SHORT PAPER

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Synthesis of novel 1,10-phenanthroline-2,9-bis-α-amino acid conjugates†

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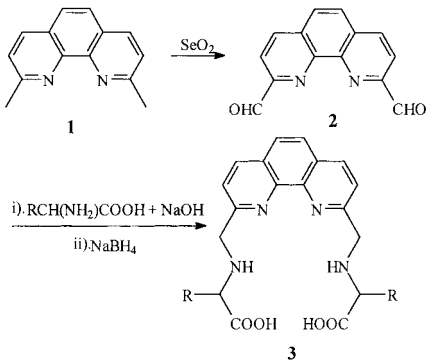
Starting from 2,9-dimethyl-1,10-phenanthroline, the syntheses of eight novel 1,10-phenanthroline-2,9-bis-α-aminoacid conjugates (α-amino acids: DL-Ala, L-Val, L-Phe, L-His, L-Ile, L-Met, L-Glu, L-Asp) are described in detail.

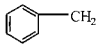
1,10-Phenanthroline is the parent of an important class of chelating agents. It has been extensively used in both analytical and preparative coordination chemistry.[1] Derivatives of 1,10-phenanthroline play an important role in the development of polypyridyl metal complexes, particularly those of Ru(II).[2] Most of the work on phenanthroline derivatives has been prompted by the intense current interest in their catalytic, redox, and photoredox properties, biological activity, and in their novel supramolecular chemistry.[3–11]

Amino acids, the building blocks of proteins, have received much attention in recent studies. As cancer cells disintegrate faster than the other common cells, they need a great deal of nutrition sources such as amino acids. Therefore, the exploitation of antitumor drug based on amino acids is important. On the one hand, the drug selectivity is increased; and on the other hand, toxic side effects are decreased. Some Schiff base derivatives of amino acids and the corresponding complexes display remarkable antibacterial and antitumor activity.[12,13] However, the α-CH_2 of amino acids is more active after the Schiff base derivatives of amino acids or the corresponding complexes are formed. Some reaction, such as an alkylating reaction, a condensation reaction and a Michael additive reaction possibly happens at the α-CH_2 site.[14–16] Thus, the corresponding compounds may be unstable.

For these reasons, we are interested in the design and synthesis of reduced Schiff base ligands, and have prepared eight new 1,10-phenanthroline-2,9-bis-α-aminoacid conjugates. α-Amino acids involve DL-Ala, L-Val, L-Phe, L-His, L-Ile, L-Met, L-Glu and L-Asp. Complexes of these derivatives with rare earth ions are possible as a new type of antitumor agent. Scheme 1 summarises the procedures for this synthesis.



1 2 3

	R	Amino Acids		R	Amino Acids
a	CH_3	DL-Ala	b	CH_3CHCH_3	L-Val
c		L-Phe	d		L-His
e	$CH_3CH_2CHCH_3$	L-Ile	f	$CH_3SCH_2CH_2$	L-Met
g	$HOOCCH_2CH_2$	L-Glu	h	$HOOCCH_2$	L-Asp

Scheme 1

Experimental

Elemental analyses were performed on a Perkin Elmer 240C elemental analyser. IR spectra were obtained as KBr disks on a Nicolet 170 SX FT-IR spectrometer. ^{1}H NMR spectra were recorded with Varian UNITY-plus 400 MHz spectrometer. D_2O was used as a solvent with trace amounts of the reference DSS (3-trimethylsilyl-1-propanesulfonic acid, sodium salt).

The starting material, 2,9-dimethyl-1,10-phenanthroline (**1**), was purchased from Fluka and used as received. Other chemicals used were of analytical reagent grade. 1,10-Phenanthroline-2,9-dicarboxaldehyde (**2**) was prepared by reported procedures.[17,18]

General procedure for syntheses of N,N'-bis-(1-carboxyethyl)-1,10-phenanthroline-2,9-dimethanamine (**3a**), *N,N'-bis-(1-carboxy-2-methylpropyl)-1,10-phenanthroline-2,9-dimethanamine* (**3b**), *N,N'-bis-(1-carboxy-2-phenylethyl)-1,10-phenanthroline-2,9-dimethanamine* (**3c**), *N,N'-bis-[1-carboxy-2-(4-imidazolyl)ethyl]-1,10-phenanthroline-2,9-dimethanamine* (**3d**), *N,N'-bis-(1-carboxy-2-methylbutyl)-1,10-phenanthroline-2,9-dimethanamine* (**3e**), *N,N'-bis-[1-carboxy-3-(methylthio)propyl]-1,10-phenanthroline-2,9-dimethanamine* (**3f**), *N,N'-bis-[1,3-dicarboxypropyl]-1,10-phenanthroline-2,9-dimethanamine* (**3g**), *N,N'-bis-(1,2-dicarboxyethyl)-1,10-phenanthroline-2,9-dimethanamine* (**3h**).

α-Amino acid (10 mmol) and NaOH (10 mmol or 20 mmol for L-aspartic acid and L-glutamic acid, respectively) were dissolved in 25 ml of distilled water, and 1,10-phenanthroline-2,9-dicarboxaldehyde (**2**) (5 mmol) solid was added to the solution in small portions over 2 h. After the solution was stirred for 15h at room temperature, the solution was filtered to remove the residue. At 0°C, $NaBH_4$ (2.5 g) was added to the filtrate in small portions over 1 h. After 24 h stirring at room temperature, concentrated HCl was slowly added to the solution in ice-water bath with stirring until the pH was *ca*. 7.5. The solution was filtered to remove the white solid. The filtrate was concentrated to 15 ml under reduced pressure. Concentrated HCl was slowly added to the solution again until the pH was *ca*. 2.0. Then EtOH (80 ml) was added to the solution. The light yellow solid product was filtered and washed several times with small portions of 95% EtOH. The resulting product was recrystallized and dried.

3a was recrystallized from water/ethanol (1:9), and **3b**, **3c**, **3d**, **3e**, **3f**, **3g** and **3h** were recrystallised from ethyl ether/ methanol (1:4). The corresponding yield and decomposing point for **3a**–**h** are given in Table 1.

The results of elemental analysis for these compounds **3a**–**h** are given in Table 2. The characteristic IR spectral data for **3a**–**h** are given in Table 3. The ^{1}H NMR spectra of **3a**–**h** have been recorded in D_2O and are given in Table 4.

Table 1 Data of yields and decomposing points of **3a–h**

Compounds	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
Yields/%	40	45	35	55	30	50	78	60
Decomposing points/°C	210	178	191	249	174	196	120	184

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 2 Data of elemental analyses of **3a–h**

Compounds	Formula	%Found (%Calc.)		
		%C	%H	%N
3a	$C_{20}H_{22}N_4O_4{\cdot}3.5H_2O$	54.2(53.93)	6.5(6.51)	12.8(12.57)
3b	$C_{24}H_{30}N_4O_4{\cdot}4H_2O$	56.4(56.45)	7.5(7.45)	11.0(10.93)
3c	$C_{32}H_{30}N_4O_4{\cdot}1.5H_2O$	68.2(68.43)	5.7(5.88)	9.8(9.97)
3d	$C_{26}H_{24}N_8O_4{\cdot}4.5H_2O$	52.9(52.61)	5.3(5.56)	18.5(18.87)
3e	$C_{26}H_{34}N_4O_4{\cdot}3H_2O$	59.7(59.98)	7.6(7.69)	10.6(10.76)
3f	$C_{24}H_{30}N_4O_4S_2{\cdot}2H_2O$	53.1(53.51)	5.9(6.32)	10.5(10.40)
3g	$C_{24}H_{26}N_4O_8{\cdot}3H_2O$	52.2(52.17)	6.0(5.80)	10.2(10.14)
3h	$C_{22}H_{22}N_4O_8{\cdot}1.5H_2O$	53.5(53.11)	5.4(5.03)	11.0(11.26)

Table 3 Some characteristic IR spectral data for the compounds **3a–h**

	ν(N–H)/cm^{-1} (vs, br)	ν(phen-ring)/cm^{-1} (s)	ν(C=O)/cm^{-1} (s, br)	ν(C–O)/cm^{-1} (s)
3a	3442	1621, 1459	1719	1317
3b	3416	1617, 1468	1712	1329
3c	3423	1621, 1454	1715	1320
3d	3423	1628, 1502	1720	1330
3e	3423	1621, 1458	1717	1259
3f	3424	1626, 1426	1718	1312
3g	3423	1613, 1446	1725	1313
3h	3442	1617, 1442	1709	1311

Table 4 ^{1}H NMR spectral data (δ/ppm) for the compounds **3a–h**

	$H_{3,8}$	$H_{4,7}$	$H_{5,6}$	-CH_2-	R
3a	7.79(d, 2H)	8.46(d, 2H)	7.88(s, 2H)	4.61(q, 4H)	1.62(d, 6H), 4.00(q, 2H)
3b	7.53(d, 2H)	8.16(d, 2H)	7.63(s, 2H)	4.10(q, 4H)	0.96(d,12H),2.99(d, 2H)1.93(d, 2H)
3c	7.40(d, 2H)	7.98(d, 2H)	7.42(s, 2H)	4.02(q, 4H)	2.91(d, 4H), 3.79(t, 2H) 7.10(d, 2H), 7.13(d, 4H)7.17(d, 4H)
3d	8.17(d, 2H)	8.40(d, 2H)	8.23(s, 2H)	3.82(q, 4H)	2.93(d,4H), 3.11(t, 2H)7.68(s, 2H), 7.78(s, 2H)
3e	7.66(d, 2H)	8.25(d, 2H)	7.67(s, 2H)	4.42(q, 4H)	0.81(t, 6H), 0.86(d, 6H)1.50(h, 4H), 1.66(t, 2H) 3.03(d, 2H)
3f	7.67(d, 2H)	8.30(d, 2H)	7.74(s, 2H)	4.13(q, 4H)	2.01(s, 6H), 1.90(h, 4H) 2.52(t, 4H), 3.27(t, 2H)
3g	7.76(d, 2H)	8.41(d, 2H)	7.87(s, 2H)	4.13(q, 4H)	1.86(h,4H), 2.20(t, 4H) 3.18(t,2H)
3h	7.81(d, 2H)	8.39(d, 2H)	7.83(s, 2H)	4.19(q, 4H)	2.54(d,4H), 3.58(t, 2H)

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