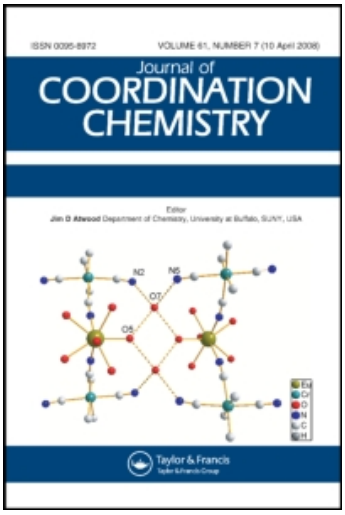

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A NEW CHIRAL SHIFT REAGENT FOR AQUEOUS SOLUTIONS: Eu{(*S*,*S*)-ETHYLENEDIAMINE-*N*,*N*'-DISUCCINATE}, Eu(EDDS)

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The utility of the Eu(III) derivative of (*S*,*S*)-ethylenediamine-*N*,*N*'-disuccinic acid, Eu(EDDS), has been investigated for its use as a chiral aqueous shift reagent. Upfield shifts were observed for the α-protons of (*R*)- and (*S*)-phenylglycine, and an enantiomeric shift difference as large as 0.4 ppm was observed at an Eu(EDDS)/substrate ratio of 0.3. It was deduced from these studies that Eu(EDDS) functions as a superior chiral shift reagent above pH 8.

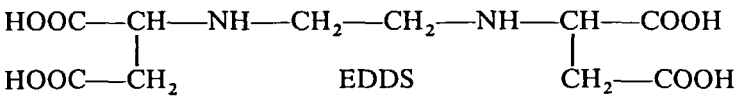
Keywords: Shift reagent, lanthanides n.m.r., *S*,*S*-ethylenediamine-*N*,*N*-disuccinic acid

INTRODUCTION

Chiral lanthanide shift reagents were separately introduced by Whitesides[1] and Goering,[2] and have been widely used since then to resolve enantiomeric resonances in ^{1}H NMR spectroscopy. The majority of studies involving chiral shift reagents are performed in organic media owing to solubility concerns, and relatively few aqueous chiral shift reagents are known. The first approach was that of Reuben, who used a "self-resolution approach to resolve the enantiomeric nuclei of α-hydroxycarboxylic acids by paramagnetic lanthanide ions.[3]

The first genuine aqueous chiral shift reagent was proposed by Peters, who used lanthanide derivatives of (*S*)-carboxymethyloxysuccinic acid (CMOS) to resolve the enantiomeric nuclei of amino acids and (oxy)carboxylic acids.[4] However, it has been shown that this particular ligand system is not a good choice for shift reagent work, due to the self-association tendency associated with lanthanide–CMOS complexes.[5] Subsequently, Kabuto and Sasaki used lanthanide derivatives of (*R*)-propylenediaminetetraacetic acid (PDTA) to resolve enantiomeric nuclei of hydroxy-, amino-, and carboxylic acids in aqueous solution.[6] However, it has been shown that substantial steric interactions exist between coordinated PDTA and substrate ligands when both bind at the inner coordination sphere of a lanthanide ion.[7] In that case any stereochemical information deduced using lanthanide–PDTA complexes would only reflect the nature of a highly perturbed ligand system.

In the present work, we report the suitability of the Eu(III) derivative of (*S,S*)-ethylenediamine-*N,N'*-disuccinic acid (EDDS) as an aqueous chiral shift reagent.



The formation constant of Eu(EDDS) is quite high, with log K equal to 13.54 having been reported.[8] It has been shown that above pH 8, the 1:1 lanthanide–EDDS complexes are monomeric and exhibit no oligomerization tendencies.[9] The three water molecules bound at the inner coordination sphere of the lanthanide ion are replaceable, and the existence of ternary complexes has been demonstrated.[10] These trends are exactly what would be required for a well-behaved chiral shift reagent.

EXPERIMENTAL

(*S,S*)-EDDS was prepared by the condensation of two molecules of (*S*)-aspartic acid with dibromoethane, using the method of Majer *et al.*,[11] as modified by Neal and Rose.[12] It was shown by these workers that under the synthetic conditions used, the EDDS ligand formed with retention of configuration at each asymmetric atom of the aspartic acid precursors. Solutions of Eu(EDDS) in D_2O were prepared by neutralization of sodium deuteroxide solution and addition of one equivalent of $EuCl_3 \cdot 6H_2O$. The ionic strength of the solutions was maintained at 2 M with NaCl. D_2O solutions of (*R*)-, (*S*)-, and (*R,S*)-phenylglycine were prepared by neutralization with one equivalent of sodium deuteroxide solution.

RESULTS AND DISCUSSION

The ^1H NMR spectra of 0.1 M D_2O solutions of (*R*)-, (*S*), and (*R,S*)-phenylglycine in the presence of 0.03 M Eu(EDDS) are shown in Figure 1. Large upfield shifts were observed for the α-proton resonances, with the (*R*)- and (*S*)-isomers being observed at different frequencies. Relatively little change was noted for the aromatic proton resonances. It was further observed that the magnitude of the induced chemical shift ($\Delta\delta$) of the α-protons was greater for the (*R*)-isomer relative to the (*S*)-isomer. The data in Figure 1 (trace c) signify total resolution of the enantiomeric proton resonances in racemic phenylglycine, for which $\Delta\Delta\delta$ equalled 0.4 ppm at an Eu(EDDS)/substrate ratio of 0.3. This is the largest lanthanide induced enantiotropic shift which has been reported for any aminoacid in aqueous solution.

The magnitude of the lanthanide induced shifts was found to increase in a regular fashion with the Eu(EDDS)/substrate ratio, as illustrated in Figure 2. This behaviour is unlike the situation often noted for shift reagents derived from chiral β-diketone ligands, where the magnitude of the induced shifts may exhibit irregular behaviour with increasing reagent concentration.[1,2] Since it has been established that the variable stoichiometry of the β-diketone adduct complexes yields compounds of differing stereochemistries[13,14] (and hence unpredictable $\Delta\Delta\delta$ values), the well-behaved nature of the Eu(EDDS) induced shifts implies the formation of a single type of Eu(EDDS) adduct species. This prediction is in agreement with other spectroscopic work, where it was noted that the chirality of Eu(EDDS) adducts was not dependent on the concentration of substrate used.[10]

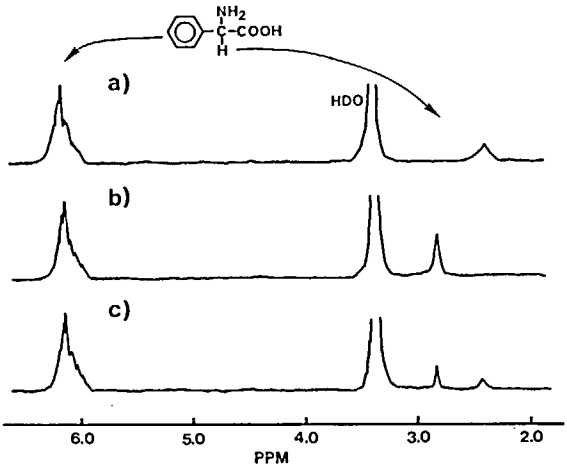


FIGURE 1 90 MHz proton NMR spectra of 0.1 M phenylglycine in the presence of 0.03 M Eu(EDDS). The data were obtained in D_2O solution at room temperature, and were referenced to *t*-butanol. Spectra are shown for (*R*)-phenylglycine (spectrum a, upper trace), (*S*)-phenylglycine (spectrum b, middle trace), and (*R*,*S*)-phenylglycine (spectrum c, bottom trace).

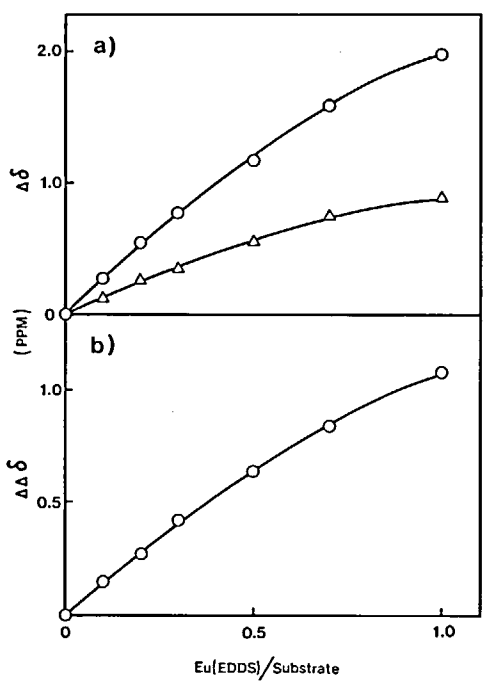


FIGURE 2 a: Dependence of the induced chemical shifts, Δδ, for the α-protons in 0.1 M (*R*)-phenylglycine (circles) and 0.1 M (*S*)-phenylglycine (triangles) as a function of the Eu(EDDS)/substrate ratio; b: Dependence of the enantiomeric shift difference, ΔΔδ, as a function of the Eu(EDDS)/substrate ratio.

At the same time, the degree of line broadening of the α-proton of (*R*)-phenylglycine was found to be greater upon association with Eu(EDDS) than was the broadening of the (*S*)-isomer. For (*R*)-phenylglycine, the addition of one equivalent of Eu(EDDS) led to such line broadening that the position of the α-proton could not be determined.

The Eu(EDDS) system is therefore a superior chiral shift reagent for aqueous work, as long as the solution pH exceeds 8. At these pH values, the Eu(EDDS) species consists of a well-defined, monomeric complex, containing a hexadentate chiral ligand and four bound water molecules.[9] These water molecules are capable of being replaced by substrates of a variety of types, and it has been shown elsewhere that formation of such ternary complexes does not lead to steric interactions between the EDDS and substrate ligands.[10] In that case, stereochemical information obtained from an analysis of the lanthanide induced shifts will not contain errors due to perturbed ligand conformations.

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