ORGANIC LETTERS

2000
Vol. 2, No. 23
3543−3545

Samarium(III)–Propylenediaminetetraacetate Complex: A Water-Soluble Chiral Shift Reagent for Use in High-Field NMR

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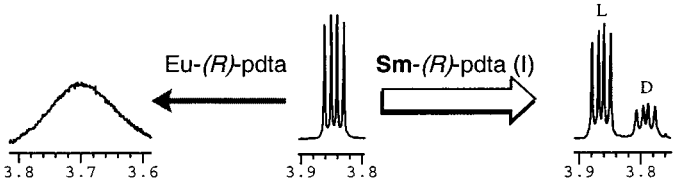
Received July 25, 2000

ABSTRACT



Samarium(III)–(*R*)- or (*S*)-propylenediaminetetraacetate complex resolved the enantiomer signals of α-amino acids on high-field ^{1}H and ^{13}C NMR with remarkably less line broadening than was previously reported for the Eu(III) complex of the same ligand. A widely observed regularity between the absolute configuration of enantiomers and the relative shift of their NMR signals is useful for the assignment of absolute configuration.

Chiral lanthanide shift reagents are known to be useful tools in determining enantiomeric composition[1] and, in limited cases, assigning the absolute configuration of chiral compounds.[2,3] However, these reagents have an inherent drawback in that they cause line broadening,[4] especially when they are used with substrates that have a strong coordinating ability.[5] It tends to be more serious in stronger magnetic fields, thus preventing the use of these reagents on high-resolution apparatus in common use. Despite the experimental value of using these reagents, there have been very few attempts to solve this problem.[5,6] We report here that the samarium(III)−(*R*)- or (*S*)-pdta complex (pdta = propylenediaminetetraacetate) ((*R*)- or (*S*)-**1**) can resolve the enantiomer signals of α-amino acids on a high-field NMR apparatus with less signal broadening[7] than the corresponding europium(III) complex ((*R*)- or (*S*)-**2**).[8]

Complex **2** was reported as a chiral shift reagent for aqueous solutions that can be used to assign the absolute configurations of α-amino acids and α-hydroxy acids.[3] In approximately 30 substrates from each group, a consistent relationship was observed between the relative shifts in the substrates NMR signals and the absolute configurations of their enantiomers. However, even with the predominantly used 90 MHz ^{1}H NMR, complex **2** often causes heavy line

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(6) An attempt to solve this problem by use of a diamagnetic lanthanum complex has been reported: Sato, J.; Jin, H.-Y.; Omata, K.; Kabuto, K.; Sasaki, Y. *Enantiomer* **1999**, *4*, 147−150.

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10.1021/ol006379b CCC: $19.00
Published on Web 10/13/2000

broadening, especially when analyzing amino acids. Attempt to use this reagent for amino acids on a 400 MHz apparatus was hampered by serious line broadening.[9] This urged us to search for reagents that cause less line broadening in higher magnetic fields.

At higher magnetic fields, it is highly possible that the primary source of the line broadening caused by complex with paramagnetic lanthanide shift reagents is an exchange between free and complexed substrates and not an enhancement of paramagnetic relaxation.[10,11] Large chemical shift differences between free and complexed substrates (bound shifts) cause more broadening. Thus, this problem is likely worse at higher magnetic fields. From this point of view, we expected that the samarium ion[12] would show less broadening because it has the smallest magnetic moment of all the paramagnetic lanthanides.[13] It should induce only a small bound shift.[4] We also expected less paramagnetic relaxation enhancement from the smallest magnetic moment of samarium.

Complex **1** was prepared in situ from $SmCl_3$ and (*R*)-pdta and was used without isolation.[14] It did not lose its activity after standing in a stock solution for a month at neutral pH. It did not form hydroxide precipitates at pH values lower than 12. Resolution of the enantiomer signals of α-amino acids were attained at pH 9−11.

As a typical example, the ^{1}H NMR spectrum of asparagine in the presence of **1** is shown in Figure 1 together with a spectrum taken in the presence of **2**. Upon addition of (*R*)-**1**, the H_α signal of the L-isomer shifted downfield, while that of D-isomer shifted upfield to give a clear separation of the enantiomer signals. The enantiomer signals due to H_β's were partially resolved, and their relative positions were opposite to those of the H_α signals.

The usefulness of **1** is also demonstrated by the resolution of signals resulting from the enantiotopic methylene protons of glycine (Figure 2).

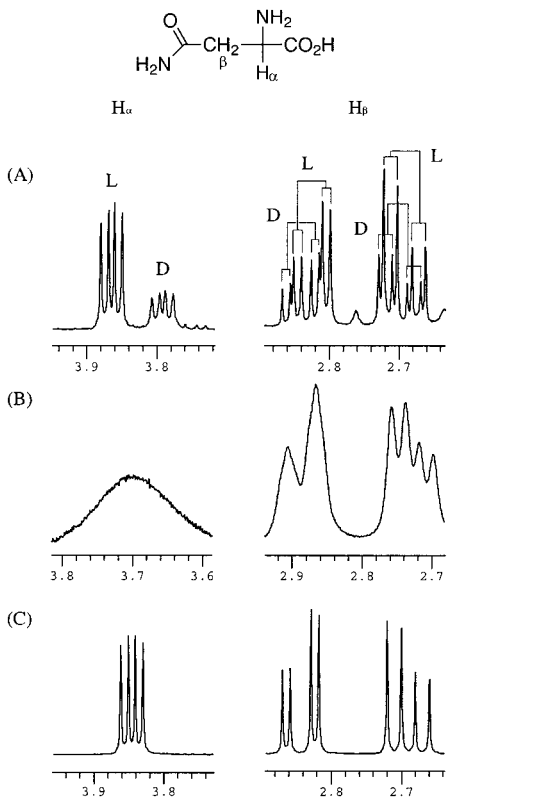

Figure 1. ^{1}H NMR spectra (400 MHz) of 0.06 M asparagine (enantiomer ratio D/L = 1/2) in D_2O at 25 °C: (A) [(*R*)-**1**]/[asparagine] = 0.10, pH 9.3; (B) [(*R*)-**2**]/[asparagine] = 0.02, pH 8.9; (C) no shift reagent, pH 9.3.

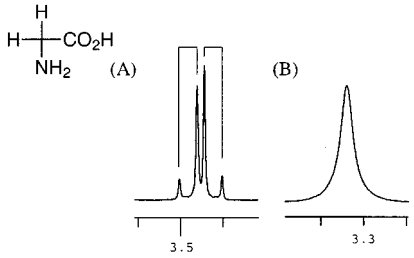

Figure 2. ^{1}H NMR spectra (400 MHz) of 0.06 M glycine in D_2O at 25 °C: (A) [(*R*)-**1**]/[glycine] = 0.20, pH 10.3; (B) [(*R*)-**2**]/[glycine] = 0.02, pH 9.7.

They were resolved by **1** to give a clear AB pattern, while using **2** resulted in broad signals. Table 1 summarizes the signal resolutions of enantiomers and enantiotopic groups within α-amino acids. Owing to the better resolution of 400 MHz ^{1}H NMR and the decline in broadening that occurs when **1** is used, a separation of the enantiomer signals could be observed for a wider range of substrates than were observed when **2** was employed using a low-field apparatus.

As can be seen in Table 1, a good correlation was observed between the location of enantiomer signals and absolute configuration, with very few exceptions. The H_α signals of D-isomers appeared upfield, while the side chains of L-isomer proton signals resonated further upfield than their counterparts. If the H_α and side chain proton signals separate according to this regularity, the spectrum can be used as an easy and reliable assignment of α-amino acids absolute configurations.

(9) Serious line broadening was also observed for other water-soluble chiral shift reagents; see: Hulst, R.; Koen de Vries, N.; Feringa, B. L. *J. Org. Chem.* **1994**, *59*, 7453−7458. Hazama, R.; Umakoshi, K.; Kabuto, C.; Kabuto, K.; Sasaki, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 15−16.

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(11) Bulsing, J. M.; Sanders, J. K. M. *J. Chem. Soc., Chem. Commun.* **1981**, 1201−1202.

(12) There have been no reports on the practical use of samarium chiral shift reagents, though preparation of a reagent was reported; see: Schurig, V. *Tetrahedron Lett.* **1972**, *13*, 3297−3300.

(13) Cotton, S. *Lanthanides and Actinides*; Oxford University Press: New York, 1991; pp 33−34.

(14) **Preparation of 0.36 M D_2O solution of (*R*)-1.** To an aqueous solution of the sodium salt of (*R*)-pdta prepared from (*R*)-H_4 pdta (55 mg, 0.18 mmol) and 0.205 M NaOH (3.5 mL, 0.72 mmol) was added a 0.12 M aqueous solution of $SmCl_3$ (1.5 mL, 0.18 mmol). Water was removed in vacuo, and the resulting residue was dissolved in 0.50 mL of D_2O. An aliquot (5 or 10 μL) was added successively to 0.60 mL of amino acid solution (0.06 M in D_2O, [D]/[L] = 1/2) in an NMR tube, and NMR spectra were determined.

Table 1. Resolution of Enantiomer Signals of α-Amino Acids in the Presence of (*R*)-**1**

entry	substrate	reagent ratio	pH	signal[a]	ΔΔδ (ppm)[b]	high field: H_α	high field: others
1	alanine	0.10	10.5	H_α	0.018	D	
				H_β	−0.007		L
2	valine	0.20	10.2	H_α	0.146	D	
				H_β	−0.015		L
				$H_\gamma{}^l$	0.000		
				$H_\gamma{}^h$	−0.073		L
3	leucine	0.10	10.3	H_α	0.047	D	
4	phenylalanine	0.10	10.0	H_α	0.059	D	
				$H_\beta{}^l$	−0.005		L
				$H_\beta{}^h$	−0.024		L
5	proline	0.10	11.2	H_α	0.022	D	
		0.05	11.1	$H_\delta{}^h$	−0.010		L
6	pipecolic acid	0.10	11.2	H_α	0.010	D	
7	serine	0.05	9.8	H_α	0.007	D	
		0.02	9.8	$H_\beta{}^l$	−0.010		L
				$H_\beta{}^h$	−0.007		L
8	threonine	0.15	9.7	H_α	0.018	D	
				H_β	−0.046		L
				CH_3	−0.055		L
9	methionine	0.20	9.8	H_α	0.081	D	
				H_γ	−0.021		L
				$S\text{-}CH_3$	−0.006		L
10	asparagine	0.20	9.3	H_α	0.072	D	
				$H_\beta{}^l$	−0.016		L
				$H_\beta{}^h$	−0.007		L
11	glutamic acid	0.15	10.0	H_α	0.051	D	
				$H_\beta{}^l$	−0.011		L
				$H_\beta{}^h$	−0.025		L
				H_γ	−0.010		L
12	cysteic acid	0.10	9.4	H_α	0.039	D	
				$H_\beta{}^l$	−0.002		L
				$H_\beta{}^h$	−0.016		L
13	2,3-diamino-propanoic acid	0.10	9.4	H_α	−0.009	L	
				$H_\beta{}^l$	−0.033		L
				$H_\beta{}^h$	−0.020		L
		0.10	7.4	H_α	0.020	D	
				$H_\beta{}^l$	−0.007		L
				$H_\beta{}^h$	−0.007		L
14	lysine	0.20	9.5	H_α	0.115	D	
				H_ϵ	−0.017		L
15	arginine	0.20	9.5	H_α	0.107	D	
				$H_\delta{}^h$	−0.016		L
16	histidine	0.10	10.0	H_α	0.052	D	
				H_β	−0.044		L
				imid-2H	0.013		D
				imid-5H	−0.032		L
17	glycine	0.10	10.2	H_α	0.059[c]		
18	α-aminoiso-butyric acid	0.20	10.4	CH_3	0.028[c]		

[a] Two resolved signals of protons bound to the same carbon are indicated by superscript h and l, which denote higher and lower field, respectively. [b] $\delta_L - \delta_D$ [c] Resolution of signals due to enantiomeric groups.

Complex **1** also resolved the ^{13}C NMR signals of amino acid enantiomers with signal broadening less than that of **2**. To provide an example, the ^{13}C NMR spectra (100 MHz) of proline are shown in Figure 3. A separation in the enantiomer signals of the α-, γ-, and δ-carbons was observed, while the γ- and δ-carbon signals of the L-isomer appeared upfield from their counterparts. Similar results were obtained for leucine, lysine, and methionine. The directions in which the side chain carbon signals separated were the same as those observed for the proton(s) on each carbon. Use of ^{13}C NMR in combination with ^1H NMR must reinforce the reliability of the assignment of absolute configuration through increasing number of probe signals, especially when the assignment of each enantiomer signal is difficult because of heavy overlapping of signals.

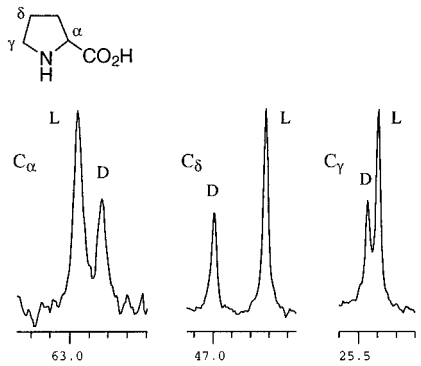

Figure 3. ^{13}C spectra (100 MHz) of 0.06 M proline (enantiomer ratio D/L = 1/2, pH 11.1) in D_2O at 25 °C in the presence of (*R*)-**1**; [(*R*)-**1**]/[proline] = 0.50.

Exceptions to the above observations were observed for the H_α signal of 2,3-diaminopropanoic acid at pH 9.4 (entry 13), and the 2-H and 2-C signals of imidazole from the side chain of histidine.[15] In the former case, the direction of signal separation returned to normal when the measurement was conducted at pH 7.4. Since lowering the pH decreases the number of free 3-amino groups through protonation, this phenomenon strongly indicates that the deviation occurred as a result of the coordination of free 3-amino groups at higher pH values. A similar coordination involving the nitrogen of imidazole might have occurred in the latter case.

In conclusion, the samarium complex **1** is the first water-soluble chiral lanthanide shift reagent to be identified that does not cause serious signal broadening in the strong magnetic fields of high-field NMR. This reagent can be used to assign the absolute configurations of α-amino acids. Further study on the range and limitations of using this reagent is in progress.

Acknowledgment. We thank the Sumitomo Foundation for financial support.

Supporting Information Available: Proton NMR spectra of α-amino acids in the presence of Sm-(*R*)-pdta. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Other proton and carbon signals of the imidazole ring conformed to the rule.