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Enantioselective catalysis. Part 133:[1] Conformational analysis of amides of 9-amino(9-deoxy)epicinchonine

Henri Brunner,* Peter Schmidt and Markus Prommesberger

Institut für Anorganische Chemie, Universität Regensburg, D-93040 Regensburg, Germany

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Abstract

Amides of 9-amino(9-deoxy)epicinchonine have been used as chiral base catalysts to induce asymmetry in enantioselective decarboxylation reactions. To understand the reaction mechanism and to optimize the bases by variation of the amide substituents, a detailed knowledge of their preferred conformation is necessary. The conformations were investigated by ^{1}H NMR spectroscopy, X-ray analysis and semi-empirical molecular orbital calculations. Principally, cinchona alkaloids may adopt four different conformations (Fig. 1), of which **open b** and **open b′** are preferred by 2-ethoxy-*N*-(9-deoxyepicinchonine-9-yl)-benzamide **2** in solution. AM1 Calculations confirm these results, and the small energy barrier between the two open conformations explains their simultaneous existence in solution. Crystal structure analyses of various amides show open conformations in the solid state. Local minimum energy conformations were found for open conformations of the compound **2** protonated at the quinuclidine system, which is the active species in the enantioselective decarboxylation reaction.

1. Introduction

Cinchona alkaloids are not only important drugs, they are also widely used as optically active bases to induce asymmetry in various chemical reactions and resolution processes. The asymmetric dihydroxylation[2,3] of olefins with derivatives of quinine or quinidine and the asymmetric hydrogenation of α-ketoesters[4] with Pt-catalysts modified with cinchona alkaloids are well-known reactions which give high enantiomeric excesses. Another example is the use of cinchona alkaloids as chiral bases in enantioselective decarboxylation reactions.[5–11] Recently, we reported the preparation of optically active Naproxen derivatives by this method using amides of 9-amino(9-deoxy)epicinchonine and 9-amino(9-deoxy)epiquinidine as catalysts which are considerably more successful than the corresponding natural products.[11–13] With 10 mol% of the 2-ethoxybenzamide **2** of 9-amino(9-deoxy)epicinchonine as a catalyst, up to 71.9% *ee* (*S*)-enantiomer

* Corresponding author. Fax: (+49) 941-943-4439; e-mail: henri.brunner@chemie.uni-regensburg.de

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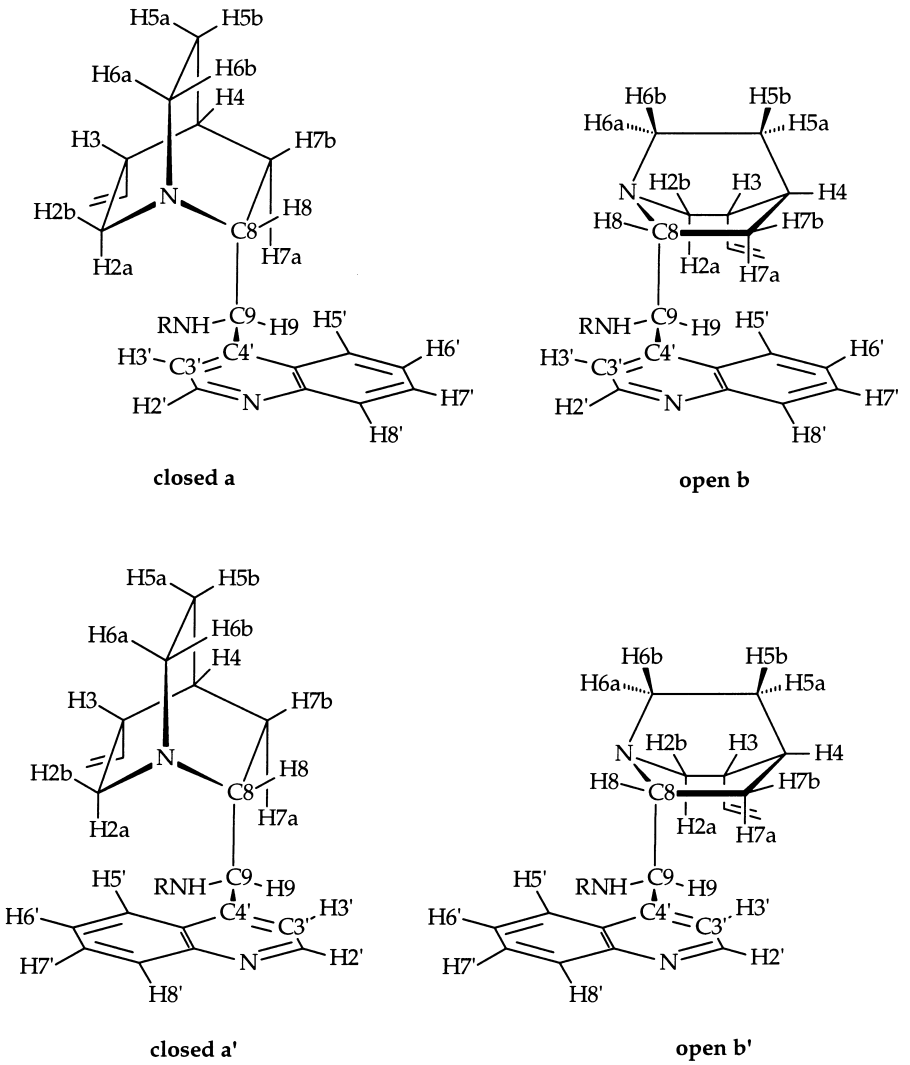
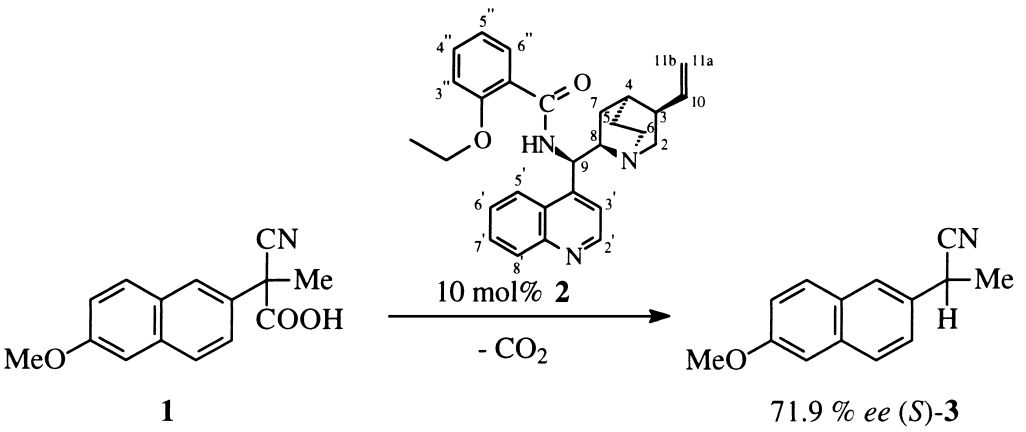


Figure 1. Schematic drawings illustrating the two closed and open conformations of 9-amino(9-deoxy)epicinchonine derivatives

of the Naproxen nitrile **3** was obtained (Scheme 1). The decarboxylation of the cyanopropionic acid **1** is induced by the alkaloid, which abstracts the carboxylic acid proton. After decarboxylation the protonated base reprotonates the carbanionic carbon atom leading to Naproxen nitrile **3**.

In a study of the mechanism of the reaction, the preferred conformation of the catalysts is of crucial importance. Conformational analyses of cinchona alkaloids and their derivatives in solution as well as in the solid state have been carried out before by Wynberg and others.[2,14,15] In this paper, the conformations of amides of 9-amino(9-deoxy)epicinchonine were determined by a combined approach consisting of ^{1}H NMR investigations, semi-empirical molecular orbital calculations and X-ray analyses.[13] We had introduced the parent 9-amino(9-deoxy)epicinchona alkaloids as the amino analogues of the natural cinchona alkaloids, from which they were prepared via a Mitsunobu reaction some time ago.[16,17]



Scheme 1. Enantioselective decarboxylation of **1** to Naproxen nitrile **3** with 2-ethoxy(9-deoxyepicinchonine-9-yl)-benzamide **2** as chiral base

2. Results and discussion

According to Wynberg, cinchona alkaloids may adopt four major conformations, two open and two closed forms, which differ in the relative orientation of the quinuclidine and quinoline moieties as a result of rotation around the C8–C9 and C9–C4′ bonds. The schematic drawings are shown in Fig. 1 for 9-amino(9-deoxy)epicinchonine derivatives.

In the closed conformations, the quinuclidine nitrogen is above the aromatic ring of the quinoline system, whereas in the open conformations the quinuclidine nitrogen points away from the quinoline unit. The two open as well as the two closed conformations differ in the orientation of the quinoline ring. In the conformations **a** and **b′** the aromatic system is turned away from the quinuclidine unit, whilst in the conformations **a′** and **b** the quinoline ring is oriented towards the quinuclidine moiety.

The hydrogens of **2** are assigned on the basis of NMR correlation spectroscopy (COSY) and nuclear Overhauser enhancement spectroscopy (NOESY) experiments. The latter was used for the conformational analysis (Fig. 2). The spectra were recorded in THF-d_8, as the non-deuterated solvent had been used in the enantioselective decarboxylation reactions.[11,13]

The hydrogens at C7 were observed as two separate multiplets, of which only one yields an NOE with H8. Therefore, this signal can be assigned to H7b. The presence of NOEs between H9 and H2a as well as H7a and H5′ indicate open conformations. The signals of the H2 and H6 protons appear together as a multiplet. An NOE between the hydrogens H6 and H9 can be excluded because of the large distance between these atoms. No NOE is observed between H9 and H8, H5′ and H2a as well as H3′ and H2a, which would be characteristic of closed conformations. In the NOESY spectrum of **2**, both H3′ and H5′ show NOE interactions with H9 and with H7a, indicating that the two open conformations **b** and **b′** are simultaneously present in THF-d_8 solution.

The geometry of **2** was investigated by semi-empirical methods with the program MacSpartan Plus[18] using the AM1 Hamiltonian.[19] As a result, four local minimum energy conformations have been found. Selected data of the calculated conformers **2α**–**δ** are presented in Table 1 and Fig. 3, showing the lowest energy structure **2α**. Similar to the experimentally determined conformation in solution, all calculated structures **2α**–**δ** show open conformations, indicated by the torsion angles **T1** and **T2**. According to **T3**, the geometries **2α**–**γ** are close to the open conformation **b**,

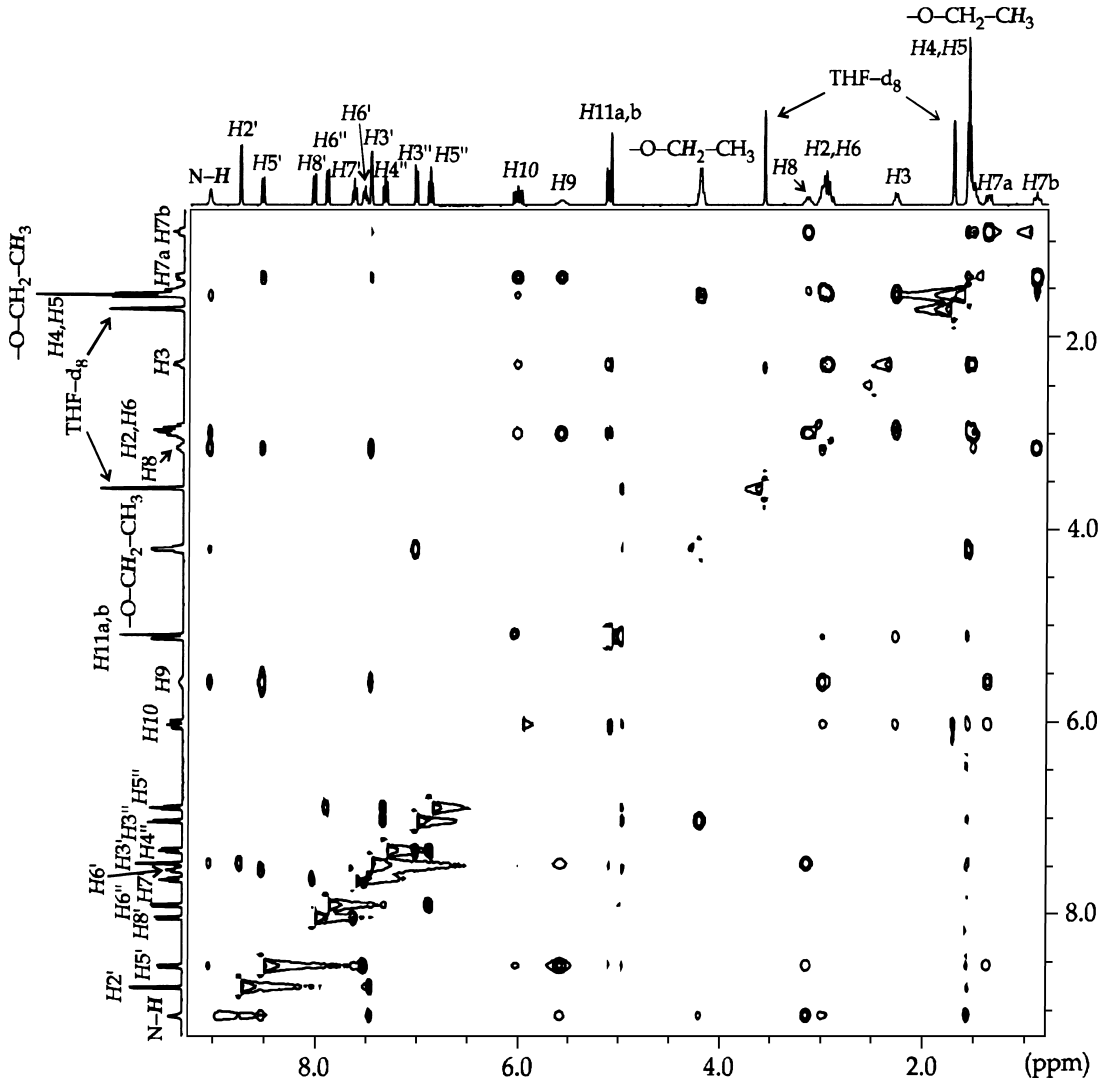


Figure 2. NOESY spectrum of 2-ethoxy-*N*-(9-deoxyepicinchonine-9-yl)benzamide **2** (400 MHz, THF-d_8, TMS). For numbering see Fig. 1 and Scheme 1

whereas **2δ** has the open conformation **b′**. The low energy difference of less than 1 kcal mol^{-1} between conformations **2α**–**δ** explains the coexistence of the two conformers **b** and **b′** in solution. In all conformers **2α**–**γ** the hydrogen atoms H9 and H12 are *anti*-orientated (**T4**) and a *Z*-conformation of the amide function is observed (**T5**, **T6**). The 2-ethoxyphenyl moiety is twisted out of the amide plain (**T7**).

Compound **2** was protonated at the quinuclidine nitrogen by equimolar addition of hydrochloric acid to investigate the conformation of the protonated species **4** in solution by ^{1}H NMR experiments. However, NOESY and ROESY spectra in THF-d_8 lacked significant information to distinguish between the various conformations. Therefore, AM1 calculations were carried out for the cation **4**. Three local minimum energy conformations **4α**–**γ** were found (Table 2), of which **4α** is represented in Fig. 4.

Table 1
Energies **E** and selected torsion angles **T** and angles **A** of four calculated local minimum energy conformations of 2-ethoxy-*N*-(9-deoxyepicinchonine-9-yl)benzamide **2**

		α	β	γ	δ
E [kcal· mol^{-1}]		27.7	27.9	28.0	28.7
T1 [°]	C4'-C9-C8-N1	-168.5	-171.5	-167.7	-168.0
T2 [°]	H8-C8-C9-H9	-170.2	-172.1	-169.6	-166.1
T3 [°]	C3'-C4'-C9-C8	66.5	44.6	68.5	-112.9
T4 [°]	H9-C9-N2-H12	179.0	-172.7	-176.2	176.6
T5 [°]	H12-N2-C12-O1	178.6	178.1	175.0	-179.3
T6 [°]	C9-N2-C12-C1''	-174.3	-174.4	-176.3	-176.3
T7 [°]	N2-C12-C1''-C2''	-38.0	-35.9	-30.2	-38.4
T8 [°]	C8-C9-N2-C12	112.0	118.1	114.3	113.0
A1 [°]	C4'-C9-C8	107.5	110.0	107.6	108.8
A2 [°]	C9-C8-N1	113.3	112.9	113.2	113.4
A3 [°]	C8-C9-N2	113.4	113.1	113.3	114.7

Table 2
Energies **E** and selected torsion angles **T**, angles **A** and bond lengths **D** of three calculated local minimum energy conformations of the protonated 2-ethoxy-*N*-(9-deoxyepicinchonine-9-yl)benzamide **4**

		α	β	γ
E [kcal· mol^{-1}]		161.5	161.5	162.0
T1 [°]	C4'-C9-C8-N1	175.2	175.6	173.0
T2 [°]	H8-C8-C9-H9	173.6	173.7	174.0
T3 [°]	C3'-C4'-C9-C8	69.2	69.8	-111.9
T4 [°]	H9-C9-N2-H12	124.3	133.6	124.7
T5 [°]	H12-N2-C12-O1	-173.1	-179.8	-173.4
T6 [°]	C9-N2-C12-C1''	162.7	169.3	163.0
T7 [°]	N2-C12-C1''-C2''	-36.4	29.1	-36.6
T8 [°]	C8-C9-N2-C12	92.4	89.0	91.6
A1 [°]	C4'-C9-C8	106.9	107.0	108.3
A2 [°]	C9-C8-N1	113.2	113.2	113.1
A3 [°]	C8-C9-N2	112.3	112.7	113.2
A4 [°]	N1-H1-O1	120.9	120.7	120.9
A5 [°]	N2-H12-O2	120.1	115.4	119.4
D1 [Å]	H1-O1	2.14	2.14	2.14
D2 [Å]	H12-O2	2.17	2.19	2.18

Similar to the calculated conformers of **2** all the geometries **4α**–**γ** show open conformations (**T1**, **T2**). **4α** and β adopt the open conformation **b**, whilst **4γ** has the open conformation **b′** (**T3**). Again, the amide function comes close to a *Z*-conformation (**T5**, **T6**) and the 2-ethoxyphenyl moiety is twisted out of the amide plane (**T7**). Remarkably, the hydrogen atoms H9 and H12 of the protonated species **4** include a torsion angle of about 130°, whereas the hydrogen atoms H9 and H12 are almost *trans* oriented in the conformers **2α**–δ (**T4**). The distances between H1 and O1 as well as H12 and O2 are somewhat over 2 Å, indicating hydrogen bonding between these atoms (**D1**, **D2**). Bond angles around 120° (**A4**, **A5**) were previously observed in X-ray structures with intramolecular N···H···O hydrogen bonds.[20] An interaction between H12 and O2 may reduce the flexibility of the 2-ethoxyphenyl moiety around the C12–C1″ bond. Hence, the increased conformational stability could be responsible for the good results obtained with base **2** in the enantioselective decarboxylation reaction.[11,13]

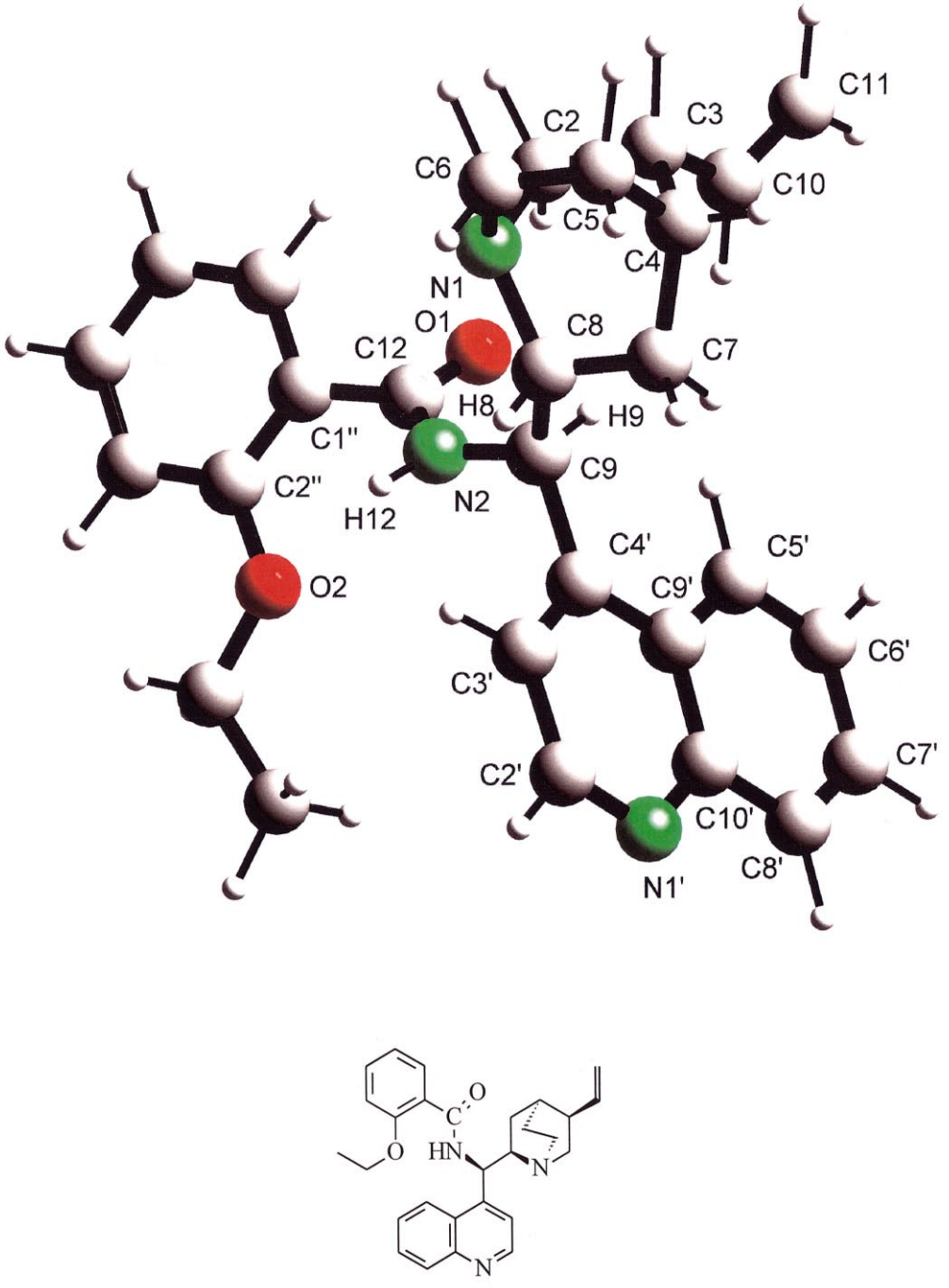
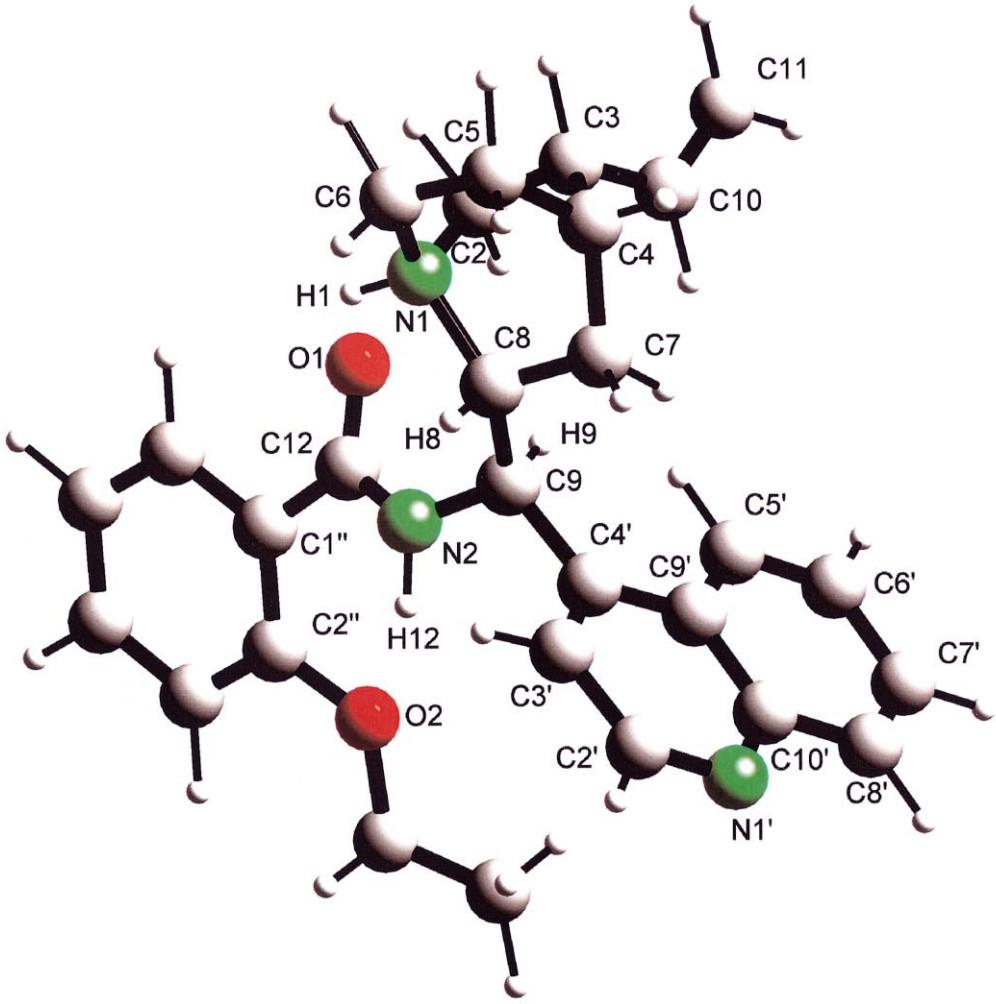


Figure 3. Structure of the calculated minimum energy conformer **2α**



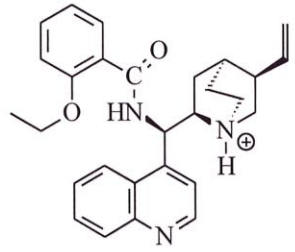


Figure 4. Structure of the calculated minimum energy conformer **4α**

X-Ray structure analyses were obtained from the phthalimide **5**, the 3-nitrobenzamide **6** and the ferrocenylcarboxylic acid amide **7** (Figs. 5–7) of 9-amino(9-deoxy)epicinchonine.[11,13,21] Selected torsion angles, angles and distances are presented in Table 3. The X-ray analyses revealed that the amides **5**–**7** in the solid state exist in open conformations. These results are in

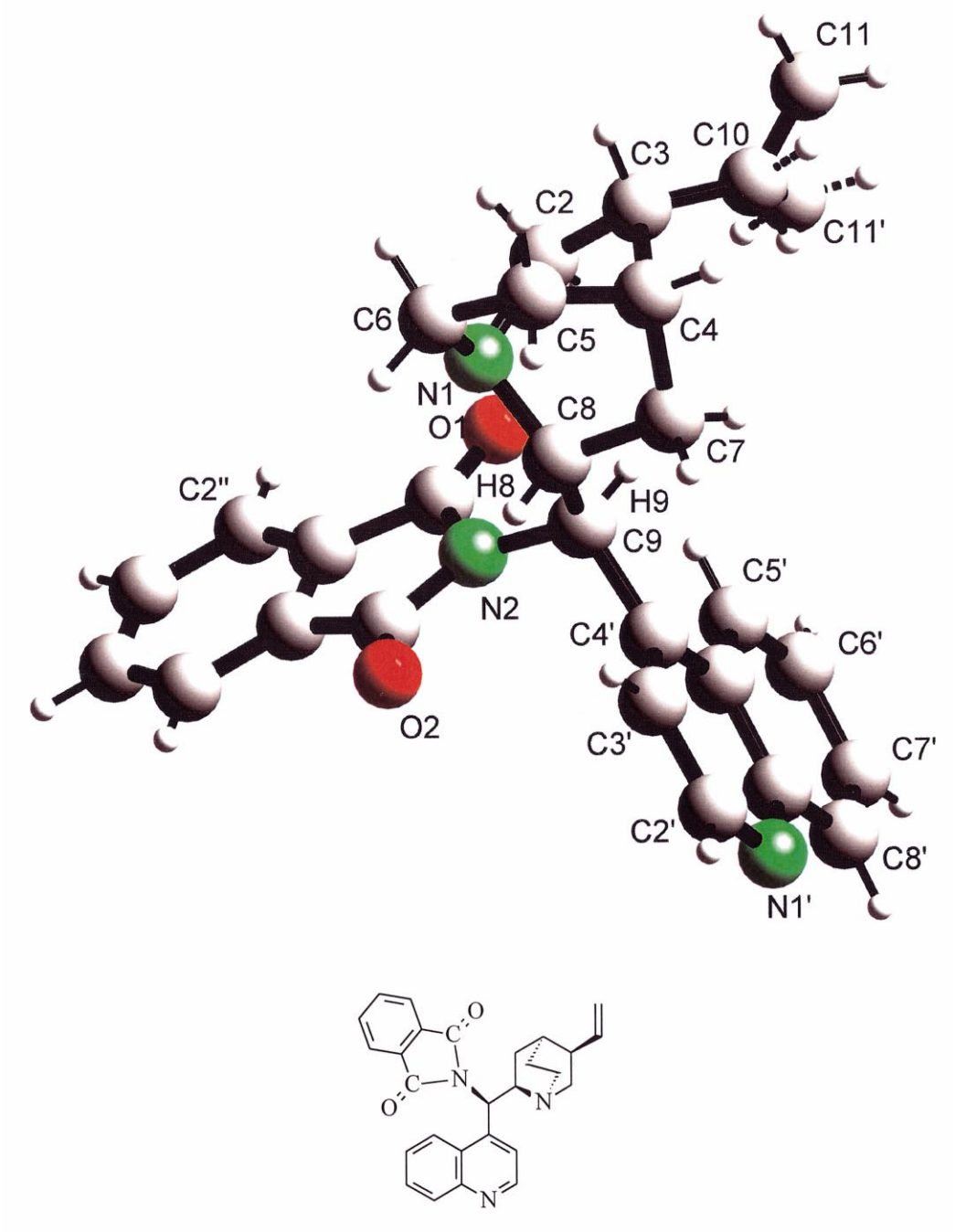


Figure 5. Crystal structure of *N*-(9-deoxyepicinchonine-9-yl)phthalimide **5**

accordance with the spectroscopically determined and calculated conformations of **2**. In **5** the vinyl group is disordered and the calculated value for C10–C11 is 44.1% and for C10–C11′ is 55.9%. According to the X-ray structure of **6**, the crystals contain 1 mol equiv. of water. In the unit cell of **7** four independent molecules are present. The four individuals of **7** are close to open conformation **b**′, whereas the 3-nitrobenzamide **6** resembles open conformation **b** (**T3**). Except for one individual of **7**, the hydrogen atoms H9 and H12 are not *trans* oriented in the X-ray structures **6** and **7** (**T4**).

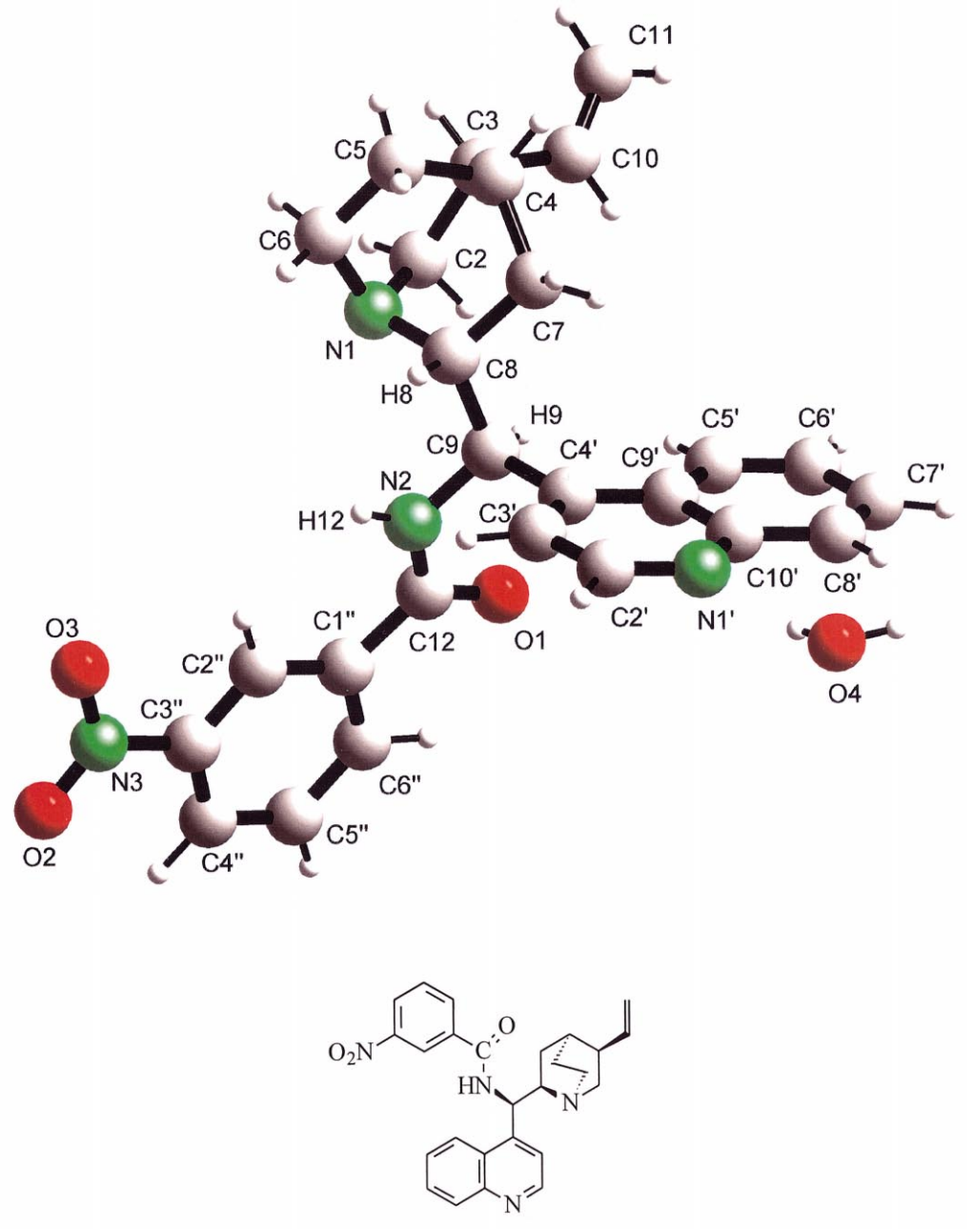


Figure 6. Crystal structure of 3-nitro-*N*-(9-deoxyepicinchonine-9-yl)benzamide **6**

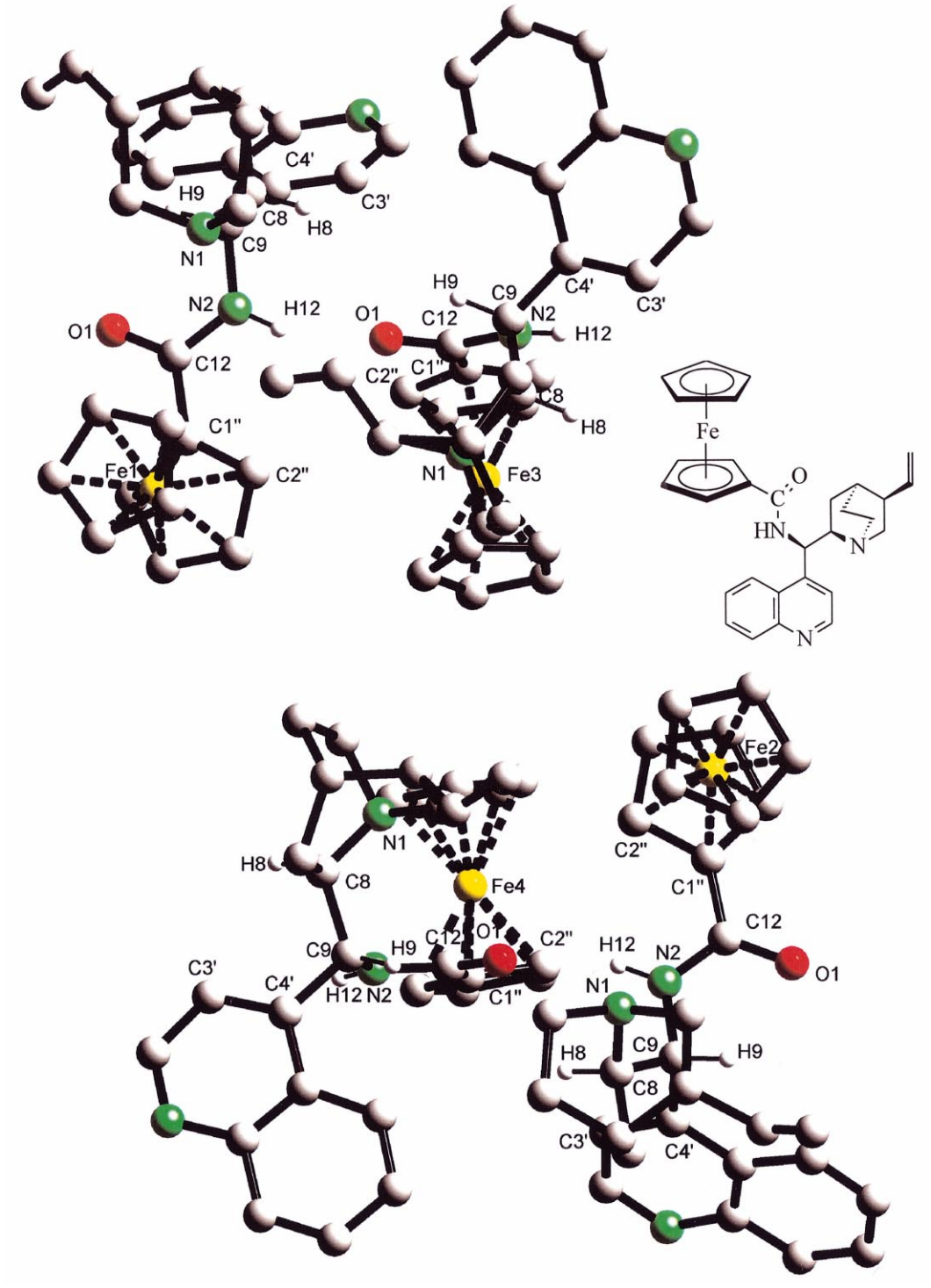


Figure 7. Crystal structure of ferrocenylcarboxylic acid-*N*-(9-deoxyepicinchonine-9-yl)amide **7**

Table 3
Selected torsion angles **T**, angles **A** and bond lengths **D** of the amides **5**, **6** and **7** of the corresponding X-ray structures

		5	6	7			
				Fe 1	Fe 2	Fe 3	Fe 4
T1 [°]	C4'-C9-C8-N1	-175.0 (2)	-177.1 (2)	-180.0 (3)	-177.2 (3)	-179.7 (3)	-175.4 (3)
T2 [°]	H8-C8-C9-H9	-177.1 (2)	175.5 (2)	178.5 (3)	-178.8 (3)	179.9 (3)	-175.2 (3)
T3 [°]	C3'-C4'-C9-C8	-156.0 (2)	-68.5 (2)	43.1 (4)	59.6 (4)	38.2 (5)	35.2 (5)
T4 [°]	H9-C9-N2-H12	--	-141.2 (2)	-178.3 (3)	-157.9 (4)	155.3 (4)	158.5 (3)
T5 [°]	H12-N2-C12-O1	--	176.4 (2)	-167.3 (4)	-173.8 (4)	-173.0 (4)	-173.5 (4)
T6 [°]	C9-N2-C12-C1''	-176.9 (1)	176.3 (2)	-168.2 (3)	-172.0 (4)	-173.3 (3)	-175.7 (3)
T7 [°]	N2-C12-C1''-C2''	-179.5 (1)	1.6 (2)	7.5 (6)	7.5 (6)	172.0 (4)	172.6 (3)
T8 [°]	C8-C9-N2-C12	110.5 (2)	154.8 (2)	119.3 (4)	140.0 (4)	94.2 (4)	97.1 (3)
T9 [°]	N1-C2-C3-C4	11.3 (2)	15.6 (2)	6.0 (6)	10.7 (6)	11.9 (5)	15.1(4)
T10 [°]	N1-C6-C5-C4	12.2 (3)	13.5 (3)	5.2 (6)	8.7 (6)	14.0 (5)	14.3 (6)
T11 [°]	N1-C8-C7-C4	16.2 (2)	17.2 (3)	10.3 (5)	13.9 (5)	14.2 (4)	16.7 (4)
A1 [°]	C4'-C9-C8	115.3 (2)	109.3 (2)	112.0 (3)	112.8 (3)	111.7 (3)	111.1 (3)
A2 [°]	C9-C8-N1	109.8 (2)	112.5 (2)	111.4 (3)	110.8 (3)	111.8 (3)	112.6 (3)
A3 [°]	C8-C9-N2	111.3 (2)	112.0 (2)	110.0 (3)	110.3 (3)	112.5 (3)	113.2 (3)
D1 [Å]	C4-C9	1.525 (2)	1.537 (2)	1.523 (5)	1.532 (5)	1.514 (5)	1.521 (5)
D2 [Å]	C9-C8	1.536 (2)	1.523 (3)	1.526 (5)	1.529 (5)	1.541 (5)	1.546 (4)
D3 [Å]	C9-N2	1.467 (2)	1.458 (2)	1.467 (4)	1.455 (4)	1.450 (5)	1.459 (5)
D4 [Å]	C12-N2	1.391 (2)	1.336 (2)	1.339 (5)	1.336 (5)	1.350 (5)	1.353 (5)

As in the calculated geometries, a *Z*-conformation of the amide moiety is observed (**T5**, **T6**). The arenes on C12 are roughly located in the N2–C12–C1″-plane (**T7**), whereas they are twisted out to a greater extent in the calculated structures. The respective torsion angles of the four individuals of **7** are virtually identical, except **T4** and, hence, **T8**, which corresponds to a different orientation of the ferrocenylamide substituent on C9. Due to the relatively rigid quinuclidine moiety, an all eclipsed position of the methylene hydrogen atoms is rather unlikely.[2] All the crystal structures show positive torsion angles **T9**, **T10** and **T11**, indicating a twist of the quinuclidine system. Viewing from N1 to C4 shows a right-handed helix, which leads to a somewhat staggered orientation of the methylene hydrogens.

3. Conclusion

The conformational analysis of amides of 9-amino(9-deoxy)epicinchonine revealed that they prefer an open conformation in solution as well as in the solid state. These results are in accordance with local minimum energy conformations found by AM1 calculations. The same method showed an open conformation for the protonated amide **4**, which was observed by protonation or complexation of most quinine and quinidine derivatives, independent of their prior conformation.[2,14] Intramolecular hydrogen bonding between H1 and O1 as well as H12 and O2 in **4** may be responsible for the high enantiomeric excess obtained in the enantioselective decarboxylation reactions with base **2**.[11,13]

Acknowledgements

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21. Structural data for **5**, **6** and **7** have been deposited at the Cambridge Crystallographic Data Centre (CCDC). The atomic coordinates, anisotropic thermal parameters, tables of bond lengths and angles are available on request from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK, citing the deposition nos. 138933 (**5**), 138934 (**6**) and 138935 (**7**) accompanied by the full literature citation for this paper.