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Configurational ^{1}H NMR Study of Optically Active 7-(1-Phenylethyl)-2-oxa-7-azabicyclo[3.2.0]heptan-6-one Derivatives Using Pirkle's Alcohols and a Chiral Shift Reagent

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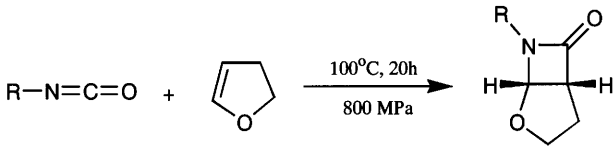
ABSTRACT: Four novel stereoisomers of 7-(1-phenylethyl)-2-oxa-7-azabicyclo[3.2.0]heptan-6-one were prepared under high pressure from [2 + 2] cycloaddition of the pure enantiomers of 1-phenylethyl isocyanate and 2,3-dihydrofuran. Their conformational preferences in solution and the absolute configurations of the bridgehead carbon atoms were unambiguously determined by ^{1}H NMR spectroscopy using tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)-*d*-camphorato]europium(III) and (*R*)- or (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle's alcohols). MM2 single-point energy calculations were consistent with the experimentally determined stereochemistry.

KEYWORDS: ^{1}H NMR; absolute configuration; chiral β-lactams; chiral solvating agent; Pirkle's alcohols; chiral shift reagent

INTRODUCTION

Several groups have investigated the [2 + 2] cycloaddition of active isocyanates to 3,4-dihydro-2*H*-pyran derivatives at normal pressure.[1–5] The monosubstituted 3,4-dihydro-2*H*-pyrans afford the corresponding cycloadducts in modest yields,[1,2,5] whereas the parent 3,4-dihydro-2*H*-pyran leads to the open chain α,β-unsaturated amides.[1–5] Analogous reactions with 3,4-dihydro-2*H*-pyrans derived from naturally occurring monosaccharides give mixtures of [2 + 2] and [4 + 2] cycloadducts along with α,β-unsaturated amides.[6] Although these [2 + 2] cycloadducts are stereospecifically produced as the main products, they are unstable and therefore *N*-deprotection is necessary before isolation or chemical transformation.[6,7] Nevertheless it is preferable to avoid *N*-deprotection because it results in further decomposition of the cycloadducts.

Recently, we have shown that the [2 + 2] cycloaddition of alkyl and phenyl isocyanate to vinyl ethers under high pressure affords the *N*-alkyl- and *N*-phenylazetidin-2-one derivatives in high yields (Scheme 1).[8] With this reaction, we have prepared novel cycloadducts derived from 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran and the above-mentioned isocyanates. Products of this type are obtained as racemic mixtures and can be kept at room temperature for several weeks without decomposition. Since the single step reaction produces stable cycloadducts having two chiral carbons in the azetidin-2-one ring, a better understanding of this reaction is essential.



Scheme 1. High-pressure cycloaddition of phenyl, benzyl and ethyl isocyanate (R = phenyl, benzyl and ethyl, respectively) to 2,3-dihydrofuran.

To investigate how this reaction could be applied to the stereoselective synthesis of chiral azetidin-2-ones, we have carried out the [2 + 2] cycloaddition of the pure enantiomers of 1-phenylethyl isocyanate to 2,3-dihydrofuran. It was found that (*R*)-1-phenylethyl isocyanate give a mixture of cycloadducts **1** and **2**; likewise, (*S*)-1-phenylethyl isocyanate affords cycloadducts **3** and **4**. These cycloadducts are produced in 87% overall yield with a 1:1.1 ratio of **1**:**2** or **3**:**4**, and can be isolated by column chromatography; **1** and **3** are oils and **2** and **4** are solids. Attempts to form suitable crystals for x-ray diffraction have been unsuccessful and for this reason we have determined their stereochemistry in solution using ^{1}H NMR.

The present paper demonstrates how the absolute configuration of bridgehead carbon atoms of **1**–**4** was determined using the ring current effect arising from the intramolecular 1-phenylethyl group and the intermolecular anthryl group of the pure enantiomers of Pirkle's alcohols [(*R*)- and (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol].

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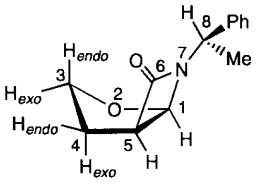

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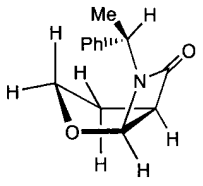

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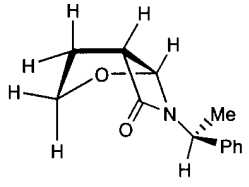

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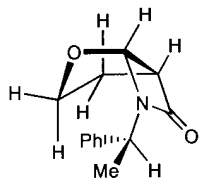

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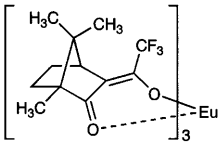
EXPERIMENTAL

Materials

(1*S*,5*R*)-7-[(1*S*)-1-Phenylethyl]-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (3) and (1*R*,5*S*)-7-[(1*S*)-1-phenylethyl]-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (4). A homogeneous mixture of (*S*)-1-phenylethyl isocyanate (442 mg, 3 mmol) and 2,3-dihydrofuran (1051 mg, 15 mmol) was sealed in a Teflon tube and placed in a high-pressure apparatus. The apparatus was compressed to 800 MPa and heated at 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 87%. The residual crude product was chromatographed on silica gel using hexane–ethyl acetate (2:1, v/v) to give 248 mg (38%) of a colorless oil. MS (EI), *m/z* 217.1106 M^+ (calculated for $C_{13}H_{15}NO_2$, 217.1102). IR (neat), 1755 cm^{-1}; $[\alpha]_D^{20} = -17.9°$ ($c = 0.76$, chloroform). Further elution gave 274 mg (42%) of yellowish flakes, m.p. 51–52 °C (hexane-ethyl acetate). MS (EI), *m/z* 217.1122 M^+ (calculated for $C_{13}H_{15}NO_2$, 217.1102); IR (KBr disk), 1736 cm^{-1}; $[\alpha]_D^{24} = -69.2°$ ($c = 0.64$, chloroform). From these data and the evidence found in the present study, the structures of the oil and the solid were unambiguously assigned to **3** and **4**, respectively.

(1*R*,5*S*)-7-[(1*R*)-1-Phenylethyl]-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (1) and (1*S*,5*R*)-7-[(1*R*)-1-phenylethyl]-2-oxa-7-azabicyclo[3.2.0]heptan-6-one (2). Under identical conditions, (*R*)-1-phenylethyl isocyanate also gave two cycloadducts: a colorless oil (42%), IR (neat) 1753 cm^{-1}, $[\alpha]_D^{20} = +20.0°$ ($c = 1.00$, chloroform), and yellowish flakes (45%), m.p. 51–52 °C (hexane–ethyl acetate), IR (KBr disk) 1736 cm^{-1}, $[\alpha]_D^{20} = +71.8°$ ($c = 1.06$, chloroform). The oil and the solid were characterized as **1** and **2**, respectively.

Tris[3-(2,2,2-trifluoro-1-hydroxyethylidene)-*d*-camphorato]europium(III) (**5**) was obtained from Aldrich Chemicals. The Pirkle alcohol (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol (**6**) and its enantiomer (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol (**7**) were obtained from Tokyo Kasei. These reagents were used without further purification.



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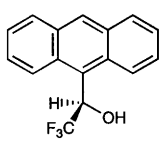

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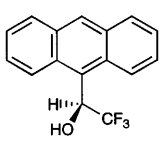

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Procedures

^{1}H NMR spectra were recorded on a JEOL GX-400 (399.65 MHz) spectrometer equipped with a 5 mm ^{1}H 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 ^{1}H 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 64K data points, resulting in a digital resolution of 0.12 Hz per point. Additional measurements carried out with 0.02, 0.05 and 0.11 M solutions of substrates **1–4** in $CDCl_3$ showed that the chemical shifts of most protons are barely influenced by the concentration in this range, since the largest variation was 2 ppb.

The measurements with the chiral shift reagent were carried out after the initial spectrum of the substrate. A 40 μl volume of a 0.02 M solution of the shift reagent **5** in $CDCl_3$ was added to the substrate contained in the NMR tube and the spectrum was recorded. This operation was performed four or five times to increase the [**5**]:[substrate] molar ratio. To a fresh solution of the substrate in $CDCl_3$ was added a weighed amount of the chiral solvating agent **6** and after 5 min the spectrum was recorded. The [**6**]:[substrate] molar ratio was calculated from the integration of the signals assigned to the methine and hydroxyl protons of **6** and those assigned to H-1 and H-8 of the substrate. This operation was performed four times, increasing the concentration of **6** consecutively to give *ca.* 1:1, 1:2, 1:3 and 1:4 molar mixtures. To a second fresh solution of the substrate were added consecutively equivalent amounts of the chiral solvating agent **7** to give *ca.* 1:1, 1:2, 1:3 and 1:4 molar mixtures. The geometry of each compound was calculated by single-point energy MM2 and a standard version of MOPAC for PC.[9] The subspectra of the aromatic protons were simulated as an AA′BB′C spin system using the LAOCN program.

RESULTS AND DISCUSSION

Interpretation and assignment of the spectra

The numbering used for the studied substrates is shown on structure **1**, and it should be noted that the exocyclic chiral carbon has been labeled as C-8 only for assignment purposes. ^{1}H NMR spectra of **1–4** consist of two isolated spin systems. The benzyl group of the *N*-(1-phenylethyl) moiety is a typical AA′BB′CX system in which the benzylic coupling is less than 1 Hz, whereas H-8 and the methyl group form an apparently isolated AX_3 spin system. The AA′BB′CX system of cycloadduct **1** looks very similar to that of cycloadduct **3**, and the same holds true for **2** and **4**. In substrates **1** and **3**, the A and B nuclei are virtually isochronous, but in cycloadducts **2** and **4**, such nuclei give well resolved signals centered at 7.37 and 7.34 ppm, respectively. The pertinent data is presented in Table 1. The protons of the

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Table 1. Chemical shifts (δ) and coupling constants (J)[a] in the ^{1}H NMR spectra (400 MHz) of cycloadducts **1–4** (0.05 M) in chloroform-*d* at 25 °C.

Sample	H-4*exo* (*J*)	H-4*endo* (*J*)	H-5 (*J*)	H-3*endo* (*J*)	H-3*exo* (*J*)	H-1 (*J*)	H-8 (*J*)	Me (*J*)
1[b]	1.729dddd	2.191dddd	3.548dd	3.928ddd	4.178ddd	5.393d	4.877q	1.621d
	(8.1, 8.6, 12.0, 13.1)	(0.5, 0.6, 5.5, 13.1)	(3.0, 8.6)	(5.5, 9.4, 12.0)	(0.6, 8.1, 9.4)	(3.0)	(7.2)	(7.2)
2[c]	1.725dddd	2.137dddd	3.574dd	3.645ddd	4.066ddd	5.522d	4.666q	1.663d
	(8.2, 8.8, 12.1, 12.9)	(0.5, 0.6, 5.5, 12.9)	(2.9, 8.8)	(5.5, 9.4, 12.1)	(0.6, 8.2, 9.4)	(2.9)	(7.2)	(7.2)
3[b]	1.730dddd	2.192dddd	3.550dd	3.929ddd	4.180ddd	5.394d	4.879q	1.621d
	(8.1, 8.7, 11.9, 13.1)	(0.5, 0.6, 5.5, 13.1)	(3.1, 8.7)	(5.5, 9.4, 11.9)	(0.6, 8.1, 9.4)	(3.1)	(7.2)	(7.2)
4[c]	1.725dddd	2.134dddd	3.574dd	3.645ddd	4.066ddd	5.519d	4.666q	1.663d
	(8.2, 8.8, 12.0, 13.1)	(0.5, 0.6, 5.5, 13.1)	(3.1, 8.8)	(5.5, 9.4, 12.0)	(0.6, 8.2, 9.4)	(3.1)	(7.2)	(7.2)

[a] Coupling constants in Hz. Parameters for aromatic protons: [b] $\delta_A = 7.368$, $\delta_B = 7.367$, $\delta_C = 7.300$, $^4J_{AA'} = 2.0$ Hz, $^3J_{AB} = {}^3J_{A'B'} = 8.2$ Hz, $^5J_{AB'} = {}^5J_{A'B} = 0.5$ Hz, $^4J_{AC} = {}^4J_{A'C} = 1.7$ Hz, $^4J_{BB'} = 1.7$ Hz, $^3J_{BC} = {}^3J_{B'C} = 7.2$ Hz; [c] $\delta_A = 7.375$, $\delta_B = 7.341$, $\delta_C = 7.271$, $^4J_{AA'} = 2.1$ Hz, $^3J_{AB} = {}^3J_{A'B'} = 8.3$ Hz, $^5J_{AB'} = {}^5J_{A'B} = 0.5$ Hz, $^4J_{AC} = {}^4J_{A'C} = 1.7$ Hz, $^4J_{BB'} = 1.7$ Hz, $^3J_{BC} = {}^3J_{B'C} = 7.2$ Hz.

fused tetrahydrofuran ring give a first order six-spin system. Also in this case, the first-order subspectrum of **1** looks very similar to that of **3**, and the same holds true for **2** and **4**.

Representative spectra of **1** and **2** are shown in Fig. 1 and the typical analysis is described here for cycloadduct **1**. The quadruplet centered at 4.87 ppm is attributed to H-8. The sharp doublet at 5.39 ppm and the doublet of doublets at 3.55 ppm show a common vicinal coupling constant [^{3}J(H-1, H-5) = 3.0 Hz], so the first is assigned to H-1 and the second to H-5. The torsion angles obtained from the calculated 3D structure of **1** and $^3J_d = 8.6$ Hz of the doublet of doublets assigned to H-5 were used to analyze the remaining protons using Karplus-type curves. The vicinal coupling of 8.6 Hz was consistent with the torsion angle H-5—C-5—C-4—H-4*exo* of 32°, so it corresponds to ^3J(H-5, H-4*exo*). H-4*exo* appears as a multiplet centered at 1.73 ppm, whereas H-4*endo* gives an apparent doublet of doublets at 2.19 ppm, the latter being consistent with the torsion angles H-3*exo*—C-3—C-4—H-4*endo* and H-5—C-5—C-4—H-4*endo* of 84° and 89°, respectively. The doublet of doublet of doublets [^3J(H-3*endo*—H-3*exo*) = 9.4 Hz, ^3J(H-3*endo*—H-4*exo*) = 12.0 Hz and ^3J(H-3*endo*—H-4*endo*) = 5.5 Hz] centered at 3.93 ppm is assigned to H-3*endo* and the apparent triplet at 4.18 ppm is assigned to H-3*exo*.

Stereochemistry

From previous results,[8] it is known that the high-pressure [2 + 2] cycloaddition of isocyanates to vinyl ethers proceeds regiospecifically. Presumably this cycloaddition goes through a concerted process and the stereochemistry of a chiral isocyanate remains unaltered during the reaction. Therefore, we have assumed that the chiral exocyclic carbon of cycloadducts **1**, **2** and **3**, **4** has the absolute configuration *R* and *S*, respectively. The experimental ^{1}H NMR data are consistent with the

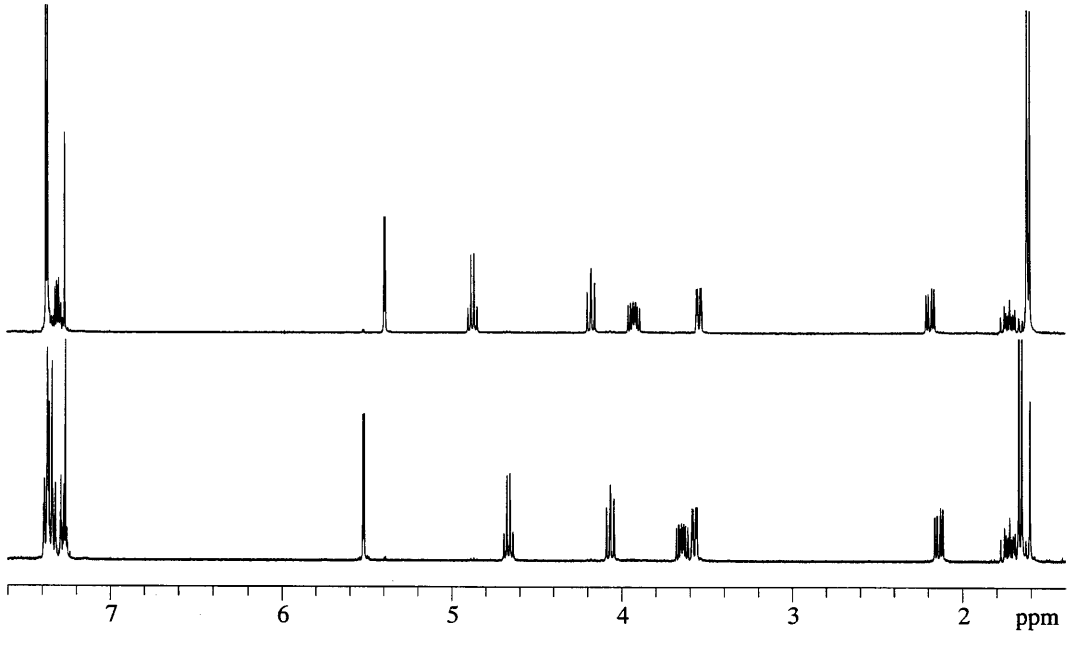

Figure 1. ^{1}H NMR spectrum (400 MHz) of cycloadducts **1** and **2** (0.05 M) in chloroform-*d* at 25 °C containing TMS. The difference of chemical shifts between the spectra of cycloadduct **1** (above) and cycloadduct **2** (below) is attributed to the intramolecular ring current effect of the phenyl group.

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specific rotation $[\alpha]_D$ and show that these cycloadducts are diastereomerically pure.

^{1}H NMR data show that cycloadducts **1**–**4**, have a vicinal *J*(H-1, H-5) of 3.0 Hz. Although this coupling appears too small for a torsion angle of 0° between H-1—C-1—C-5—H-5, it is characteristic of the *cis* arrangement in azabicyclo[3.2.0]heptane[10] and bicyclic azetidin-2-ones derived from glycals,[7] and effectively eliminates the possibility of the *trans* arrangement. This means that the only possible configurations for the bridgehead atoms of cycloadducts **1**, **2** or **3**, **4** are 1*S*,5*R* and 1*R*,5*S*, respectively. Hence, the cycloadducts **1**–**4** may consist of two pairs of enantiomers. Accordingly, our experimental data show that the oily cycloadduct **1** may be the mirror image of **3** and the solid cycloadduct **2** the mirror image of **4**.

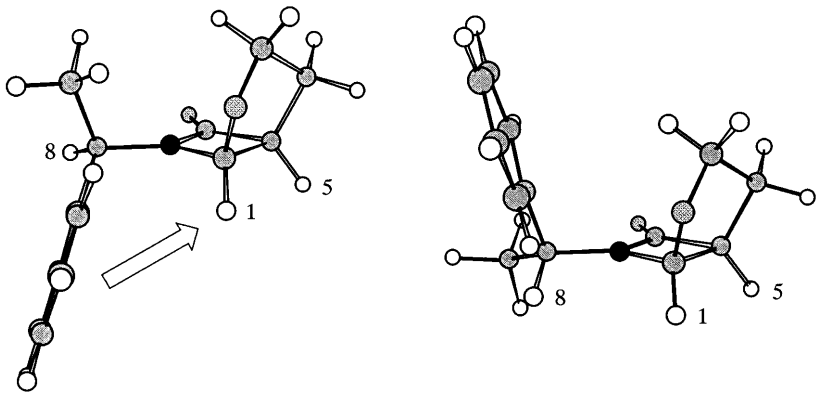
Three-dimensional molecular structures calculated by MM2 show that cycloadducts **1**–**4** consist of a rigid framework. The azetidinone ring is almost planar but the tetrahydrofuran ring has an envelope conformation on which C-3 is out of the plane.[7] To minimize steric interactions, the phenyl group is oriented almost parallel to the imaginary plane defined by H-1—C-1—O-2. In spite of the free internal rotation of the 1-phenylethyl group about the *N*—C-8 bond, ^{1}H NMR data obtained at 25 °C reveal the trend for a preferred orientation. Compared with **2** and **4**, the averaged chemical shifts of H-1 and H-5 in **1** and **3** are shielded by 127 and 25 ppb, respectively. Since the magnitude of such shieldings is assumed to be proportional to the distance from the phenyl group, this is a clear manifestation of the ring current effect,[11] which enables us to propose the rotamer **A** (Fig. 2) as the most important conformation for **1** and **3**. Furthermore, in rotamer **A** the orientation of H-8 is *syn* to the carbonyl group and, in such an arrangement, an anisotropic deshielding effect can be anticipated for H-8. The averaged deshielding of 212 ppb shown by the H-8 resonance in the spectra of **1** and **3** is consistent with this interpretation.[12] It is noteworthy that rotamer **A** resembles very much the generally accepted conformation for methoxy(trifluoromethyl)phenylacetyl esters and amides of α–branched primary amines in solution.[13]

The fact that the carbonyl anisotropic effect is not manifested in the chemical shift of nucleus H-8 of **2** and **4** suggests that these molecules adopt different conformations from that proposed for **1** and **3**. Single-point energy MM2 calculations showed that one of the low-energy structures for **2** and **4** is that in which the H-8 is *gauche* to the carbonyl group, as depicted in Fig. 3. In such a geometry, the phenyl ring is oriented towards C-3 and therefore the H-3*endo* and H-3*exo* resonances should be shielded by the ring current effect. Also in this case, the experimental shifts are consistent with the proposed model; for example, compared with **1**, the chemical shifts of H-3*endo*, H-3*exo* and H-4*endo* in diastereomer **2** exhibit upfield shifts of 283, 112 and 54 ppb, respectively. From this interpretation, plausible configurations can be anticipated for the oily and the solid cycloadducts **1**, **3** and **2**, **4**, respectively. However, such configurations would still be considered as relative unless evidence for the proposed conformations of the 1-phenylethyl group can be found. In this context, we carried out the following experiments in order to determine the absolute configuration of the liquid and solid cycloadducts.

Effect of chiral shift reagent

Cycloaducts **1**–**4** are donor substrates capable to form *in situ* coordinate complexes with Lewis acids. In favorable cases, the stereochemistry of chiral donor substrates can be rationalized on the basis of the induced effects caused by the chiral acidic compound of known configuration. Therefore, we studied the effect of the chiral shift reagent **5** on substrates **1** and **2**.

The addition of **5** to a solution of **1** or **2** in $CDCl_3$ induces downfield shifts of all the signals in the ^{1}H NMR spectra, and the corresponding induced shifts are shown in Fig. 4. A [**5**]:[substrate] ratio larger than 0.1 causes severe broadening of the H-8, H-5 and H-3*endo*



A **B**

Figure 2. Three-dimensional structure of cycloadduct **1** showing two of the several rotamers in solution. In rotamer **A**, the H-1 and H-5 nuclei are shielded by the ring current effect and H-8 is placed *syn* and close to the plane of the carbonyl group.

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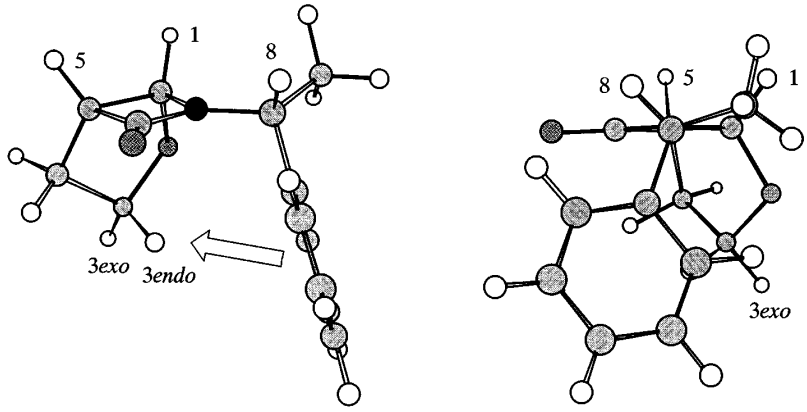

Figure 3. Three-dimensional structure for one of the low energy rotamers of cycloadduct **2** showing the phenyl ring oriented towards C-3. The eclipsed view shows H-8 *gauche* to the carbonyl group.

resonances; for this reason, small [**5**]:[substrate] ratios were used in the present investigation to constrain the binding of the substrate to the shift reagent. A qualitative interpretation of the data plotted in Fig. 4 reveals two important features about the interaction between **5** and the donor substrates. First, the deshielding of H-8 indicates that the most important complex in solution has the H-8 nucleus oriented on the same side of the carbonyl group, and second, the deshielding of H-5 indicates that the shift reagent coordinates preferentially to the carbonyl oxygen. The former feature confirms the validity of our interpretation of the ^{1}H NMR spectra based on the intramolecular ring current effect of the phenyl group, and the second, which is consistent with published studies performed on racemic 6-azabicyclo[3.2.0]heptan-7-one,[14] indicates that the ether oxygen and the nitrogen do not complex significantly with the chiral shift reagent. Three-dimensional molecular structures show that within a rigid framework, a bidentate-type interaction between **5** and the two oxygens of the substrates is not favored. Interaction between the shift reagent and the carbonyl oxygen and nitrogen seems less favored owing to the orientation of the lone electron pairs and the bulkiness of the 1-phenylethyl group.

Effect of Pirkle's alcohols

A complete screening in $CDCl_3$ was performed on substrates **1**–**4** by the addition of a severalfold excess of the chiral solvating agents **6** or **7**. These solvating agents

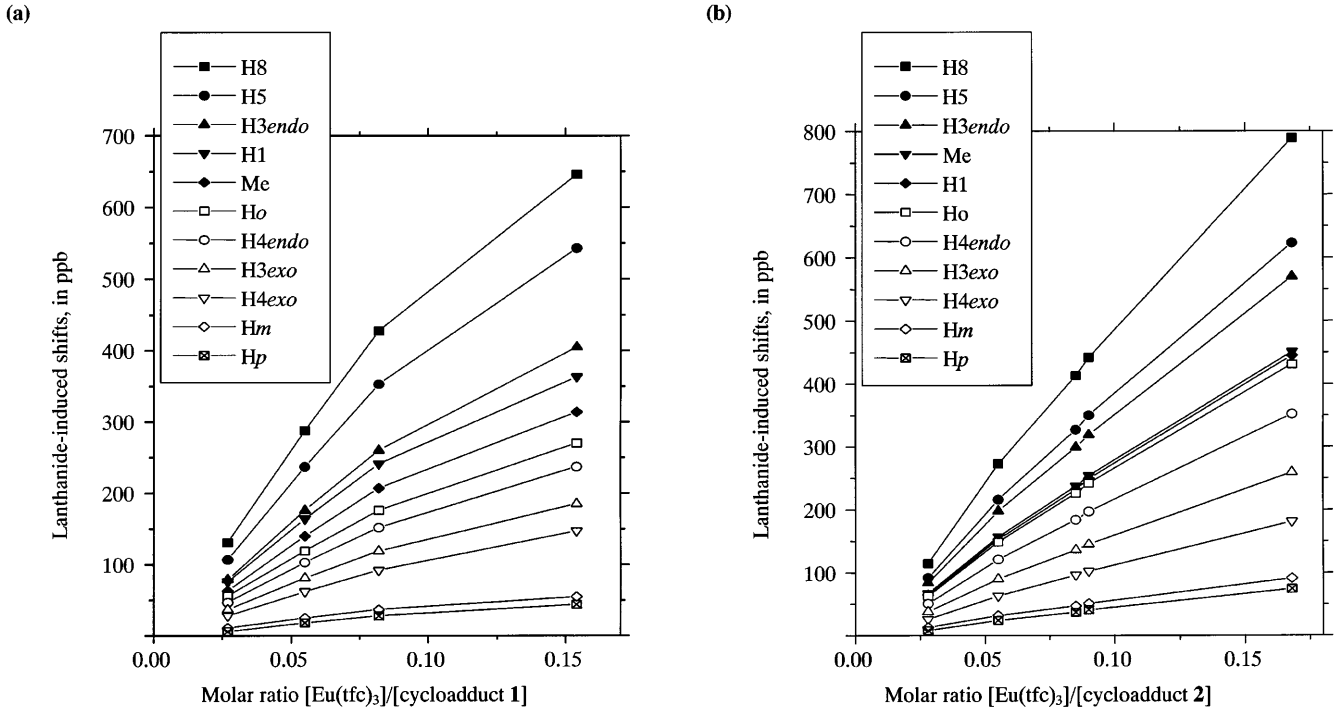

Figure 4. Plot of the lanthanide-induced shifts of cycloadducts **1** and **2** (0.05 M in chloroform-*d*) as a function of the chiral shift reagent **5** to substrate ratio at 25 °C for **(a)** cycloadduct **1** in the presence of **5** and **(b)** cycloadduct **2** in the presence of **5**. Note that the two graphs are plotted on different scales.

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induce upfield shifts of all the resonances in the spectra of **1-4**, including the singlet of chloroform. The corresponding shifts for **1** are plotted in Fig. 5.

The effects of chiral solvating agents on the ^{1}H NMR spectrum of **1** are less systematic than the effects caused by shift reagent **5**; however, they both show that the primary interaction site is the carbonyl oxygen. Assuming that the hydroxylic proton of **6** may be 'tied' to the carbonyl oxygen of **1** by a strong hydrogen bond, the possible complexes were constructed using the CHEM 3D program.[9] Interaction between the ether oxygen of **1** and the methine proton of **6** gives a nine-membered ring complex, whereas interaction between nitrogen and the methine proton gives a seven-membered ring complex. Within the rigid structure of **1**, interaction with nitrogen is favored, even though it may be weak enough to allow free rotation about the O—C-1 bond of the solvating agent **6**. The net consequence of the 'untied' methine proton is an apparent shielding of all the resonances. Although this may partially explain why the solvating agent **6** or **7** shields the resonances of nuclei that are relatively far from the primary interaction site, the phenyl ring that can act as a secondary basic site[15] might give rise to additional complexes that contribute to the observed effect.

Since the H-1, H-3*endo* and H-3*exo* resonances are susceptible to intramolecular ring current effects from the phenyl group, it is convenient to center the discussion on the shielding observed for the H-5, H-4*endo* and H-4*exo* resonances. The large shifts induced by **6** on the H-5 and H-4*exo* resonances of **1** confirm the interaction between the chiral solvating agent and the carbonyl oxygen and nitrogen atoms, and indicate that the interaction occurs preferentially on the *exo* side of the substrate [Fig. 6(a)]. Although steric hindrance around the nitrogen might prevent interactions on the *endo* side, the interaction models for **1** and **6** show that a second complex, of minor concentration, is possible when the ether oxygen becomes the primary and the nitrogen the secondary interaction sites. In this minor complex the anthryl ring of **6** locates close to C-4 of the substrate and shields the H-4*endo* resonance, which is in agreement with the observed effects. On the other hand, chiral solvating agent **7**, which is the enantiomer of **6**, induces the largest shielding on H-4*endo* of cycloadduct **1** [Fig. 5(b)]. The solvation model that explains this shielding effect may have the chiral solvating agent **7** approaching the substrate **1** on the *endo* side, the carbonyl oxygen and nitrogen atoms being the interaction sites, as depicted in Fig 6(b).

It should be noted that the data plotted in Figure 5 give complementary information about the stereochemistry of the substrate and show that the above-mentioned effects are exclusively valid for the depicted geometry of **1**. Incidentally, the reverse was true for cycloadduct **2**, as can be deduced from the largest induced shift by the chiral solvating agent **7** on the H-5 resonance, and by **6** on the H-4*endo* resonance. For example, at a [chiral solvating agent]:[substrate] molar ratio of 4, the corresponding induced shielding effects were −307 and −279 ppb, respectively. Hence the data are entirely consistent with the geometries

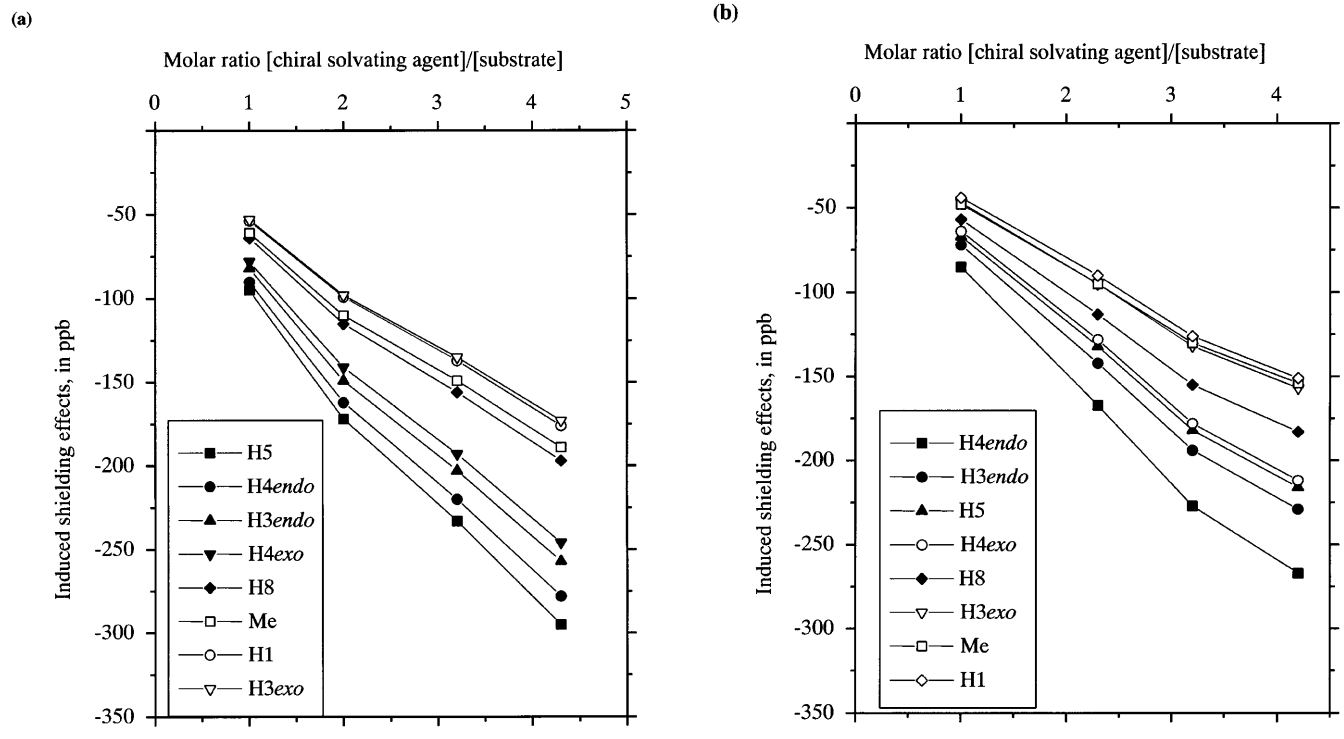

Figure 5. Plots of the shielding effects of cycloadduct **1** (0.05 M in chloroform-*d*) as a function of the ratio chiral solvating agent to substrate at 25 °C for **(a) 1** in the presence of **6** and **(b) 1** in the presence of **7**. In each case the ordinate is the difference of the chemical shifts of **1** in the presence of **6** referred to pure **1**.

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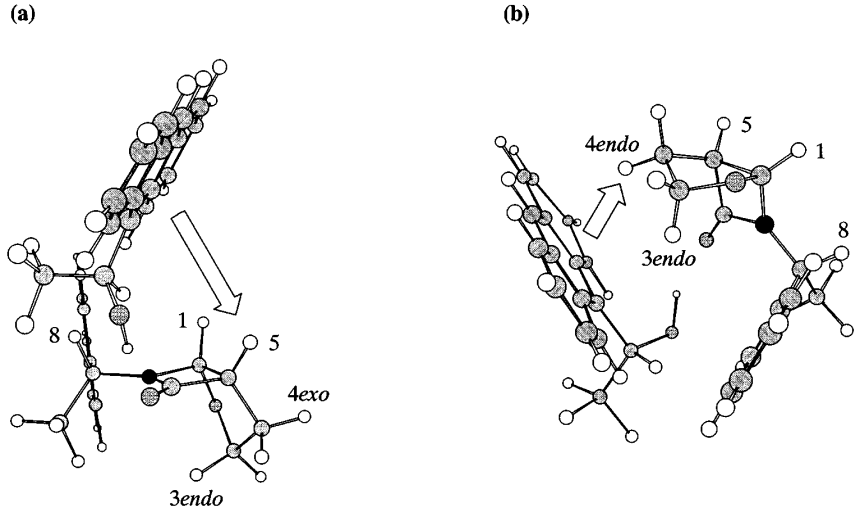

Figure 6. Proposed two-point interaction between cycloadduct **1** and the chiral solvating agents **6** and **7** for **(a)** the main complex [cycloadduct **1**–chiral solvating agent **6**] that explains the shielding of H-5 and H-4*exo* and **(b)** the main complex [cycloadduct **1**–chiral solvating agent **7**] that explains the shielding of H-4*endo*.

shown for **1** and **2** (Figs 2 and 3), and enable the absolute configurations 1*R*,5*S* and 1*S*,5*R* to be assigned to bridgehead carbon atoms of cycloadducts **1** and **2**, respectively.

In a similar way, we analyzed the stereochemistry of cycloadducts **3** and **4**. The experimental data for **3** and **4** in the presence of Pirkle's alcohols were consistent with the data for **1** and **2**. It should be mentioned that the magnitude of shieldings induced by the chiral solvating agent **7** in cycloadduct **3** almost parallels those induced by chiral solvating agent **6** in cycloadduct **1**. Likewise, the magnitude of shieldings induced by **6** in cycloadduct **4** almost parallels those induced by **7** in cycloadduct **2**. This result confirms that cycloadduct **1** is the mirror image of **3** and **2** is the mirror image of **4**. Consequently, the absolute configurations 1*S*,5*R* and 1*R*,5*S* can be assigned to cycloadducts **3** and **4**, respectively.

In this way, we definitely characterized the oily cycloadduct **1** as (1*R*,5*S*)-7-[(1*R*)-1-phenylethyl]-2-oxa-7-azabicyclo[3.2.0]heptan-6-one, the solid cycloadduct **2** as (1*S*,5*R*)-7-[(1*R*)-1-phenylethyl]-2-oxa-7-azabicyclo-[3.2.0]heptan-6-one and **3** and **4** as the enantiomers of **1** and **2**, respectively.

In conclusion, we have shown that pure enantiomers of 1-(9-anthryl)-2,2,2-trifluoroethanol can be used to determine the absolute configuration of pure diastereomers of 7-[(1*R*)-1-phenylethyl]- and 7-[(1*S*)-1-phenylethyl]-2-oxa-7-azabicyclo[3.2.0]heptan-6-one. Our ^{1}H NMR data show that the phenyl ring is suitably oriented in solution, so these cycloadducts can be used as probes of anisotropic aromatic shieldings in fused azetidin-2-one derivatives. Although the present method is reliable and powerful for unambiguously determining the absolute configuration of fused azetidin-2-ones of type **1**–**4**, it should be proved to be general for chiral molecules containing three basic sites.

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