Stereochemical Assignment of Diastereomeric Imidazolidinone-Ring-Containing Bicyclic Sugar-Peptide Adducts: NMR Spectroscopy and Molecular Calculations

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A combination of NMR spectroscopy and molecular simulations is used to determine *trans*/*cis* configurational features of two diastereomeric bicyclic imidazolidinone compounds obtained by intramolecular cyclization of the monosaccharide ester of leucine-enkephalin related to D-glucose. The stereochemical assignment of the five-membered imidazolidinone ring system was performed by consideration of long-range proton-proton coupling observed between protons at C2 and C4 in the COSY spectrum of the major isomer only. A long-range $^4J_{H,H}$ coupling across the nitrogen atoms is larger in the *trans* isomer than in the *cis*. In addition, comparison of these results with the NMR spectroscopic data obtained for the major isomer of D-galactose-related imidazolidinone and those previously obtained by X-ray methods for the corresponding minor isomer, show that the substituents attached to the imidazolidinone ring moiety in the studied compounds preferentially adopt the *trans* (2*R*,4*S*) orientation. The experimental results were complemented by density functional theory calculations of NMR-observable parameters, such as ^{1}H and ^{13}C chemical shifts and $^4J_{H,H}$ coupling constants, performed on simplified imidazolidinone ring systems.

Introduction

Three decades ago, interest in the area of an endogenous opioid system was aroused by two key discoveries: the binding of opiates to specific receptors[1−3] and shortly thereafter the discovery of the first endogenous "morphine-like compounds", Leu- and Met-enkephalin.[4,5] Today, it is well-known that these two endogenous opioid pentapeptides (Tyr-Gly-Gly-Phe-Leu/-Met) produce a wide range of central and peripheral effects, which, in addition to spinal and supraspinal analgesia, include involvement in stress, gastrointestinal, renal and hepatic functions, cardiovascular and immunological responses, respiration and thermoregulation, and also in neurological disorders.[6,7] Since enkephalins exhibit such a broad spectrum of biological activity it is obvious that they represent an important target as potential peptide therapeutic agents. Unfortunately, successful clinical development of biologically active peptides is hampered by their undesirable pharmaceutical properties, such as low water solubility and poor stability, which include susceptibility against endo- or exopeptidases, and finally low permeability through two major biological membrane barriers, the intestinal barrier and the blood−brain barrier. Recent approaches to avoid these obstacles and target bioactive peptides to their receptors have focused on prodrug strategies, the major goal being to create peptide prodrugs with improved physico-chemical properties and low or no toxicity for the host.[8−12] The syntheses of peptide prodrugs are generally based on masking the main functional groups of peptides in such a way that the prodrug can easily cross the biological membranes and then undergo spontaneous or enzymatic transformation to release the peptide, which then can exhibit its pharmacological effect.

The prodrug concept for delivering enkephalins to the central nervous system has utilized different N-terminal tyrosine-based imidazolidinone derivatives of both Leu- and Met-enkephalin. These compounds have been designed in order to obtain temporarily modified bio-reversible molecules with enhanced membrane-permeation characteristics and increased stability against peptidases.[13−15] Synthetic approaches to obtain enkephalin-related imidazolidinones have been based upon solution chemistry strategies, involving direct condensation of an α-amino amide moiety from the N-terminal end of the peptide with simple reactive aldehydes or ketones. Furthermore, five positional analogues of Leu-enkephalin based on the same sequence and different

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location of the imidazolidinone-construct have been synthesized by a solid-phase method[16] and examined for their affinity to μ-, δ- and κ-opioid receptors.[17] The cyclic prodrug approach, which allows for the simultaneous masking of an amino and a carboxyl group of a peptide, indicates that cyclization of linear peptides, such as opioid peptides, has a dramatic effect on their metabolic stability and their ability to permeate across a biological barrier.[18,19]

Several research groups have recognized carbohydrates as an important class of compounds useful in peptide-based drug design to create opioid ligands with adequate bioavailability, in vivo stability and reduced side-effects.[20−24] As regards the carbohydrate ligands, the variety afforded by stereochemical differences at the anomeric position, ring size and subunit modification (e.g., acylation, alkylation, phosphorylation) and combinations of these variables has resulted in carbohydrate-modified peptides having altered receptor selectivity, conformation, stability and bioavailability in relation to the parent peptides.[6]

In this article we present the structural investigation of a novel class of cyclic opioid peptide prodrugs in which the endogenous opioid pentapeptide Leu-enkephalin has been modified with different carbohydrate moieties in such a way as to ensure resistance to both aminopeptidases and carboxypeptidases. The objective of the structural studies of the carbohydrate-containing bicyclic diastereoisomeric imidazolidinone derivatives **4**−**6** (Figure 1) has been to provide information on the *trans* or *cis* relative geometry of the pentitolyl-residue and the hydroxybenzyl group at the five-membered imidazolidinone ring moiety by using 2D NMR spectroscopy and molecular modeling techniques.

Compounds **4**−**6** are obtained from the corresponding monosaccharide esters of Leu-enkephalin (**1**−**3**) in which either D-glucose, D-galactose or D-mannose is linked through its C-6 hydroxy group to the C-terminal carboxy group of the parent pentapeptide[25] by a spontaneous intramolecular cyclization reaction (Figure 1).[26,27] Two isomers may be formed in the intramolecular reactions. However, the transformation of **3** into the corresponding imidazolidinone compound took place with complete stereoselectivity, resulting in the formation of (2*R*)-**6** in which the pentitolyl residue and hydroxybenzyl group have a *trans* arrangement and C2 of the imidazolidinone ring has the *R* configuration.[27] Consequently, the protons at C2 and C4 have a *trans* relative geometry. The conversion of either **1** or **2** to the corresponding imidazolidinones exhibited a low degree of stereocontrol and resulted in different amounts of *trans* and *cis* isomers. Diastereomers of imidazolidinones **4** and **5**, obtained in a 2.7:1 and 1.3:1 ratio, respectively, were separated by semi-preparative reverse-phase (RP) HPLC and denoted as the major and minor isomers.[26] In the minor isomer of the *galacto*-related imidazolidinone **5** the absolute configuration of the new chiral center at the imidazolidinone moiety was recently established as C2(*S*) on the basis of X-ray crystallography, with a *cis* arrangement of the substituents attached to the C2 and C4 atoms of the imidazolidinone ring moiety[28] and suggesting a *trans* orientation of the same substituents in the major product.

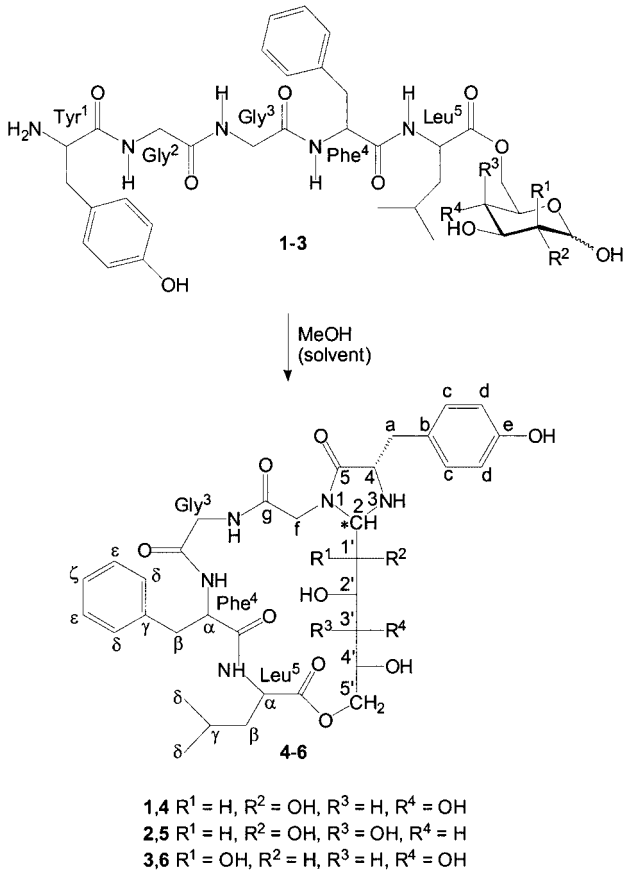

Figure 1. Formation of the bicyclic D-*gluco*- (**4**), D-*galacto*- (**5**) and D-*manno*-related (**6**) imidazolidinones from the corresponding monosaccharide esters of Leu-enkephalin **1**−**3**; an asterisk indicates either an (*R*)- or (*S*)-configuration at the new *N*,*N*′-acetal center

In the present study we elucidate the structures of the major and minor isomers produced from **1**. In addition, our results for the major isomer obtained from **2** corroborate the previous findings for the cyclized model peptides.

Results and Discussion

The ^{1}H and ^{13}C NMR assignments for both the major and the minor isomers of the D-*gluco*-related imidazolidinone **4** in CD_3CN as a solvent were made through a combination of 1D ^{1}H NMR and 2D ^{1}H,^{1}H COSY, ^{1}H,^{1}H TOCSY, ^{1}H,^{13}C HSQC and ^{1}H,^{13}C HMBC experiments; they are summarized in Table 1. The notation of particular atoms is given in Figure 1 and the observed coupling constants are listed in Table 2. In general, the major isomer of compound **4**, as compared to the minor isomer, shows a much better spectral resolution with narrow and sharp peaks in the ^{1}H NMR spectrum, thus allowing many of the coupling constants to be determined. Due to low resolution and peak overlap in the ^{1}H NMR spectrum of the minor isomer, unambiguous coupling constant determination was not possible. The chemical shifts of H2 in the imidazolidinone ring are observed at $\delta = 4.81$ ppm in both isomers, whereas C2 is found at $\delta = 76.0$ and 74.8 ppm in the major

Table 1. NMR chemical shift data (ppm) of the major (*trans*) and the minor (*cis*) isomers of D-*gluco*-related imidazolidinone compounds **4**

Residue	Atom[a]	Major (*trans*) isomer		Minor (*cis*) isomer	
		δ_H	δ_C	δ_H	δ_C
Imidazolidinone ring	CH-2	4.81	76.0	4.81	74.8
	CH-4	4.20	60.6	4.12	59.6
	CO-5		171.7		—[b]
p-Hydroxybenzyl	a/a′	2.92/3.15	35.4	2.93/3.04	37.0
	b		127.8		127.7
	c	7.16	131.4	7.12	132.0
	d	6.78	116.4	6.76	116.0
	e	9.29	157.0	—[b]	156.9
N^1-CH_2	f/f′	3.72/4.24	44.8	3.97/4.14	46.0
CO	g		170.1		—[b]
Sugar moiety	1′	3.73	70.0	3.57	—[b]
	2′	3.86	70.7	4.08	71.0
	3′	3.82	71.8	3.65	70.6
	4′	3.66	71.0	3.77	70.0
	5′/5′′	4.17/4.36	67.5	4.16/4.32	67.2
Gly	NH	7.36		—[b]	
	α/α′	3.72/3.76	43.7	3.61/3.88	42.3
	CO		170.4		—[b]
Phe	NH	6.88		7.25	
	α	4.57	54.4	4.56	55.7
	β/β′	2.94/3.17	38.1	2.95/3.17	38.5
	γ		137.7		138.3
	δ	7.22	130.5	7.29	130.1
	ε	7.29	129.3	7.31	129.3
	ζ	7.23	127.6	7.24	127.5
	CO		172.2		—[b]
Leu	NH	7.12		7.26	
	α	4.19	53.0	4.25	53.0
	β/β′	1.59/1.65	40.0	1.64/1.80	40.0
	γ	1.62	25.1	1.64	25.1
	δ_1	0.90	21.8	0.90	21.5
	δ_2	0.94	22.9	0.94	22.9
	CO		174.4		—[b]

[a] Designations of particular atoms are given in Figure 1. [b] Not assigned.

Table 2. Observed $J_{H,H}$ coupling constants (Hz) in the major (*trans*) and minor (*cis*) isomers of D-*gluco*-related imidazolidinone compounds **4**

Residue	Type[a]	Major (*trans*) isomer	Minor (*cis*) isomer
p-Hydroxybenzyl	$^3J_{\delta\varepsilon}$	8.3	8.3
N^1-CH_2	$^2J_{\alpha\alpha'}$	17.3	
Sugar moiety	$^3J_{2'3'}$	3.2	
	$^3J_{3'4'}$	7.5	
	$^3J_{4'5'}$	4.3	
	$^3J_{4'5''}$	3.2	
	$^2J_{5'5''}$	11.7	
Gly	$^3J_{\alpha NH}$	6.0	4.9
	$^3J_{\alpha' NH}$		6.9
	$^2J_{\alpha\alpha'}$	16.7	17.2
Phe	$^3J_{\alpha NH}$	7.8	
	$^3J_{\delta\varepsilon}$	7.4	
Leu	$^3J_{\alpha NH}$	5.9	
	$^3J_{\gamma\delta}$	5.9	6.1
	$^3J_{\gamma\delta'}$	5.9	6.1

[a] Designations of particular atoms are given in Figure 1.

and the minor isomer, respectively. Specific downfield chemical shifts of the H5′/H5′′ and C5′ atoms from the carbohydrate region confirmed the existence of the ester bond between the C-terminal carboxy group of the peptide and the 5′-hydroxy group of the sugar moiety.

NOESY experiments were performed on both isomers of compound **4** in order to determine the relative arrangement of the substituents at the five-membered ring moiety. Generally, in the *trans* arrangement, the 2- and 4-substituents on the imidazolidinone ring point in opposite directions with respect to the plane defined by the heterocyclic moiety. If free rotation around the C4−Ca bond is allowed, then the H2 proton and protons from the hydroxybenzyl substituent at C4 are expected to be spatially closer in the *trans* arrangement than in the *cis*. A *trans* arrangement of substituents in the isolated *manno*-related imidazolidinone compound (2*R*)-**6** has been determined from the NOE interactions observed between H2 on the imidazolidinone ring and the Hc/Hc′ protons of the hydroxybenzyl substituent at C4 of that ring.[27] No characteristic NOE interactions were observed in the corresponding part of the NOESY spectra in either of the isomers of compound **4**. Furthermore, the effective distances between H2 and H4, averaged according to a r^{-6} relationship from the LD (Langevin Dynamics) simulations, showed $<r>$ = 3.9 Å

and $<r>$ = 3.3 Å for (2*R*)-**4** and (2*S*)-**4**, respectively. Although, such a difference can be determined experimentally from a careful analysis of NOESY spectra, this approach was judged less reliable and another procedure was chosen.

For the *trans*/*cis* assignments of the two diastereoisomeric compounds (2*R*)- and (2*S*)-**4**, a detailed analysis was carried out based on 2D NMR homonuclear scalar coupling techniques (COSY and TOCSY) in order to unravel the relative configuration of the C-atom substituents on the imidazolidinone ring in the major and the minor isomers of **4**. Comparison of the COSY spectra of both isomers of **4** revealed that the distinctive feature of the major isomer is a long-range, four-bond correlation between the H2 and H4 protons of the imidazolidinone ring (Figure 2a). As a result of concentration effects, moderately different chemical shifts of H2, H4 and H1′ protons have been observed in COSY spectra of the major isomer of **4**, compared to those listed in Table 1. In the corresponding spectrum of the minor isomer of **4** there is no observable cross-peak that shows the existence of a long-range H2-H4 coupling, just the three-bond correlation from H2 to H1′ of the pentitolyl residue (Figure 2b). A similar trend was observed in the COSY spectra of both *trans* and *cis* isomers of *galacto*-imidazolidinones **5**, with only the major (*trans*) isomer displaying a long-range H2-H4 correlation (δ_H = 4.81/4.22 ppm). These experiments allow us to conclude that the major isomer of **4** has a *trans* arrangement and the minor isomer a *cis* arrangement of the bulky groups placed at positions 2 and 4 of the imidazolidinone ring. Different long-range, four-bond coupling constants for the *cis*- and *trans*-forms, as a result of a dual-path mechanism between two protons across the heteroatom in five-membered rings, have been reported on several simple compounds of this type.[29−31] Moreover, in addition to COSY experiments further stereochemical differentiation of imidazolidinones is observed in the ^{1}H TOCSY spectra. During the spin-lock period, TOCSY maps of *trans*-**4** (Figure 3) as well as *trans*-**5** (H2, H4, H1′ and Ha/Ha′ at δ = 4.81, 4.22, 3.98 and 2.97/3.15 ppm, respectively) contain strong correlations from H2 to the protons of the pentitolyl spin-system, but also progressively weaker ones to the H4 and Ha/Ha′ protons of the imidazolidinone ring. H2 of *cis*-**4** and *cis*-**5** shows TOCSY correlations only to the protons from the pentitolyl spin-system.

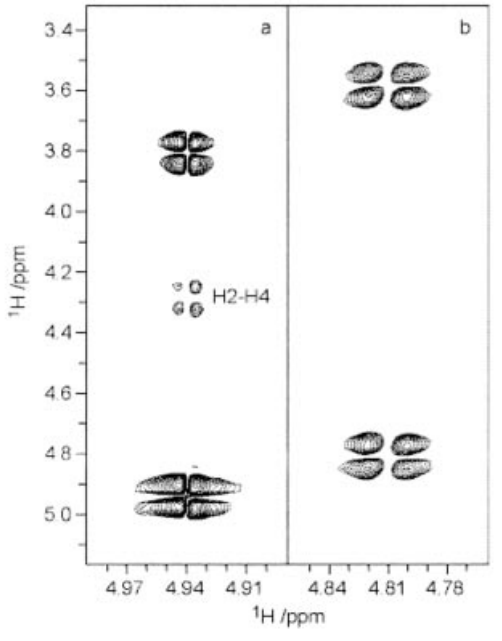

Figure 2. Part of the 400 MHz ^{1}H,^{1}H COSY spectrum of: (a) the (2*R*)-**4** major isomer (*trans* isomer) (36 mM solution) and (b) the (2*S*)-**4** (*cis* isomer) of the bicyclic D-*gluco*-related imidazolidinones in acetonitrile at 25 °C

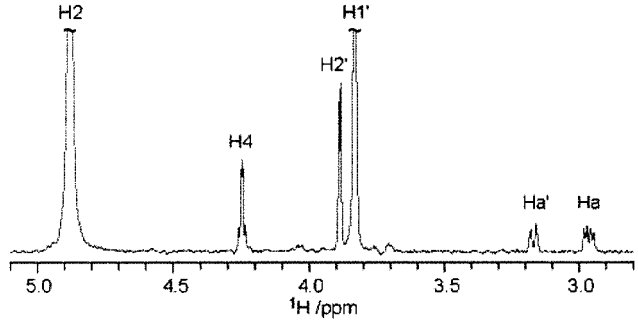

Figure 3. Part of the 1D ^{1}H,^{1}H TOCSY spectrum of (2*R*)-**4** in acetonitrile at 50 °C (36 mM solution) obtained by selective excitation of H2 with a spin-lock period of 120 ms

The stereochemical arrangements were further investigated by density functional theory (DFT) calculations of NMR-observable parameters, namely the ^{1}H and ^{13}C chemical shifts and spin-spin coupling constants. DFT was chosen over the more computationally demanding ab initio methods due to the incorporation of electron correlation effects and its lower computational cost. Previous studies have shown the importance of electron correlation, especially when calculating indirect nuclear spin-spin coupling constants,[32,33] and that accurate predictions cannot be made at the Hartree−Fock self-consistent field level of theory alone. Investigation of the spin-spin couplings involves the interaction between the nuclear magnetic moment and the electrons, which, according to the nonrelativistic description by Ramsey,[34] is a sum of four perturbative operators: the Fermi Contact (FC) and the Spin-Dipolar (SD) operators, which represent the interaction between the magnetic moment arising from the nuclear spin and the electron spin respectively, and the paramagnetic (PSO) and the diamagnetic (DSO) spin-orbit terms, which involve the interaction between the nuclear magnetic moment and the electron current. Studies have been made on the individual importance of these terms on the indirect nuclear spin-spin coupling, with somewhat conflicting conclusions. Although the FC term was unanimously found to be the largest contributing factor, some studies have shown that the other components would cancel each other out and it should therefore be sufficient to only determine the FC element of the Ramsey expression, which we initially did using the Gaussian 98 program suite. However, later calculations of the homonu-

clear ^{1}H-^{1}H coupling constants using the Gaussian 03 program suite showed that the contribution from the non-contact terms cannot be neglected.

Calculations of the magnetic shielding can generate problems in the absence of a complete basis set. Due to the insufficient description of the molecular wave function in the calculations of the magnetic properties, one does not obtain gauge invariance. The most significant effect from this is that the results retrieved may depend on the position of the molecule in the Cartesian coordinate frame. There have been several procedures suggested to work around this problem. One approach is to set up a local gauge origin in order to define the potential vector of the external magnetic field at the atomic center. This spawned a variety of methods, such as the gauge-independent atomic orbital (GIAO) method.

The spin-spin coupling constant has been reported to be sensitive to changes in molecular geometry. For a more accurate description of the spin-spin coupling constant one should compute a coupling surface as a function of a full set of independent nuclear coordinates.[35] In order to reduce the computational effort the structures were limited to the model compounds 3-*N*-methyl-(2*R*,4*S*)-dimethylimidazolidinone and 3-*N*-methyl-(2*S*,4*S*)-dimethylimidazolidinone referred to as (2*R*)-**7** and (2*S*)-**7**, respectively (Figure 4). We probed the coordinate surface for both structures by setting the pseudo torsion angle (θ = H2−C2−C4−H4) to the LD simulated average ($\theta = -158.3°$ in the *trans* case and $\theta = -1.3°$ in the *cis* case, with standard deviations of 12.0° and 6.6°, respectively). Subsequently, we did a small scan in both the positive and negative directions for this torsion. Both the potential energy and $^4J_{H,H}$ were evaluated as a function of conformational changes. Results given by this route further indicated that the *trans* ^{1}H-^{1}H coupling is higher than that of the *cis* configuration. At first glance the ^{1}H-^{1}H coupling difference is too small to distinguish between the two isomers, but, as seen by the energy surface (Figure 5), the *trans* ^{1}H-^{1}H coupling rises even more when averaged out according to the DFT calculations, which give a larger difference between the two isomers. It is worth noting the large negative contribution in the *trans* case for

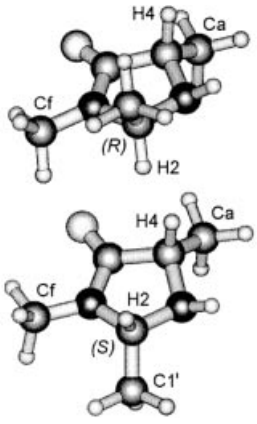

Figure 4. Optimized structures of the imidazolidinone analogues (2*R*)-**7** (*trans* isomer) and (2*S*)-**7** (*cis* isomer)

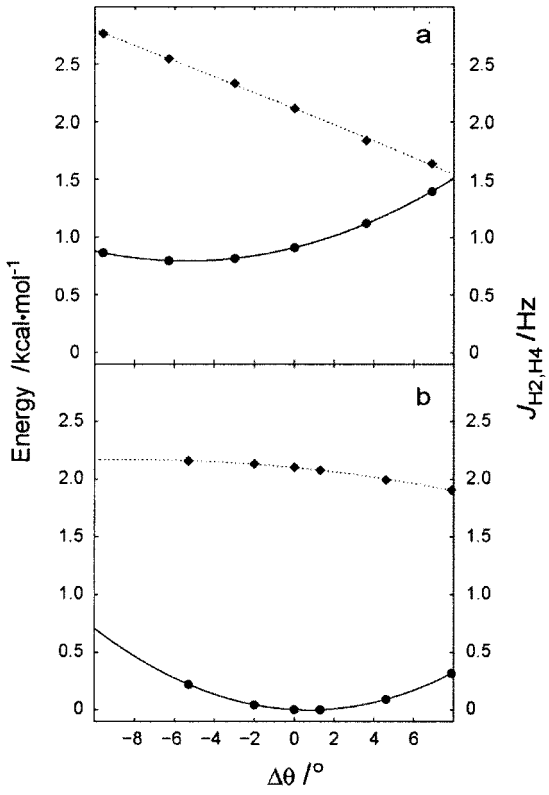

Figure 5. Calculated $^4J_{H,H}$ (black diamond) and relative potential energy (black circle) as a function of deviation ($\Delta\theta$) from the mean pseudo torsion angle (θ = H2−C2−C4−H4) in the LD simulations: (a) (2*R*)-**7** (*trans* isomer) and (b) (2*S*)-**7** (*cis* isomer)

the DSO compared to the *cis* case. We note that previous NMR investigations on imidazolidinones have shown $^4J_{H,H}$(*trans*) ≈ 2 Hz and $^4J_{H,H}$ (*cis*) < 1 Hz.[30]

Further analysis shows that the two isomers can be separated on the basis of their different chemical shielding. Using the C4 atoms as the reference of the chemical shifts the DFT calculations showed C2 at δ = 78.6 and 73.5 ppm in the *R* and *S* isomers, respectively, in agreement with the relative positions from the ^{13}C NMR spectra. Likewise, using H2 as a reference, H4 was calculated to occur at δ = 4.06 and 3.84 ppm in the *R* and *S* isomers, respectively. Interestingly, the relative difference between H2 and H4 is $\Delta(^1H)R$ = 0.75 ppm and $\Delta(^1H)S$ = 0.97 ppm — a smaller chemical-shift difference is present in the former, as in the experimental data. It should also be possible to differentiate

Table 3. Calculated *J* coupling constants (Hz) in (2*R*)-**7** and (2*S*)-**7** — the *trans* and the *cis* isomer, respectively — with contributions from different terms

Isomer	Coupling pair	*J*	FC	SD	PSO	DSO
trans	H2-H4	2.115	2.384	−0.009	1.724	−1.984
	C2-H2	138.690	137.780	−0.164	−0.204	1.279
	C4-H4	122.751	121.302	−0.167	0.351	1.266
cis	H2-H4	2.103	2.049	0.003	−0.528	0.556
	C2-H2	127.871	126.850	−0.194	−0.100	1.315
	C4-H4	120.629	119.166	−0.179	0.375	1.267

between the two isomers based on the $^1J_{C,H}$ coupling constants of C2 and C4 (Table 3).

Conclusions

The stereogenicity of the new chiral centre on the imidazolidinone ring in two diastereomeric bicyclic glucose-enkephalin-related compounds was determined by a combination of NMR spectroscopy and molecular calculations. Knowing the stereochemistry and *trans*/*cis* arrangement of the bulky substituents in such biomolecules is believed to be an important step in understanding the structure-activity relationships in the area of prodrug development.

Experimental Section

Materials: The bicyclic D-*gluco*-pentitolyl-imidazolidinone compounds (2*R*)-**4** (*trans*) and (2*S*)-**4** (*cis*) and the D-*galacto*-pentitolyl-imidazolidinone compound (2*R*)-**5** (*trans*) (Figure 1), were prepared by incubation of the corresponding 6-*O*-(L-tyrosylglycylglycyl-L-phenylalanyl-L-leucyl)-D-glycopyranoses in dry MeOH, according to the reported procedure.[26]

NMR Spectroscopy: NMR experiments were carried out at a concentration of 6 mM in CD_3CN at 25 °C on 400 and 600 MHz Varian Inova spectrometers equipped with 5 mm PFG triple-resonance probes, unless otherwise stated. Assignments of ^1H and ^{13}C resonances were carried out using standard 2D NMR techniques.

Molecular Simulations: Langevin dynamics (LD) simulations used CHARMM[36] (parallel version, C27b4) employing a CHARMM22 type of force field[37] known as PARM22 (Molecular Simulations Inc., San Diego, CA, USA). Each simulation was carried out for 20 ns at 300 K using a collision frequency, γ, of 2 ps^{-1} in order to sample the conformational space more efficiently.[38] The simulations were carried out with the leap-frog algorithm,[39] a dielectric constant of unity, a time step of 1 fs, and data were saved every 0.5 ps for analysis. A heuristic non-bond frequency update was used together with a force-shift cutoff[40] acting to 15 Å. NMR chemical shifts and coupling constants were obtained by DFT calculations on the two isomers of **7** (generated as average structures from the LD simulations).

For the geometry optimization we used the 6-31+G* basis-set, which is a split-valence double-ζ basis set by Pople and co-workers,[41] with added diffuse s- and p-orbitals on all non-hydrogen atoms and an added polarizable function (6 d-type orbitals), as it gives a good prediction of the geometry within a reasonable time frame. For the determination of the magnetic properties we chose a larger contracted triple-ζ basis set,[42] namely 6-311++G(2d,2p), with added diffuse s- and p-functions for all non-hydrogen atoms and diffuse s-functions for all hydrogen atoms, (++), and also added extra polarization functions (2d, 2p). For our model system (Figure 4) this gave a total of 363 contracted Gaussian-type orbitals (GTOs), with a total of 522 primitive Gaussian functions. This basis set was used for the calculations of both the magnetic-shielding tensors and the Fermi Contact (FC) terms with the Gaussian 98 program.[43] Calculations made with the newer Gaussian 03 program[44] used the same level of theory as for the NMR parameters. The DFT method used was the popular hybrid functional by Becke (B3) with the exchange-correlation potential by Lee, Yang and Parr (LYP). This method has shown promising results in previous studies.[45,46] The geometries of (2*R*)-**7** and of (2*S*)-**7** were optimized with the pseudo torsion angle between the two hydrogens frozen to the LD mean angle. For the calculation of the magnetic shielding tensor, the GIAO method was chosen due to its many advantages.[47–49] Calculation of the FC term using Gaussian 98 was done with the Field keyword with a perturbation applied to both the hydrogen and carbon atoms of interest. We used a perturbation of 0.1-times the spin density (i.e., $\lambda = 1000$). For the Gaussian 03 program suite to retrieve the magnetic properties we utilized the NMR=SpinSpin keyword, which gave both the magnetic shielding as well as the indirect nuclear coupling constants in matrix form for all atoms in the molecule as well as the contributing terms. The isotropic magnetic shielding for tetramethylsilane was calculated as $\sigma_C = 182.27$ and $\sigma_H = 31.60$ at the 6-311++G(2d,2p) level of theory.

Acknowledgments

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