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Ring current effects of phenyl and naphthyl groups: internal probes for determining the absolute configuration of chiral azetidin-2-ones by ^{1}H NMR

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Abstract

The ring current effects of the phenyl and 1-naphthyl rings are used to determine the absolute configuration of ten chiral azetidinones prepared from the [2+2] cycloaddition of (S)-1-(1-naphthyl)ethyl and (S)-1-phenylethyl isocyanate to vinyl ethers under high pressure. The (S)-1-arylethyl group of the studied azetidinones adopts a preferred conformation that can be distinguished by ^{1}H NMR spectroscopy. The application of this principle to other azetidinones containing the arylethyl substituent is consistent with the configurations determined by chemical correlation and X-ray diffraction and verifies the reliability of the proposed method.

1. Introduction

Chiral azetidinones are important intermediates in the synthesis of a variety of biologically active compounds. They can be used as starting materials for the preparation of β-lactam antibiotics[1] and precursors of the phenylisoserine chain of docetaxel analogs.[2] In addition, chiral azetidinones can be transformed into acyclic α- and β-amino acid derivatives, and other important building blocks for the synthesis of natural products.[3] Besides the development of efficient stereoselective syntheses of azetidinones, the discovery of simple and reliable methods to determine the absolute configuration in the liquid state is essential. In most cases, the configuration of chiral azetidinones has been assigned by X-ray analysis,[4] chemical correlation,[2,5] or by comparison with the physical and spectroscopic data of compounds of known configuration.[6]

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In our previous paper[7] we reported that the high pressure [2+2] cycloaddition of (S)-1-phenylethyl isocyanate **1a** to 2,3-dihydrofuran **2a**, produces (1S,5R)-7-[(1S)-1-phenylethyl]- and (1R,5S)-7-[(1S)-1-phenylethyl]-2-oxa-7-azabicyclo[3.2.0]heptan-6-one, **3a** and **3′a**, respectively. The bicyclic azetidinone **3a** was isolated as an oil and **3′a** as a solid, which did not form crystals suitable for X-ray diffraction; however, the corresponding absolute configurations were unambiguously determined in solution by ^{1}H NMR spectroscopy using tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)-*d*-camphorato]europium(III), Eu(tfc)$_3$, and Pirkle's alcohols. In the configurational study of **3a**, **3′a** and their pure enantiomers in solution,[7] we found that the preferred conformation of the O=C–N–CH(Me)Ph segment resembles the generally accepted conformation of the open chain amides of α-branched primary amines.[8] Since this finding may enable the determination of the absolute configuration of analogous azetidinones through the proper interpretation of the ring current effect of the aromatic ring, we have undertaken the ^{1}H NMR study of the chiral derivatives of 7-[(1S)-1-(1-naphthyl)ethyl]-2-oxa-7-azabicyclo[3.2.0]heptan-6-one **3b** and **3′b**, 8-[(1S)-1-phenylethyl]-2-oxa-8-azabicyclo[4.2.0]octan-7-one **3c** and **3′c**, and 4-alkoxy-1-[(1S)-1-phenylethyl]azetidin-2-one **3d–f** and **3′d–f** in order to determine whether the preferred conformation of the O=C–N–CH(Me)Ph segment is not an exclusive feature of **3a**, **3′a** and their pure enantiomers.[7] The present paper demonstrates how the absolute configuration of these novel chiral azetidinones can be determined in solution using the ring current effect of the intermolecular (S)-1-phenylethyl and (S)-1-(1-naphthyl)ethyl groups as probes in ^{1}H NMR spectroscopy.

2. Results

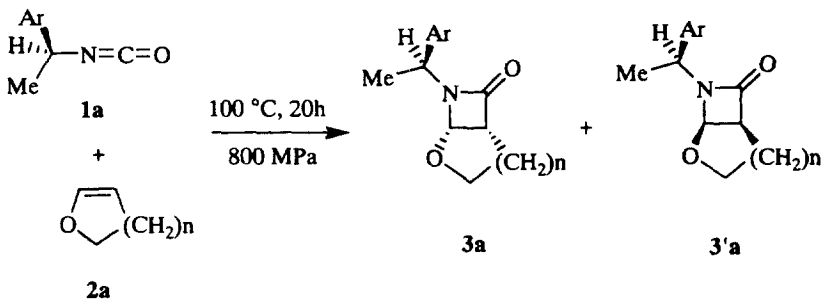
The synthesis of azetidinones **3b–f** and **3′b–f** is shown in Scheme 1. The relevant physical properties of these cycloadducts and the conditions of the ^{1}H NMR measurements are given in the Experimental section.

The aliphatic protons of most of the studied azetidinones gave a first order subspectrum, hence the corresponding signals were assigned through the analysis of the coupling constants and according to the dihedral angles of the 3D molecular structures obtained by MM2 single-point energy calculations.[9] The aromatic protons of the naphthyl ring of bicyclic azetidinones **3b** and **3′b** also gave a first order spin system, but the phenyl group of azetidinones **3c–f** and **3′c–f** gave a complex AA′BB′C pattern which was analyzed by computer simulation. The eight protons of the tetrahydropyran ring of **3c** and **3′c** gave complex spin patterns and they were partially assigned. The pertinent data are presented in Tables 1 and 2. The assignments of **3c** and **3′f** were corroborated by recording the ^{1}H NMR spectra in the presence of known amounts of the chiral shift reagent Eu(tfc)$_3$.

2.1. *Interpretation of the spectra*

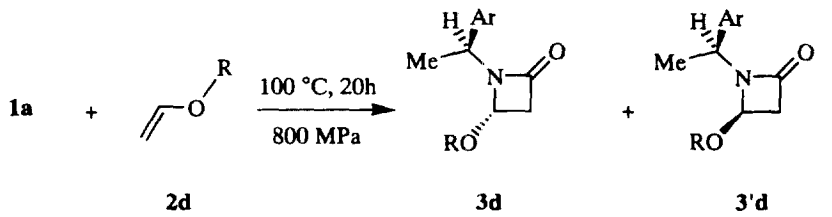
In order to facilitate the comparison of the ^{1}H NMR data, we have adopted the particular numbering system and descriptors of the relative orientation of protons shown by the structures of **3b**, **3c** and **3d**.

a)



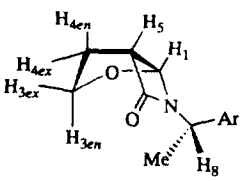
Isocyanate	Vinyl ether	Products (yield %)		Ratio 3/3'
1a	**2a**	**3a, 3'a** (80)	n = 1, Ar = Phenyl	53/47
1b	**2a**	**3b, 3'b** (94)	n = 1, Ar = 1-Naphthyl	52/48
1a	**2b**	**3c, 3'c** (46)	n = 2, Ar = Phenyl	52/48

b)



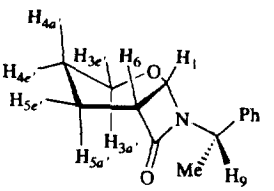
Vinyl ether	Products (yield %)		Ratio 3/3'
2d	**3d, 3'd** (86)	R = Ethyl	49/51
2e	**3e, 3e'** (68)	R = Isobutyl	47/53
2f	**3f, 3'f** (45)	R = n-Butyl	45/55

Scheme 1. Synthesis of azetidinones **3a–f** and **3'a–f** from the [2+2] cycloaddition of (a) (S)-1-phenylethyl and (S)-1-(1-naphthyl)ethyl isocyanate, **1a** and **1b**, respectively, to 2,3-dihydrofuran **2a** and to 3,4-dihydro-2H-pyran **2b** and (b) (S)-1-phenylethyl isocyanate **1a** to ethyl, isobutyl and n-butyl vinyl ether, **2d**, **3e**, **3f**, respectively, at 800 MPa



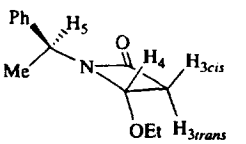
en = endo, ex = exo

3b



a' = pseudo-axial,
e' = pseudo-equatorial

3c



3d

The three aliphatic protons of the four-membered ring of the monocyclic azetidinones **3d–f** and **3'd–f**, give an ABX spin system, where X corresponds to the H_4 nucleus. In all the spectra of these azetidinones, the H_4 resonance has a J_{AX}=1.3 Hz and J_{BX}=3.8 Hz. From our previous studies[7] it is known that a $^3J \approx 3.0$ Hz of the protons attached to C_3 and C_4 of the azetidin-2-one ring, is characteristic of the *cis* arrangement and therefore in the present study, the nucleus A is assigned to H_{3trans} and the nucleus B to H_{3cis}. This

Table 1
Chemical shifts (δ) and coupling constants (J) in the ^{1}H NMR spectra (400 MHz) of bicyclic azetidinones **3b**, **3'b**, **3c** and **3'c** (0.05 M) in chloroform-*d* at 25°C

Compound	**3b**[a]	**3'b**[b]	**3c**[c]	**3'c**[d]
δ				
H_{4exo} or $H_{4a'}$ (J)[e]	1.688dddd	1.675dddd	2.031m	1.990m
	(8.4, 8.6, 12.1, 13.2)	(8.4, 8.4, 11.9 13.1)	(not determined)	(not determined)
H_{4endo} or $H_{4e'}$ (J)	2.209dddd	2.117dddd	1.869m	1.853m
	(0.5, 0.6, 5.6, 13.2)	(0.5, 0.6, 5.4, 12.9)	(not determined)	(not determined)
H_5 or H_6 (J)	3.451dd	3.607dd	3.075ddd	3.142ddd
	(3.0, 8.7)	(3.0, 8.7)	(4.1, 4.1, 8.4)	(4.1, 4.1, 8.3)
H_{3endo} or $H_{3a'}$ (J)	4.026ddd	3.471ddd	3.798ddd	3.560ddd
	(5.4, 9.3, 11.9)	(5.5, 9.4, 11.9)	(5.1, 7.1, 11.2)	(6.4, 6.4, 11.2)
H_{3exo} or $H_{3e'}$ (J)	4.187ddd	3.910ddd	3.701ddd	3.406ddd
	(0.6, 8.4, 9.3)	(0.6, 8.4, 9.4)	(5.9, 5.9, 11.2)	(5.4, 6.9, 11.2)
H_1 (J)	4.983d	5.496d	5.019d	5.191d
	(3.2)	(3.2)	(4.6)	(4.5)
H_8 or H_9 (J)	5.741q	5.528q	4.907q	4.748q
	(7.0)	(7.4)	(7.2)	(7.2)
Me (J)	1.791d	1.832d	1.656d	1.693
	(7.0)	(7.0)	(7.2)	(7.2)

[a] Naphthyl: δH_2 = 7.644d (^3J = 7.2), δH_3 = 7.499t (^3J 7.0), δH_4 = 7.840d (^3J = 8.2), δH_5 = 7.889dm (^4J =1.3, ^3J = 8.0), δH^*_6 = 7.518ddd (^4J = 1.3, ^3J = 6.8, ^3J = 8.1), δH^*_7 = 7.572ddd (^4J = 1.5, ^3J = 6.8, ^3J = 8.4), δH_8 8.099d (^3J = 8.6). [b] Naphthyl: δH_2 = 7.601d (^3J =6.8), δH_3 = 7.477t (^3J = 7.8), δH_4 = 7.801d (^3J = 8.3), δH_5 = 7.877dm (^4J = 1.2, ^3J = 7.8), δH^*_6 = 7.502ddd (^4J = 1.2, ^3J = 7.1, ^3J = 7.8), δH^*_7 = 7.562ddd (^4J = 1.5, ^3J = 6.9, ^3J = 8.4), δH_8 = 8.187d (^3J = 8.3). [c] Phenyl: δ_A = 7.377m ($^4J_{AA'}$ = 2.0, $^3J_{AB}$ = $^3J_{A'B'}$ = 8.2, $^5J_{AB'}$ = $^5J_{A'B}$ = 0.5, $^4J_{AC}$ = $^4J_{A'C}$ = 1.7), δ_B = 7.358m ($^4J_{BB'}$ = 1.7, $^3J_{BC}$ = $^3J_{B'C}$ = 7.2), δ_C = 7.292m. [d] Phenyl: δ_A = 7.396m ($^4J_{AA'}$ = 2.0, $^3J_{AB}$ = $^3J_{A'B'}$ = 8.2, $^5J_{AB'}$ = $^5J_{A'B}$ = 0.5, $^4J_{AC}$ = $^4J_{A'C}$ = 1.7), δ_B = 7.346m ($^4J_{BB'}$ = 1.7, $^3J_{BC}$ = $^3J_{B'C}$ = 7.2), δ_C = 7.272m. [e] Coupling constants in Hz.

interpretation is consistent with the reported data for 4-D-glucofuranosyl azetidinones.[10] In the spectra of azetidinones **3d–f**, the H_{3trans} resonance appears as a clear doublet of doublets, but as a broad doublet in the spectra of **3'd–f**.

The resonances of the O-alkyl groups were assigned by inspection of the multiplicity. The resonance of the O-CH_2 methylene appears as a quartet in the spectra of **3d** and as a triplet in **3f**. In the spectra of the other monocyclic azetidinones, the methylene resonance of the O-CH_2 segment appears as a multiplet that can be described as the AB part of an ABM, ABM_2 or an ABM_3 spin system.

The aromatic protons of the 1-phenylethyl group can be described as an AA'BB'C system since the benzylic coupling is less than 1 Hz. In **3d–f**, the H_{meta}, H_{ortho} and H_{para} resonances are centered at 7.361, 7.349 and 7.297 ppm, respectively; and in **3'd–f**, the H_{ortho}, H_{meta} and H_{para} resonances are centered at

Table 2
Chemical shifts (δ) and coupling constants (J) in the ^{1}H NMR spectra (400 MHz) of the monocyclic azetidinones (0.05 M) in chloroform-*d* at 25°C

Compound	**3d**	**3'd**	**3e**	**3'e**	**3f**[a]	**3'f**[b]
δ						
H_{3trans} (J)[c]	2.802dd	2.815dd	2.775dd	2.805dd	2.785dd	2.810dd
	(1.4,-14.7)	(1.0,-14.4)	(1.2,-14.6)	(0.7,-14.8)	(1.4,-14.7)	(0.9,-14.7)
H_{3cis} (J)	2.906dd	2.973dd	2.894dd	2.963dd	2.890dd	2.965dd
	(3.8,-14.8)	(3.9,-14.8)	(3.8,-14.6)	(3.8,-14.7)	(3.7,-14.6)	(3.8,-14.8)
H_4 (J)	4.774dd	4.919dd	4.746dd	4.907dd	4.756dd	4.907dd
	(1.5, 3.8)	(1.4, 3.8)	(1.3, 3.7)	(1.3, 3.8)	(1.3, 3.8)	(1.4, 3.8)
H_5 (J)	4.925q	4.694q	4.922q	4.697q	4.921q	4.690q
	(7.2)	(7.1)	(7.2)	(7.2)	(7.2)	(7.2)
Me (J)	1.639d	1.703d	1.639d	1.693d	1.636d	1.698d
	(7.2)	(7.2)	(7.2)	(7.1)	(7.2)	(7.2)
R (J)	A_3X_4	ABX_3	ABX	ABX	$A_2M_2N_2X_3$	$ABM_2N_2X_3$
	A 3.408 (7.1),	A 3.403	A 3.114	A 3.097	A 3.329	A 3.326
	X 1.152	(7.0, -9.2)	(6.6, -8.9)	(6.7, -8.8)	(6.5)	(6.5, -8.8)
		B 3.357	B 3.071	B 3.071	M 1.491	B 3.293
		X 1.102	X 1.776	X 1.734	N 1.340	M 1.442
			Me 0.889	Me 0.852	X 0.899	N 1.282
			Me 0.868	Me 0.835		X 0.875

[a] Representative data for aromatic protons: [b] $\delta_A = 7.349$ ($^4J_{AA'} = 2.0$, $^3J_{AB} = {}^3J_{A'B'} = 8.2$, $^5J_{AB'} = {}^5J_{A'B} = 0.5$, $^4J_{AC} = {}^4J_{A'C} = 1.7$), $\delta_B = 7.361$ ($^4J_{BB'} = 1.7$, $^3J_{BC} = {}^3J_{B'C} = 7.2$), $\delta_C = 7.297$. [b] $\delta_A = 7.368$ ($^4J_{AA'} = 2.0$, $^3J_{AB} = {}^3J_{A'B'} = 8.1$, $^5J_{AB'} = {}^5J_{A'B} = 0.5$, $^4J_{AC} = {}^4J_{A'C} = 1.7$), $\delta_B = 7.341$ ($^4J_{BB'} = 1.7$, $^3J_{BC} = {}^3J_{B'C} = 7.2$), $\delta_C = 7.269$. [c] Coupling constants in Hz.

7.368, 7.341 and 7.269 ppm, respectively. The methyl group and the methine proton H_5 form an apparent isolated AX_3 spin system.

The six protons of the tetrahydrofuran ring of **3b** and **3'b** were assigned by comparison with their analogs **3a** and **3'a**.[7] In a similar way, the seven protons of the 1-naphthyl group were assigned by comparison with the spectrum of (S)-1-(1-naphthyl)ethylamine.[11]

The eight protons of the tetrahydropyran ring of **3c** and **3'c** give a complex spin pattern. In the spectrum of **3c**, the H_1 resonance appears as a doublet at 5.019 ppm (J_{H1H6}=4.6 Hz) and H_6 as an apparent quintet at 3.075 ppm ($J_{H6H5a'}$=8.4 Hz, $J_{H6H5e'}$=4.1 Hz). The $H_{3a'}$ resonance appears as a doublet of doublet of doublets at 3.798 ppm (J_{gem}=11.2 Hz, $J_{H3a'H4a'}$=7.1 Hz, $J_{H3a'H4e'}$=5.1 Hz) and the $H_{3e'}$ as an apparent doublet of triplets at 3.701 ppm ($J_{H3e'H4a'} \approx J_{H3e'H4e'}$=5.9 Hz). The remaining protons appear as multiplet signals within the range of 2.071 to 1.578 ppm. As can be deduced from the vicinal coupling constants contained in Table 2, the pattern of the eight protons of the tetrahydropyran ring of **3'c** is similar to that of **3c**. However, the chemical shifts of H_1, $H_{3a'}$, $H_{3e'}$ and H_6, are remarkably different between the two bicyclic cycloadducts.[12]

3. Discussion

3.1. Bicyclic azetidinones

The $^3J_{H1H5}$=3.2 Hz of **3b** and **3′b**, and the $^3J_{H1H6}$=4.6 Hz of **3c** and **3′c** are similar to the reported values for bicyclic azetidinones having the *cis* arrangement[7,12] and therefore, the only possible configurations for the bridgehead carbon atoms of each pair of bicyclic azetidinones are (S,R) and (R,S). Compared with **3′b**, the chemical shifts of H_1 and H_5 in **3b**, are shielded by 513 and 156 ppb, respectively, and the chemical shifts of H_{3endo}, H_{3exo} and H_{4endo} are deshielded by 555, 277 and 92 ppb, respectively. These differences arise from the anisotropy of the anthryl ring[13] and indicate that this aromatic ring adopts a preferred conformation in solution at 25°C. Accordingly, the anthryl ring is oriented towards the *exo* side of the rigid framework of **3b** and towards the *endo* side in **3′b**. Similar tendencies are observed between the chemical shifts of the protons H_1, H_6, $H_{3a'}$ and $H_{3e'}$ of the homologous azetidinones **3c** and **3′c**.

The consecutive addition of fixed amounts of Eu(tfc)$_3$ to a solution of **3c** in chloroform-*d*, causes the largest induced shift on H_9, as it is depicted in Fig. 1. Since the most important interaction is expected to occur between the chiral shift reagent and the carbonyl oxygen,[14] the large induced shift of H_9 indicates that the methine proton of the 1-phenylethyl group is oriented on the same side of the carbonyl group. This model is consistent with the observed deshielding of H_9 as seen in the ^{1}H NMR spectrum of the pure **3c** and may be attributed to the anisotropy of the carbonyl group.[15] Furthermore, the induced shifts on the H_1 and H_6 resonances of **3c**, are in agreement with the two-point interaction complex between the shift reagent and the substrate.

The bicyclic azetidinones **3b**, **3c**, **3′b** and **3′c** were prepared from commercial (S)-1-(1-naphthyl)ethyl- or (S)-1-phenylethyl isocyanate of 96% ee. The reaction produces exclusively the azetidinones with the *cis* arrangement, and therefore we have assumed that it proceeds through a concerted mechanism with retention of configuration of the stereogenic carbon of the isocyanate. Hence, the configuration of the exocyclic carbon of the resulting bicyclic azetidinones must be S. Since the resonances of the bridgehead protons of **3b** and **3c** are shielded by the ring current effect, these protons and the aryl ring are on the same side and H_9 is *syn* to the carbonyl group. It follows that the absolute configuration of the two bridgehead carbons of **3b** and **3c** must be (1S,5R) and (1S,6R) respectively, as depicted in Fig. 2. By the same principle, the absolute configurations of the bridgehead carbon atoms of **3′b**, and **3′c** are determined as (1R,5S) and (1R,6S) respectively.[16]

3.2. Monocyclic azetidinones

The configuration of monocyclic azetidinones **3d–f** and **3′d–f** can also be determined from the shielding effects induced by the phenyl ring. For instance, compared with the azetidinone **3′f**, the H_4 and H_{3cis} resonances of **3f** are shielded by 151 and 75 ppb, respectively. Therefore these two protons and the phenyl ring must be on the same side. The deshielding of the methine proton of the 1-phenylethyl group in the spectrum of **3f**, is consistent with the assumption that this proton is oriented *syn* to the carbonyl group. The 3D structures of **3′f** obtained by single point energy MM2 calculations, show restricted rotation about the σ bond of the O–CH_2 segment due to the steric interactions between this methylene with the phenyl ring. The observed AB spin system of the O–CH_2 segment is consistent with the calculated 3D structure: the doublets of the A and B spins are centered at 3.326 and 3.293 ppm, respectively, with J_{AB}=−8.8 Hz. Accordingly, in the spectrum of **3f** the methylene resonance of the OCH_2 segment appears as a triplet centered at 3.329 ppm. Furthermore, the resonances of the AA′BB′C system in **3′f** are spread over a wider spectral width than in **3f**.

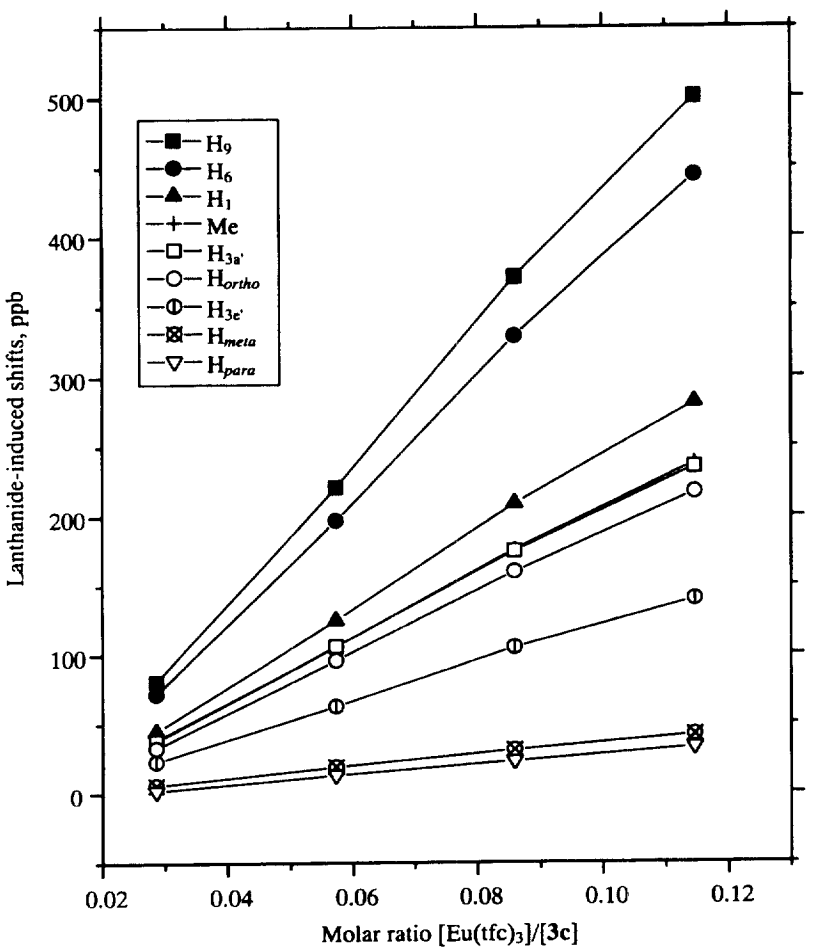
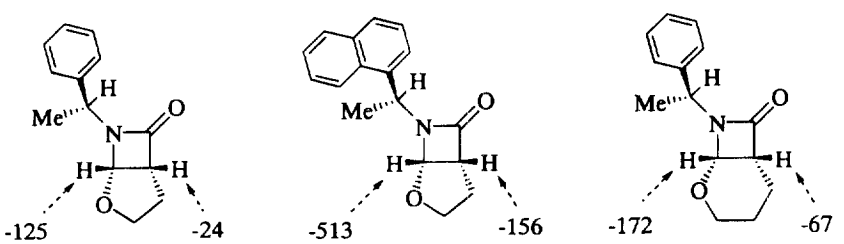


Fig. 1. Plots of the lanthanide-induced shifts in (1S,6R)-8-[(1S)-1-phenylethyl]-2-oxa-8-azabicyclo[4.2.0]octan-7-one **3c** (0.05 M in chloroform-*d*), as a function of the concentration of the chiral shift reagent to the substrate at 25°C. The lanthanide-induced shifts on $H_{3a'}$ and Me are overlapped



3a **3b** **3c**

Fig. 2. The structures depict the absolute configuration of the bridgehead carbons of azetidinones **3a**,[7] **3b** and **3c** determined from the shielding effects, in ppb, of the aryl ring attached to the chiral exocyclic carbon having the S configuration

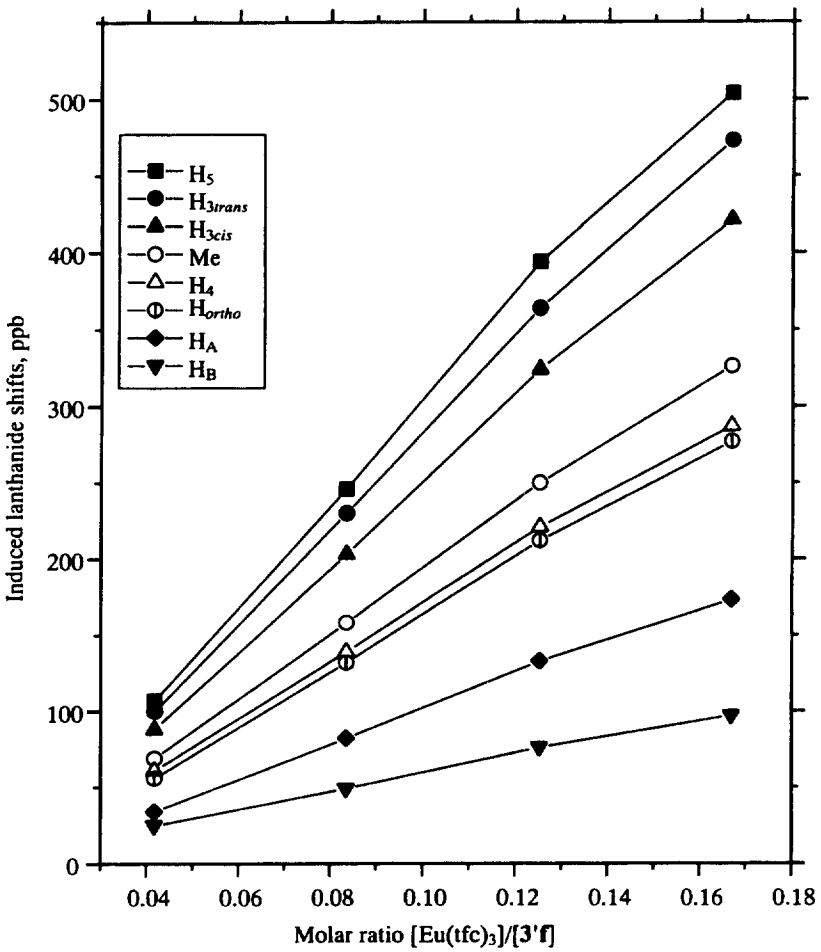


Fig. 3. Plots of the lanthanide-induced shifts in (4R)-1-[(1S)-1-phenylethyl]-4-butoxyazetidin-2-one **3′f** (0.05 M in chloroform-*d*), as a function of the ratio of the concentration of the chiral shift reagent to the substrate at 25°C. The signals that underwent smaller induced shifts are omitted

The orientation of the 1-phenylethyl group in these monocyclic azetidinones, was inferred from the spectra of **3′f** in the presence of fixed amounts of $Eu(tfc)_3$. The corresponding induced shifts plotted in Fig. 3, suggest that even the coordination to the ether oxygen is significant,[17] although the coordination to the carbonyl oxygen is dominant. The largest induced shift on the methine proton of the 1-phenylethyl group is similar to the results found for the bicyclic azetidinones **3a–c** and **3′a–c** and therefore the monocyclic and the bicyclic azetidinones have identical orientations in solution. It should be noted that the preferred orientation of the methine proton of the 1-phenylethyl group resembles the generally accepted conformation for open chain amides of α-branched primary amines.[8] On this basis, the absolute configuration of the stereogenic center C_4 of **3f** and **3′f** can be assigned as (4S) and (4R), respectively. The azetidinones **3d** and **3e** have the configuration assigned to **3f**, likewise **3′d** and **3′e** have the configuration assigned to **3′f**.

Chiral azetidinones having the N-(1-arylethyl) group have been prepared from the Staudinger reaction by several groups. In most cases, the corresponding absolute configuration has been determined by X-ray diffraction,[4] chemical correlation[2,5] or by comparison of the physical properties and the spectroscopic data with the information on compounds of known configuration.[6] We have taken from the literature

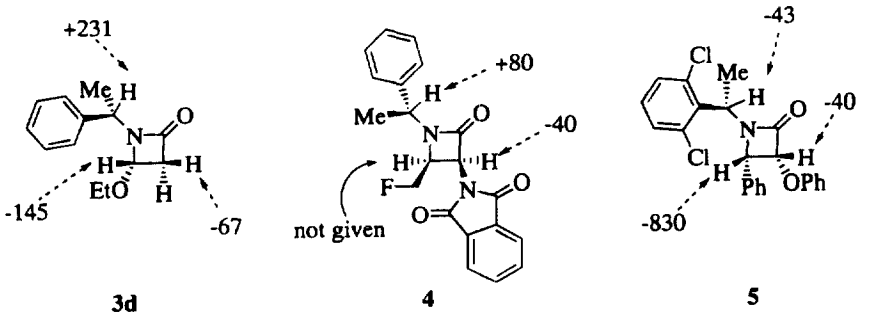


Fig. 4. The shielding effects in ppb of H_3 and H_4, and the deshielding of the methine proton attached to the chiral exocyclic carbon of **3d**, are consistent with the ^1H NMR data reported for the depicted azetidinones **4** and **5**. The configurations of **4** and **5** have been determined by chemical correlation[5a] and X-ray diffraction,[17] respectively

the ^1H NMR data of the azetidinone **4** (Fig. 4) and its diastereomer obtained from the Staudinger reaction.[5a] Applying our method we obtained the reported configurations. Also, from the ^1H NMR data of a diastereomeric pair of 1-(2,6-dichlorophenylethyl)-3-phenoxy-4-phenyl azetidin-2-one (**5**), we also obtained the configurations previously determined by X-ray diffraction,[4b] therefore the method described herein is very reliable.

In conclusion, we have demonstrated that the absolute configuration of the stereogenic centers of monocyclic and bicyclic azetidinones derived from (S)-1-(1-naphthyl)ethyl and (S)-1-phenylethyl isocyanates can be unambiguously determined by ^1H NMR in solution using the ring current effects arising from the aryl ring. The analysis of the reported ^1H NMR data for related heterocycles prepared from the Staudinger reaction, show that our method is applicable to all azetidinones having the (R)- or (S)-1-arylethyl group attached to the nitrogen atom.

4. Experimental

4.1. General

GC analyses were performed on a Shimadzu GC-14A using a Frontier Lab Ultra Alloy-1 column, 30 meters; injector and detector temperature: 270°C. IR spectra were recorded on a JASCO A-302 spectrophotometer. Specific rotations were measured with a JASCO DIP-100 polarimeter. Mass spectra were recorded on a Hitachi M-80B spectrometer. Melting points were determined with a Mettler FP 90 apparatus.

^1H NMR spectra were recorded on a JEOL GX-400 (399.65 MHz) spectrometer equipped with a 5 mm ^1H probe. A weighed amount of the appropriate substrate was dissolved in $CDCl_3$ to give a 0.05 M solution at 25°C. The chemical shifts were referenced to internal TMS. Typical ^1H NMR spectra were obtained using a pulse width of 2.4 μs (30°), a pulse delay of 10 s, 32 transients and a spectral width of 4000 Hz digitized into 64 K data points, resulting in a digital resolution of 0.12 Hz per point.

The measurements with the chiral shift reagent were carried out after the initial spectrum of the substrate. 40 μL of a 0.02 M solution of $Eu(tfc)_3$ in $CDCl_3$ was added to the substrate contained in the NMR tube and the spectrum was recorded. This operation was performed four times to increase the molar ratio of [$Eu(tfc)_3$]/[substrate]. The molecular structures were calculated by single point energy MM2.[9] The subspectra of the aromatic protons were simulated as an AA′BB′C spin system using the LAOCN program.

4.2. Materials

4.2.1. (1S,5R)-7-[(1S)-1-(1-Naphthyl)ethyl]-2-oxa-7-azabicyclo[3.2.0]heptan-6-one **3b** and (1R,5S)-7-[(1S)-1-(1-naphthyl)ethyl]-2-oxa-7-azabicyclo[3.2.0]heptan-6-one **3'b**

A homogeneous mixture of (S)-1-(1-naphthyl)ethyl isocyanate (395 mg, 2 mmol) and 2,3-dihydrofuran (701 mg, 10 mmol) was sealed in a Teflon® tube and placed in a high-pressure apparatus. The apparatus was compressed to 800 MPa and heated to 100°C for 20 h. After releasing the pressure and cooling to room temperature, the excess of 2,3-dihydrofuran was removed under reduced pressure. The yield determined by GC was 94%. The residual crude product was chromatographed on silica gel using a mixture of hexane:ethyl acetate (2:1 v/v), to give 262 mg (49%) of a colorless oil, which solidifies on standing (mp 68–70°C). MS (EI) *m/z* 267.1245 M^+ (calcd for $C_{17}H_{17}NO_2$, 267.1258); IR (neat) 1750 cm^{-1}; $[\alpha]_D^{26}=-6.6$ (c=0.58, chloroform). Further elution gave 240 mg (45%) of colorless oil. MS (EI) *m/z* 267.1233 M^+ (calcd for $C_{17}H_{17}NO_2$, 267.1258); IR (neat) 1750 cm^{-1}; $[\alpha]_D^{24}=+6.9$ (c=0.47, chloroform). From these data and the results in the present study, the structures of the solid and the oil were unambiguously assigned to **3b** and **3'b**, respectively.

From this general method were prepared the following cycloadducts.

4.2.2. (1S,6R)-8-[(S)-1-Phenylethyl]-2-oxa-8-azabicyclo[4.2.0]octan-7-one **3c**

Colorless oil which solidifies on standing (mp 41–43°C, 24% yield). MS (EI) *m/z* 231.1268 M^+ (calcd for $C_{14}H_{17}NO_2$, 231.1258); IR (neat) 1753 cm^{-1}; $[\alpha]_D^{26}=-104$ (c=0.85, chloroform).

4.2.3. (1R,6S)-8-[(S)-1-Phenylethyl]-2-oxa-8-azabicyclo[4.2.0]octan-7-one **3'c**

Colorless oil (22% yield). MS (EI) *m/z* 232.1358 M^++1 (calcd for $C_{14}H_{18}NO_2$, 232.1336); IR (neat) 1753 cm^{-1}; $[\alpha]_D^{26}=+15.6$ (c=0.64, chloroform).

4.2.4. (4S)-1-[(S)-1-Phenylethyl]-4-ethoxyazetidin-2-one **3d**

Colorless oil (42% yield). MS (EI) *m/z* 219.1267 M^+ (calcd for $C_{13}H_{17}NO_2$, 219.1258); IR (neat) 1759 cm^{-1}; $[\alpha]_D^{27}=-26.5$ (c=0.91, chloroform).

4.2.5. (4R)-1-[(S)-1-Phenylethyl]-4-ethoxyazetidin-2-one **3'd**

Colorless oil (44% yield). MS (EI) *m/z* 219.1265 M^+ (calcd for $C_{13}H_{17}NO_2$, 219.1258); IR (neat) 1759 cm^{-1}; $[\alpha]_D^{23}=-17.3$ (c=0.91, chloroform).

4.2.6. (4S)-1-[(S)-1-Phenylethyl]-4-isobutyloxyazetidin-2-one **3e**

Colorless oil (32% yield). MS (EI) *m/z* 247.1585 M^+ (calcd for $C_{15}H_{21}NO_2$, 247.1571); IR (neat) 1761 cm^{-1}; $[\alpha]_D^{27}=-30.1$ (c=1.05, chloroform).

4.2.7. (4R)-1-[(S)-1-Phenylethyl]-4-isobutyloxyazetidin-2-one **3'e**

Colorless oil (36% yield). MS (EI) *m/z* 247.1550 M^+ (calcd for $C_{15}H_{21}NO_2$, 247.1571); IR (neat) 1761 cm^{-1}; $[\alpha]_D^{25}=-8.3$ (c=0.93, chloroform).

4.2.8. (4S)-1-[(S)-1-Phenylethyl]-4-butyloxyazetidin-2-one **3f**

Colorless oil (20% yield). MS (EI) *m/z* 247.1570 M^+ (calcd for $C_{15}H_{21}NO_2$, 247.1571); IR (neat) 1761 cm^{-1}; $[\alpha]_D^{25}=-27.4$ (c=0.92, chloroform).

4.2.9. (4R)-1-[(S)-1-Phenylethyl]-4-butyloxyazetidin-2-one 3′f

Colorless oil (25% yield). MS (EI) *m/z* 247.1558 M^+ (calcd for $C_{15}H_{21}NO_2$, 247.1571); IR (neat) 1761 cm^{-1}; $[\alpha]_D^{22}$=+1.5 (c=1.07, chloroform).

$Eu(tfc)_3$ was obtained from Aldrich Chemicals and was used without further purification.

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