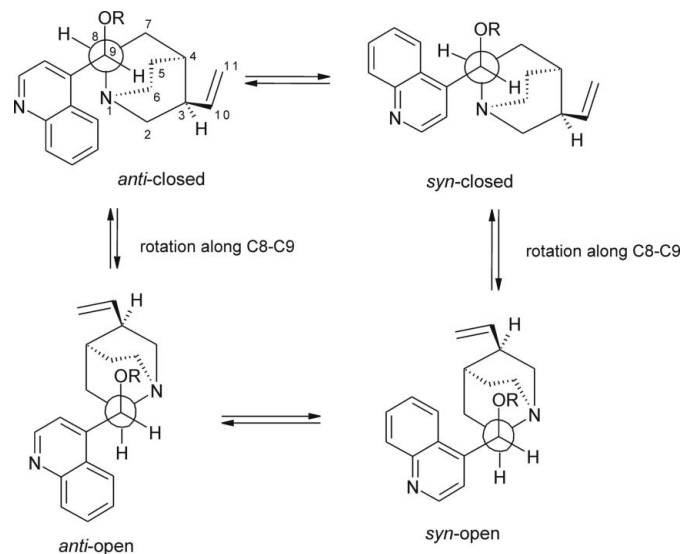

Figure 3
The four conformers of cinchonine showing the lowest energies.

order to confirm this conclusion, the hydrolysis process was modelled using the N1-protonated molecules of (I) and (II) in 'crystallographic' *anti*-closed conformation and an anion of salicylic acid in a water environment (as an aqueous weak acid medium). The water environment was simulated by locating the alkaloid and salicylate ion in the centre of the box surrounded by 17 water molecules equilibrated at 300 K and 1013 hPa (Jorgensen *et al.*, 1983). The energy minimization and geometry optimization of the (I)-H$^+$–salicylate$^-$–H$_2$O system using the semi-empirical AM1 method implemented in the *HYPERCHEM* package (Hypercube, 1998) give molecule (I) an *anti*-open conformation ($\varphi_1 = -63.7°$, $\varphi_2 = 175.4°$, $\varphi_3 = -17.1°$ and $\varphi_4 = 102.3°$) which is closely related by rotation
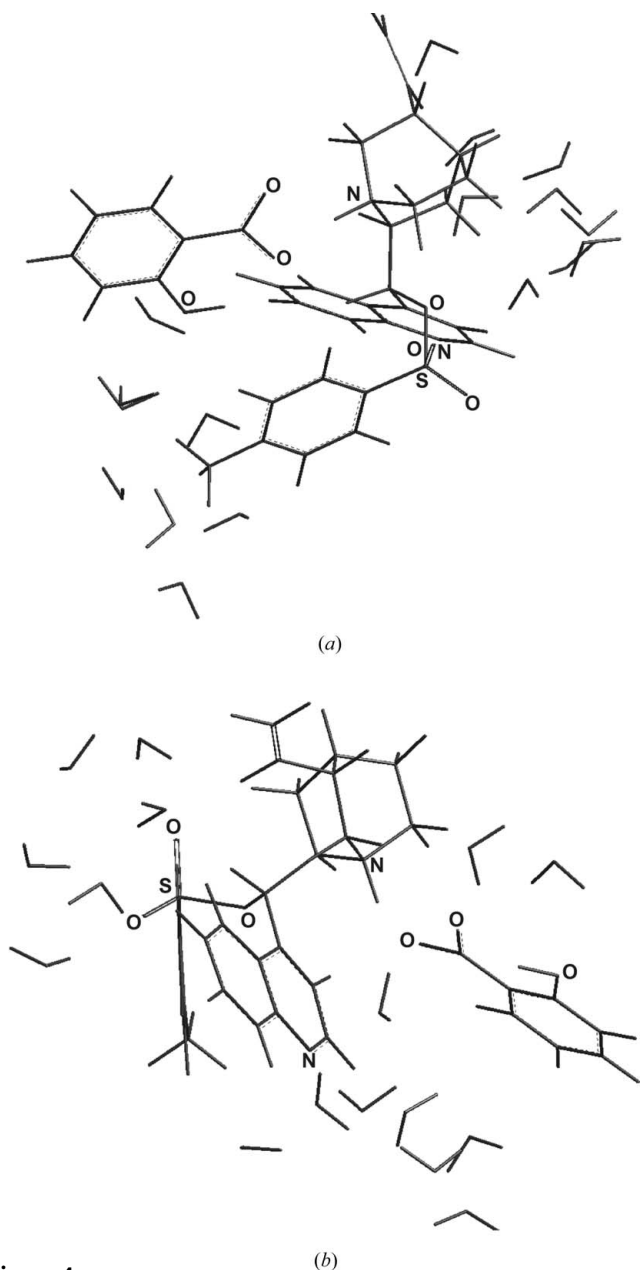
around the C9—C24 bond to the *syn*-open conformation preferred for 9-epicinchonidine formation in the hydrolysis reaction (Figs. 3 and 4*a*). The parallel calculation for the (II)-H$^+$–salicylate$^-$–H$_2$O system retains molecule (II) in an *anti*-closed conformation, unfavourable for the hydrolysis reaction ($\varphi_1 = -146.0°$, $\varphi_2 = -28.5°$, $\varphi_3 = 49.4°$ and $\varphi_4 = -65.4°$) as shown in Fig. 4(*b*). Additionally, the (I)-H$^+$–salicylate$^-$ system in the gaseous phase with (I) in an *anti*-open conformation is more energetically stable than the (II)-H$^+$–salicylate$^-$ system with (II) in an *anti*-closed conformation with a ΔE value of 8.062 kcal mol^{-1}. As can be seen in Fig. 4, the steric hindrance of the aryl ring of the tosylate group and the quinoline ring can restrain the free rotation on the C24—C9 bond, making the C9 atom more accessible to nucleophilic attack by the water molecule in an *anti*-open conformation of (I)-H$^+$ in comparison with an *anti*-closed conformation of (II)-H$^+$. The stabilizing influence of the tosylate group on the conformations of (I)-H$^+$ and (II)-H$^+$ can result in their different behaviour in the hydrolysis reaction and their higher hydrolytic stability in comparison to *O*-mesyl and *O*-acyl *Cinchona* alkaloid derivatives.

In conclusion, the X-ray analysis and theoretical calculations provided the geometric, conformational and energetic parameters of the diastereoisomeric molecules *O*-tosyl cinchonidine, (I), and *O*-tosyl cinchonine, (II), which were used to explain their different reactivity in the hydrolysis to the respective 9-epibases. It appears that the different energetic profit during protonation on the N1 atom and the different propensity to change from an *anti*-closed conformation in the crystal to a *syn*-open one favoured in the hydrolysis process can be correlated with the different reactivity of (I) and (II) towards 9-epibases in the S$_N$2 hydrolysis process.

Figure 4
The optimized conformations of (*a*) the (I)-H$^+$–salicylate$^-$ and (*b*) the (II)-H$^+$–salicylate$^-$ system in a water environment using the AM1 method.

Experimental

Compounds (I) and (II) were obtained according to the method described by Kowalik *et al.* (1999). The analytical data (IR, ^{1}H NMR and ^{13}C NMR) are in good agreement with those found by Brunner & Bügler (1997) for (I) and Kowalik *et al.* (1999) for (II). Crystals of both compounds suitable for X-ray diffraction analysis were grown by slow evaporation from diethyl ether–hexane (1:1 *v/v*) solutions.

Compound (I)

Crystal data

C$_{26}$H$_{28}$N$_2$O$_3$S	$V = 2326.9$ (7) Å^3
$M_r = 448.56$	$Z = 4$
Orthorhombic, $P2_12_12_1$	Cu $K\alpha$ radiation
$a = 9.4591$ (13) Å	$\mu = 1.48$ mm^{-1}
$b = 10.094$ (2) Å	$T = 293$ K
$c = 24.370$ (4) Å	$0.45 \times 0.40 \times 0.10$ mm

Data collection

Kuma KM-4 four-circle diffractometer	3508 independent reflections
	1717 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (Blessing, 1995)	$R_{int} = 0.034$
$T_{min} = 0.363$, $T_{max} = 0.748$	2 standard reflections every 100 reflections
3726 measured reflections	intensity decay: 0.0%

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.064$

$wR(F^2) = 0.167$

$S = 1.06$

3508 reflections

290 parameters

1 restraint

H-atom parameters constrained

$\Delta\rho_{max} = 0.30$ e Å^{-3}

$\Delta\rho_{min} = -0.33$ e Å^{-3}

Absolute structure: Flack (1983), 604 Friedel pairs

Flack parameter: 0.00 (3)

Compound (II)

Crystal data

$C_{26}H_{28}N_2O_3S$

$M_r = 448.56$

Orthorhombic, $P2_12_12_1$

$a = 6.8350$ (13) Å

$b = 17.7364$ (16) Å

$c = 18.6632$ (17) Å

$V = 2262.5$ (5) Å^3

$Z = 4$

Cu $K\alpha$ radiation

$\mu = 1.52$ mm^{-1}

$T = 293$ K

$0.40 \times 0.10 \times 0.10$ mm

Data collection

Kuma KM-4 four-circle diffractometer

Absorption correction: ψ scan (North et al., 1968)

$T_{min} = 0.571$, $T_{max} = 0.847$

2806 measured reflections

2723 independent reflections

1710 reflections with $I > 2\sigma(I)$

$R_{int} = 0.026$

2 standard reflections every 100 reflections

intensity decay: 0.0%

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.051$

$wR(F^2) = 0.177$

$S = 1.01$

2723 reflections

290 parameters

1 restraint

H-atom parameters constrained

$\Delta\rho_{max} = 0.45$ e Å^{-3}

$\Delta\rho_{min} = -0.21$ e Å^{-3}

The assumed absolute stereochemistry of compound (I) was confirmed by refinement of the Flack (1983) parameter. In the absence of Friedel pairs, the absolute configuration of compound (II) was assigned from the absolute configuration of cinchonine as starting reagent in the stereoconservative synthesis. For both compounds, all H atoms were fixed geometrically and treated as riding on their parent C atoms, with C—H distances of 0.93 (aromatic), 0.96 (CH$_3$), 0.97 (CH$_2$) and 0.98 Å (CH), and with U_{iso}(H) = 1.5U_{eq}(C). For both molecules, C10 and C11 of the terminal vinyl group showed large displacement parameters, which result in unrealistic C10—C11 bond lengths of 1.177 (8) and 1.206 (12) Å in (I) and (II), respectively. An electron-density map did not reveal the alternate sites for the C10 and C11 atoms. Therefore, a DFIX restraint (SHELXL97; Sheldrick, 2008) with a target value of 1.300 (5) Å for the C10═C11 vinyl bonds in (I) and (II) was used.

For both diastereoisomers, data collection: KM4B8 (Gałdecki et al., 1996); cell refinement: KM4B8; data reduction: DATAPROC (Gałdecki et al., 1995); program(s) used to solve structure: SIR92 (Altomare et al., 1993); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008); molecular graphics: ORTEP-3 for Windows (Farrugia, 1997); software used to prepare material for publication: SHELXL97 and WinGX (Farrugia, 1999).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: YF3003). Services for accessing these data are described at the back of the journal.

Table 1
Hydrogen-bond geometry (Å, °) for (I).

CgA, CgB and CgC are the centroids of the benzene, toluene and pyridine rings, respectively.

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C32—H321$\cdots$O2	0.93	2.60	2.944 (9)	103
C10—H101$\cdots$O3^i	0.93	2.48	3.377 (7)	163
C11—H111$\cdots$CgA^{ii}	0.93	2.98	3.775 (8)	144
C23—H231$\cdots$CgB^i	0.93	2.87	3.619 (5)	138
C37—H371$\cdots$CgC^{iii}	0.96	2.81	3.746 (7)	165

Symmetry codes: (i) $x - \frac{1}{2}, -y + \frac{1}{2}, -z + 1$; (ii) $-x, y + \frac{1}{2}, -z + \frac{3}{2}$; (iii) $x, y + 1, z$.

Table 2
Hydrogen-bond geometry (Å, °) for (II).

CgD and CgE are the centroids of the pyridine and quinoline rings, respectively.

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
C32—H321$\cdots$O2	0.93	2.58	2.936 (7)	103
C22—H221$\cdots$CgD^i	0.93	2.92	3.689 (7)	141
C11—H111$\cdots$CgE^{ii}	0.93	2.92	3.681 (7)	140

Symmetry codes: (i) $x + \frac{1}{2}, -y + \frac{1}{2}, -z + 1$; (ii) $-x + 1, y - \frac{1}{2}, -z + \frac{3}{2}$.

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