Bull Soc Chim Fr (1997) 134, 487-493

Synthesis of new bis bidentate ligands: catalase activities of the corresponding bis(1,3-diketonato)iron(III) complexes

Christophe Provent, Pierre Chautemps*, Gisèle Gellon, Jean-Louis Pierre

Laboratoire de Chimie Biomimétique, LEDSS (UMR CNRS 5616), Université Joseph Fourier, BP 53, 38041 Grenoble Cedex 9, France

(Received 16 December 1996; accepted 19 March 1997)

Summary — The syntheses of five new tetradentate ligands of bis(1,3-diketonate) type are described. The two diketonate moieties are connected by various long-chain spacers which allow the folding of the ligands for the formation of bis(1,3-diketonato)iron(III) complexes. These complexes exhibit, in the presence of imidazole, a catalytic activity towards the decomposition of hydrogen peroxide (catalase activity).

1,3-diketonato iron(III) complex / catalase activity

Résumé — Synthèse de nouveaux ligands tétradentés β-dicétoniques : activité catalase des complexes de fer (III) correspondants. Cet article décrit la synthèse de cinq nouveaux ligands tétradentés 1,3-dicétoniques. Deux entités pentane-2,4-dione sont reliées entre elles par des espaceurs de longueurs différentes qui autorisent le repliement des ligands et la formation de complexes de fer(III). L'activité catalytique de décomposition du peroxyde d'hydrogène par ces complexes est étudiée.

complexe de fer(III) de type 1,3-dicétonique / activité catalase

Introduction

1,3-diketonato iron(III) complexes are known to catalyse the epoxidation of olefinic compounds by iodosylbenzene [1] or molecular oxygen [2]. When hydrogen peroxide was used, the decomposition of hydrogen peroxide was observed as a major side reaction [3, 4]. The catalytic decomposition of hydrogen peroxide to oxygen and water is an important biological process which is promoted by catalases [5]. These enzymes play an important role in the protection of living organisms against oxidative diseases. Thus, the design of synthetic functional mimics of these enzymes is an interesting challenge for medicinal chemistry. To our knowledge, compounds of the 1,3-diketonato iron(III) type have never been studied with this purpose. In this paper, we describe the syntheses of new bis-(1,3-diketones) designed for the preparation of bis-(1,3-diketonato)iron(III) complexes. These ligands may allow the obtention of complexes in which the coordination sphere of the iron atom is completed by one or two easily exchangeable ligands (water, solvent, non-coordinating counter anion) to preserve the feasibility of catalytic reactions (fig 1). The iron(III) complexes and their 'catalase-like' activities are also presented in this paper.

* Correspondence and reprints

Results and discussion

The syntheses have been performed according to the retrosynthetic pathway depicted in figure 1.

Preparation of the ligands

The spacers incorporating the subunits Z_1 and Z_2 are the commercial ω,ω'-diacids with twelve- and sixteen-carbon linear chains respectively. The spacer incorporating Z_3 (eleven-carbon chain ω,ω'-diacid with a central carbonyl group) has been prepared according to Durham et al [6]. The spacers derivated from Z_4 and Z_5 have been described previously by us [7]. The synthon 3-(3-aminophenyl)pentane-2,4-dione has been prepared according to the synthetic pathway depicted on figure 2.

The nitro derivative **2** has been prepared according to Dell'Erba et al [8]. The critical step of the synthesis is the reduction of the nitro group into the amino group in the presence of the β-diketone subunit. As a matter of fact, the usual processes used for the reduction of nitro groups (catalytic hydrogenation with Pd/C, PtO_2, ...) are not selective. Stannous chloride is known to allow the reduction of nitro groups in the presence of carbonyl groups [9]. Nevertheless, the usual procedure ($SnCl_2$/HCl) applied to **2** gives only **4**, resulting from a hydro-deacetylation process. A modified procedure [10]

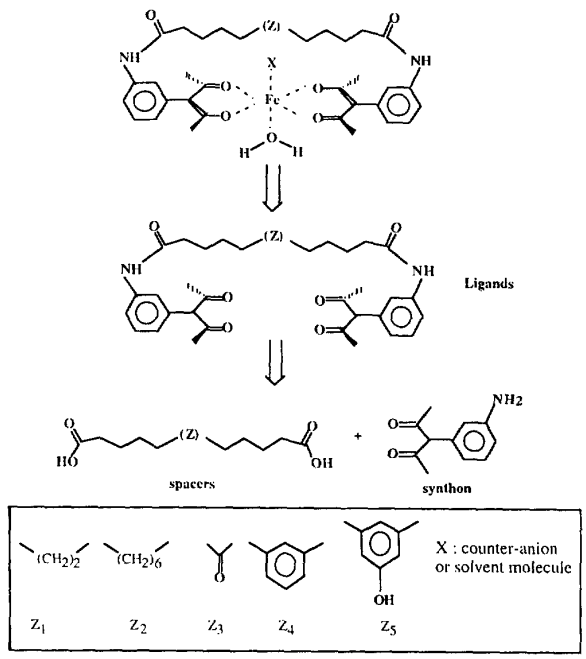

Fig 1. Targeted iron complexes and retrosynthetic pathway.

($SnCl_2$/EtOH) allows the obtention of **3** with a 87% yield. The reaction has to be carefully monitored by TLC to stop the reaction before the formation of **4**. Even under an inert atmosphere, **3** decomposes easily and it should be used immediately after its isolation.

The preparations of the ligands $\mathbf{Ac}_{1-4}$ from the synthon **3** and the spacers with Z_{1-4} subunits are depicted in figure 3. The two acidic groups of the spacers are activated by 2-mercaptothiazol-2-ine in CH_2Cl_2 in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and with a catalytic amount of 4-(dimethylamino)pyridine (DMAP) [11, 12]. The thiazolidine-2-thione derivatives of the spacers have been isolated and characterized. These compounds are condensed with two equivalents of the synthon, leading to the ligands $\mathbf{Ac}_{1-4}$.

The preparation of $\mathbf{Ac}_5$ requires the protection of the phenolic group, hence the starting material **5** (previously described [7]) has been used. The condensation of the synthon with the diacid bearing a methoxymethyl ether-protected group is realized via the thiazolidine-2-thione derivative as previously described for $\mathbf{Ac}_{1-4}$. The removing of the methoxymethyl protecting group should be run carefully to avoid the cleavage of the β-diketone moiety (see Experimental section). The preparation of $\mathbf{Ac}_5$ is depicted in figure 4. $\mathbf{Ac}_{1-5}$ are new compounds and the analytical data are given in the Experimental section.

The iron(III) complexes

The complexes are obtained by slow addition at room temperature of a methanolic solution of $Fe(NO_3)_3$, $9H_2O$ to a solution of the ligand in CH_2Cl_2. The solid purple complexes are identified and characterized from FAB^+ mass spectra, UV-visible and EPR spectra and microanalysis.

The main features of mass spectra are summarized in table I. Besides the fragments corresponding to the iron(III) complex, the mass spectra reveal peaks which are attributed to iron(II) species. This observation is explained from redox processes implying the oxidation of the nitrobenzyl alcohol matrix by iron(III) [13]. Only mononuclear species with 1/1 stoichiometry are detected.

The 1/1 stoichiometry is unambiguously established from UV-visible spectroscopy. The ligand metal charge transfer transition 1,3-diketonate-to-iron (LMCT transition) which is observed in the range 430–500 nm [14] (see table I) is monitored in CH_2Cl_2 during the progressive addition of $FeCl_3$ to a solution of the ligand. For example, this titration is depicted in figure 5 for $\mathbf{Ac}_2$ and $\mathbf{Ac}_4$. The complexation is notably slower with this latter ligand, the 1/1 stoichiometry requiring around 15 minutes to be achieved. This is clearly shown on the graph (fig 5) where a couple of absorption values is given for every ratio [Fe]/[$\mathbf{Ac}_4$] at $t = 0$ (complete addition of the Fe III salt) and 15 minutes later. The more rigid spacer may be the cause of the slower formation of the complex.

EPR spectra in frozen methanol (100 K) are characteristic of mononuclear hexacoordinated high-spin iron(III) complexes with a signal at $g = 4.3$, but in the absence of crystal structure, no pertinent data can actually support the planar arrangement of the four β-diketonato oxygen atoms. The typical spectrum of $\mathbf{FeAc}_1$ is given in figure 6.

$\mathbf{FeAc}_5$: the ligand bearing a phenolic subunit in the spacer had been designed with the aim of an apical ligation of the phenolate group in the complex. Unfortunately, this has not been realized: a LMCT transition phenolate-to-iron is not detected and the ν_{OH} vibration of the phenol, observed in the free ligand, is still observed in the complex. A possible non-planar arrangement of the two β-diketonato moities in the complex could explain the observed lack of coordination. The addition of triethylamine during complexation or on the formed

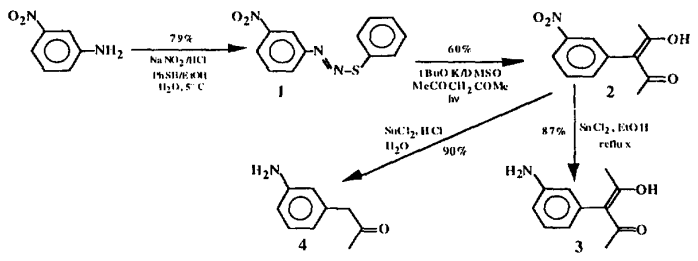

Fig 2. Preparation of 3-(3-aminophenyl)pentane-2,4-dione.

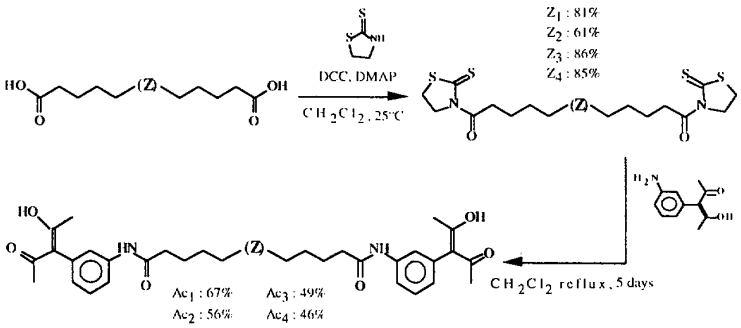

Fig 3. Preparation of the ligands $\mathbf{Ac_{1-4}}$.

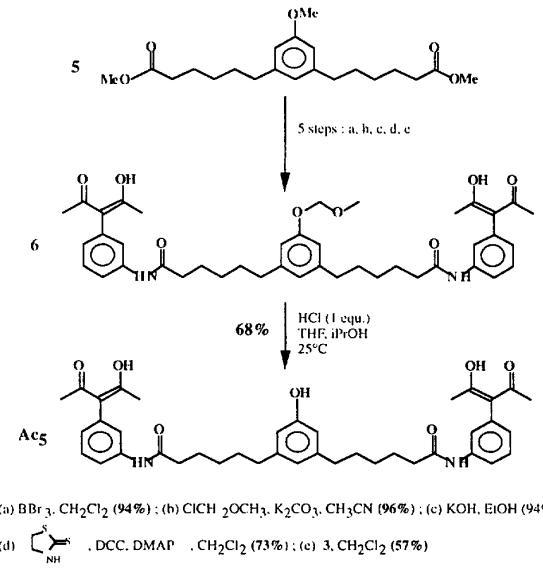

Fig 4. Preparation of $\mathbf{Ac_5}$.

Table I. Physicochemical data for the complexes and the free ligands.

Complex	*FAB + MS (m/e)*	*LMTC band (nm)* (ε: M^{-1} cm^{-1}; *in* CH_3OH)
$\mathbf{FeAc_1}$	631 $[Fe(II)\ L + 1]^+$ 630 $[Fe(III)\ L]^+$ 577 $[LH_2 + 1]^+$	480 (2 540)
$\mathbf{FeAc_2}$	687 $[Fe(II)\ L + 1]^+$ 686 $[Fe(III)\ L]^+$ 633 $[LH_2 + 1]^+$	448* (2 500)
$\mathbf{FeAc_3}$	631 $[Fe(II)\ L + 1]^+$ 630 $[Fe(III)\ L]^+$ 577 $[LH_2 + 1]^+$	447* (2 500)
$\mathbf{FeAc_4}$	707 $[Fe(II)\ L + 1]^+$ 706 $[Fe(III)\ L]^+$ 653 $[LH_2 + 1]^+$	480 (2 700)
$\mathbf{FeAc_5}$	723 $[Fe(II)\ L + 1]^+$ 722 $[Fe(III)\ L]^+$ 669 $[LH_2 + 1]^+$	486 (2 490)

* Chloride counter-anion in CH_2Cl_2.

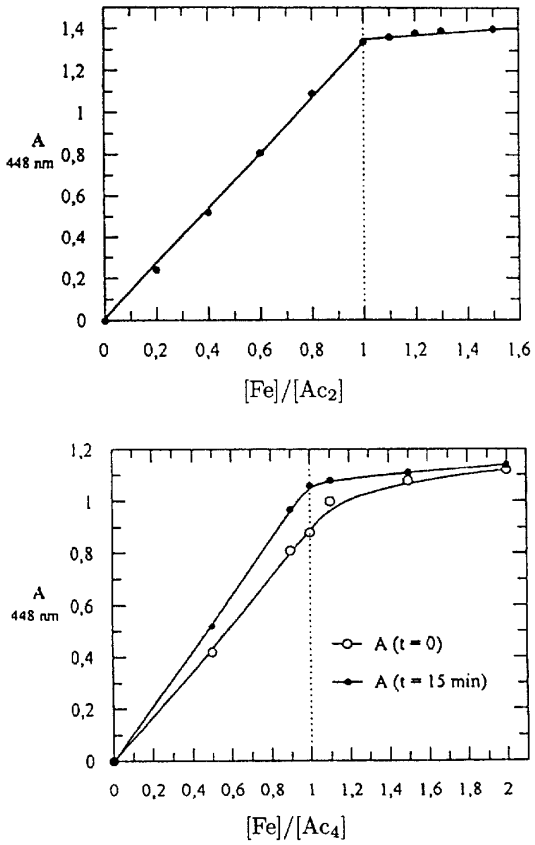

Fig 5. Titration of 5×10^{-4} M solutions of $\mathbf{Ac_2}$ and $\mathbf{Ac_4}$ by $FeCl_3$ in CH_2Cl_2 at 20 °C.

complex does not induce noticeable modification of the spectral data (it has to be emphasized that the use of more than one equivalent of triethylamine during the formation of the complexes leads to polynuclear species for all the ligands studied herein).

Catalase activities

Almost all of the assays described in literature imply generalized acido-basic catalysis. Imidazole plays a major role in the catalytic decomposition of hydrogen peroxide. This is true for the enzyme as well as for syn-

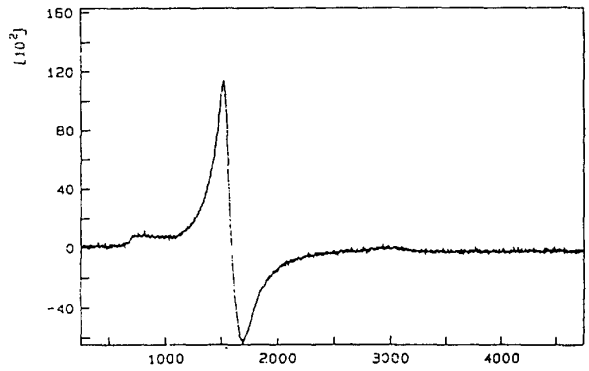

Fig 6. EPR spectrum (100 K) of **FeAc$_1$** in methanol (9×10^{-3} M).

thetic models [15–17]. We have used the assay described in the literature [16] and examined the role of variable amounts of imidazole. The results are summarized in table II. The assays have been realized in ethanol and except for **Ac$_3$** only nitrate salts have been used (nitrate is a more easily exchangeable ligand and will favor catalytic reactions). Blank experiments using: i) iron(III) nitrate with or without imidazole, ii) synthon-3 with iron(III) nitrate, have been done under the same conditions and in both cases no noticeable catalase activity has been observed.

The catalase activities of our complexes are noticeable but less than those observed with porphyrinic models. Our results evidence the role of imidazole: its presence is necessary to induce the catalase activity, probably due to the 'distal effect' [16].

Unfortunately, the phenolic group in **FeAc$_5$** is not a proximal ligand for the iron atom and in the absence of imidazole, the catalase activities are very poor.

This fact confirms that an apical group (histidine, imidazole or phenol) *trans* to the peroxide is required in the first steps of the hydrogen peroxide dismutation by iron complexes.

Conclusion

We have described the syntheses of several bis(1,3-diketonato) iron(III) complexes. The catalytic activities of these complexes in the presence of imidazole have been observed, but this activity is lower than for porphyrinic catalase-mimics. The new free ligands described herein may serve for the preparation of interesting complexes with metals other than iron. For instance, copper(II) complexes are actually studied in our laboratory. Further studies are also in progress concerning the catalytic activities of the complexes in epoxidation reactions.

Experimental section

Materials and equipment

^{1}H and ^{13}C NMR spectra were recorded on a Bruker A C 200 using a 5 mm probe at 25 °C. Chemical shifts are given in δ values (ppm) downfield from internal TMS. EI (70 eV) and FAB$^+$ (nitrobenzyl alcohol) mass spectra were collected by using a Nermag R1010 C. Melting points (Mp) were determined on a Buchi 530 apparatus and are uncorrected. Elemental analyses were performed by the CNRS microanalysis laboratory of

Table II. Catalase assays.

Complex (2×10^{-6} *mole in* V_{tot} = 10 mL)	*[Im]/[com]*[a]	*Volume O_2 (mL)*[b]		*Turnover number*[c]		*Yield*[d]	
		5 min	*15 min*	*5 min*	*15 min*	*5 min*	*15 min*
FeAc$_1$·NO_3 (ethanol)	–[e]	0	0	0	0	0%	0%
	25	0.40	0.50	18	22	4%	5%
	100	0.60	0.70	27	31	6%	7%
	200	0.60	0.70	27	31	6%	7%
FeAc$_2$·NO_3 (ethanol)	–[e]	0	0	0	0	0%	0%
	25	0.40	0.40	18	18	4%	4%
	100	0.40	0.40	18	18	4%	4%
	200	0.35	0.40	16	18	3.5%	4%
FeAc$_3$·Cl^- (acetone)	–[e]	0	0	0	0	0%	0%
	25	0.70	1.00	31	45	7%	10%
	100	0.80	0.95	36	42	8%	9.5%
FeAc$_4$·NO_3 (ethanol)	–[e]	0	0	0	0	0%	0%
	25	0.30	0.35	13	16	3%	3.5%
	100	0.70	0.75	31	33	7%	7.5%
	200	0.50	0.60	22	27	5%	6%
FeAc$_5$·NO_3 (ethanol)	–[e]	0	0.10	0	4	0%	1%
	25	0.60	0.90	27	40	6%	9%
	100	0.70	0.90	31	40	7%	9%
	200	0.70	1.00	31	44	7%	10%

[a] Number of equivalent of imidazole. [b] Measured in a 10 mL burette (graduation: 1/20 mL). [c] Number of O_2 moles produced per mole of catalyst. [d] Referred to the initial amount of H_2O_2 (9×10^{-4} mol). [e] Without imidazole.

Vernaison (France). Electronic spectra were recorded on a Perkin-Elmer lambda 2 spectrometer. EPR spectra were recorded at 100 K on a Varian E112 working at 9.46 Hz with 2,2-diphenyl-1-picrylhydrazyl (DPPH) as an external calibrant.

• *Preparation of synthon* **3**

Compounds **1** and **2** were prepared according to the literature [8] and references cited there.

■ *3-(3-Aminophenyl)pentane-2,4-dione.* M: 191 g mol^{-1} (**3**). A mixture of 3-(3-nitrophenyl)pentane-2,4-dione (4.5 g; 20.3 mmol) and $SnCl_2,2H_2O$ (22 g, 0.1 mol) in EtOH (150 mL) was vigorously stirred at 70 °C for 1.5 h, then poured into ice and adjusted to pH 8–9 with $NaHCO_3$. Extraction with AcOEt gave **3** as a yellow white solid (3.4 g, 87%).

TLC (SiO_2; 7 CH_2Cl_2/3 ethyl acetate): R_f = 0.74.

Mp = 59–60 °C.

IR (cm^{-1}): 3 430, 3 343, 3 236 (ν_{NH_2}), 3 017 (ν_{CHar}), 2 920–2 966 (ν_{CH}), 1 650–1 400 ($\nu_{C=O}$).

^1H NMR (200 MHz, $CDCl_3$) ppm: 1.91 (6H, s, CH_3), 3.75 (2H, NH_2), 6.48–6.68 (3H, m, CHar), 7.11–7.20 (1H, m, CHar), 16.65 (1H, s, C=C(CH_3)OH).

^{13}C NMR (50 MHz, $CDCl_3$) ppm: 24.0 (CH_3), 114.1, 117.5, 121.2, 129.6 (CHar), 115.2 (Ar-C=C), 137.9 (Car-C), 146.7 (Car-NH_2), 190.8 (C=O).

Diacid spacers have been previously described by us [7] and were used as their bisthiazolidine derivatives $\mathbf{Z_1}$ to $\mathbf{Z_4}$.

• *Preparation of bisthiazolidine derivatives of diacid spacers*

To a solution of 10 mmol of the appropriate diacid and 2.5 g (21 mmol) of 2-mercapto-2-thiazoline in 50 mL of cooled CH_2Cl_2 (0–5 °C) was added a solution of 4.2 g (20.4 mmol) of dicyclohexylcarbodiimide and 100 mg of DMAP in CH_2Cl_2 (50 mL). The resulting solution was stirred for 18 h at room temperature. A white precipitate was filtered out and evaporation of the filtrate gave the compounds $\mathbf{Z_1}$ to $\mathbf{Z_4}$ as yellow powders (yields from 60 to 85%).

■ *Decane-1,10-dicarbonyl-3,3'-bisthiazolidine-2-thione.* M: 432.70 g mol^{-1} ($\mathbf{Z_1}$).

Mp = 102.5 °C; yield: 81%.

IR (cm^{-1}): 2 916–2 849 (ν_{CH}), 1 706 ($\nu_{C=O}$), 1 032 ($\nu_{C=S}$).

^1H NMR (200 MHz, $CDCl_3$) ppm: 1.28 (12H, m, 6 CH_2), 1.67 (4H, m, CH_2: β from CON), 3.23 (4H, t, J = 7.4 Hz, CH_2: α from CON), 3.28 (4H, t, J = 7.5 Hz, CH_2 thiazolidinethione), 4.57 (4H, t, J = 7.5 Hz, CH_2 thiazolidinethione).

^{13}C NMR (50 MHz, $CDCl_3$) ppm: 24.7, 28.2, 29.0, 29.3 (CH_2), 38.4 (CH_2-S), 56.0 (CH_2-N), 174.9 (CON), 200.5 (C=S).

MS (FAB$^+$, NBA): m/z = 433; m/z = 314 (M − thiazolidinethione).

■ *Tetradecane-1,14-dicarbonyl-3,3'-bisthiazolidine-2-thione.* M: 488.8 g mol^{-1} ($\mathbf{Z_2}$).

TLC (SiO_2; CH_2Cl_2): R_f = 0.59.

Mp = 110 °C.

IR (cm^{-1}): 2 916–2 848 (ν_{CH}), 1 706 ($\nu_{C=O}$), 1 035 ($\nu_{C=S}$).

^1H NMR (200 MHz, $CDCl_3$) ppm: 1.17–1.50 (20H, m, 10 CH_2), 1.60–1.75 (4H, m, CH_2: β from CON), 3.23 (4H, t, J = 7.4 Hz, CH_2: α from CON), 3.28 (4H, t, J = 7.55 Hz, CH_2 thiazolidinethione), 4.58 (4H, t, J = 7.55 Hz, CH_2 thiazolidinethione).

^{13}C NMR (50 MHz, $CDCl_3$) ppm: 24.7, 28.2, 29.0, 29.3, 29.4, 29.6 (CH_2), 38.4 (CH_2-S), 56.0 (CH_2-N), 174.9 (CON), 201.4 (C=S).

MS (DCI, NH_3^+ isobutane): m/z = 489; m/z = 370 (M − thiazolidinethione); m/z = 120 (thiazolidinethione + 1).

■ *5-Oxononane-1,9-dicarbonyl-3,3'-bisthiazolidine-2-thione.* M: 432 g mol^{-1} ($\mathbf{Z_3}$).

TLC (SiO_2; 8 CH_2Cl_2/2 ethyl acetate): R_f = 0.84.

Mp = 85 °C.

IR (cm^{-1}): 2936–2850 (ν_{CH}), 1 708 ($\nu_{C=O}$), 1 693 ($\nu_{C=O}$ ketone), 1 052 ($\nu_{C=S}$).

^1H NMR (200 MHz, $CDCl_3$) ppm: 1.60–1.70 (8H, m, 4 CH_2), 2.43 (4H, t, J = 6.7 Hz, CH_2: α from CO), 3.20–3.35 (8H, m, CH_2: α from CON and CH_2 thiazolidinethione), 4.57 (4H, t, J = 7.5 Hz, CH_2 thiazolidinethione).

^{13}C NMR (50 MHz, $CDCl_3$) ppm: 22.9, 24.2, 28.3 (CH_2: α from CON), 38.2 (CH_2: α from S), 42.3 (CH_2: α from CO), 56.0 (CH_2: α from N), 174.4 (CONH), 201.6 (C=S), 210.2 (C=O).

MS (DCI, NH_3^+ isobutane): m/z = 433; m/z = 314 (M − thiazolidinethione); m/z = 195 (M − 2 thiazolidinethione − 1); m/z = 120 (thiazolidinethione + 1).

■ *1,3-Bis[5-oxo-5-(2-thioxothiazolidin-3-yl)pentyl]-benzene.* M: 508.8 g mol^{-1} ($\mathbf{Z_4}$).

TLC (SiO_2; 95 CH_2Cl_2/5 ethyl acetate): R_f = 0.91.

Mp = 61–62 °C.

IR (cm^{-1}): 3 020 (ν_{CHar}), 2 941–2 848 (ν_{CH}), 1 705 ($\nu_{C=O}$), 1 051 ($\nu_{C=S}$).

^1H NMR (250 MHz, $CDCl_3$) ppm: 1.30–1.42 (4H, m, CH_2: γ from Ar), 1.60–1.78 (8H, m, CH_2: β from CON and Ar), 2.59 (4H, t, J = 7.6 Hz, CH_2: α from Ar), 3.24 (4H, t, J = 7.6 Hz, CH_2: α from CON), 3.27 (4H, t, J = 7.5 Hz, CH_2 on thiazolidinethione), 4.57 (4H, t, J = 7.5 Hz, CH_2 on thiazolidinethione), 6.97–7.00 (3H, m, CHar), 7.18–7.35 (1H, m, CHar).

^{13}C NMR (62.5 MHz, $CDCl_3$) ppm: 24.6, 28.3, 28.7, 31.2, 35.7 (CH_2), 38.4 (CH_2-S), 56.0 (CH_2-N), 125.7 , 127.9, 128.5 (CHar), 142.4 (Car-CH_2), 174.8 (CON), 201.4 (C=S).

MS (EI): m/z = 508; m/z = 389 (M − thiazolidinethione); m/z = 270 (M − 2 thiazolidinethione); m/z = 119 (thiazolidinethione).

• *Condensation of* **Z** *compounds with 3-(3-aminophenyl)pentane-2,4-dione*

■ *N,N'-Bis[3-(2,4-dioxopentan-3-yl)phenyl]dodecanediamide.* M: 576 g mol^{-1} ($\mathbf{Ac_1}$). To a solution of 310 mg of 3-(3-aminophenyl)pentane-2,4-dione (1.62 mmol) in CH_2Cl_2 was added 340 mg of $\mathbf{Z_1}$ (0.8 mmol) in CH_2Cl_2 (15 mL). The solution was refluxed for 5 days (TLC monitoring). After evaporation of the solvent and purification on a silica gel column, 305 mg (67%) of $\mathbf{Ac_1}$ was obtained as a beige solid.

TLC (SiO_2; 8 CH_2Cl_2/2 ethyl acetate): R_f = 0.63.

Mp = 144 °C.

IR (cm^{-1}) 3 300 (ν_{NH}), 3 400–3 100 (ν_{OH}), 3 090 (ν_{CHar}), 2 928–2 852 (ν_{CH}), 1 669–1 588 ($\nu_{C=O}$).

^1H NMR (200 MHz, $CDCl_3$) ppm: 1.27–1.45 (12H, m, 6 CH_2), 1.65–1.82 (4H, m, CH_2: β from CONH), 1.90 (12H, s, CH_3), 2.36 (4H, t, CH_2: α from CONH), 6.91 (2H, d, J = 7.4 Hz, 2 CHar), 7.27–7.52 (8H, m, 6 CHar and 2 CONH), 16.70 (2H, s, C=C(CH_3)OH).

^{13}C NMR (50 MHz, $CDCl_3$) ppm: 24.1, 29.1 (CH_2), 25.4 (CH_3), 37.7 (CH_2: α from CONH), 114.9 (Ar-C), 118.8, 122.3, 126.8, 129.4 (CHar), 137.7, 138.4 (Car-C and Car-NH), 171.5 (CONH), 190.9 (C=O).

MS (FAB$^+$): m/z = 577; (FAB$^-$): m/z = 575.

Elemental analysis: calc for $C_{34}H_{44}N_2O_6$: C = 70.81%, H = 7.69%, N = 4.86%; found: C = 70.60%, H = 7.65%, N = 4.84%.

According to the same procedure, were also obtained:

■ *N,N'-Bis[3-(2,4-dioxopentan-3-yl)phenyl]hexadecanediamide.* M: 633 g mol^{-1} (**Ac$_2$**).

TLC (SiO_2; 8 CH_2Cl_2/2 ethyl acetate): R_f = 0.80; yield = 56%.

Mp = 125 °C.

IR (cm^{-1}): 3 300 (ν_{NH}), 3 350–3100 (ν_{OH}), 3 050 (ν_{CHar}), 2 920–2 850 (ν_{CH}), 1 660 ($\nu_{C=O}$).

^{1}H NMR (200 MHz, $CDCl_3$) ppm: 1.22–1.50 (20H, m, 10 CH_2), 1.65–1.87 (4H, m, CH_2: β from CONH), 1.93 (12H, s, CH_3), 2.40 (4H, t, CH_2: α from CONH), 6.94 (2H, d, J = 7.5 Hz, 2 CHar), 7.28–7.55 (8H, m, 6 CHar and 2 CONH), 16.60 (2H, s, C=C(CH$_3$)OH).

^{13}C NMR (50 MHz, $CDCl_3$) ppm: 24.2 (CH_3), 25.5, 29.3, 29.5 (CH_2), 37.8 (CH_2: α from CONH), 114.9 (Ar–C), 118.8, 122.3, 126.9, 129.4 (CHar), 137.8, 138.4 (Car–C and Car–NH), 171.5 (CONH), 190.9 (C=O).

MS (DCI, NH_3^+ isobutane): m/z = 634 (M + 1); m/z = 592 (M – $COCH_3$ + 2); m/z = 549 (M – 2$COCH_3$ + 2).

Elemental analysis: calc for $C_{38}H_{52}N_2O_6$: C = 72.12%, H = 8.28%, N = 4.43%; found: C = 72.01%, H = 8.19%, N = 4.32%.

■ *N,N'-Bis[3-(2,4-dioxopentan-3-yl)phenyl]-6-oxoundecanediamide.* M: 576.7 g mol^{-1} (**Ac$_3$**).

TLC (SiO_2; 8 CH_2Cl_2/2 ethyl acetate): R_f = 0.09; yield = 49%.

Mp = 129 °C.

IR (cm^{-1}): 3 302 (ν_{NH}), 3 500–3 100 (ν_{OH}), 3 088 (ν_{CHar}), 2 940–2 870 (ν_{CH}), 1 702–1 673 ($\nu_{C=O}$).

^{1}H NMR (200 MHz, $CDCl_3$) ppm: 1.55–1.83 (8H, m, CH_2: β from C=O and CONH), 1.89 (12H, s, CH_3), 2.35–2.60 (8H, m, CH_2: α from C=O and CONH), 6.90 (2H, d, J = 7.5 Hz, CHar), 7.31 (2H, t, CHar), 7.45 (2H, s, CHar), 7.56 (2H, d, J = 8 Hz, CHar), 8.47 (2H, s, CONH), 16.20 (2H, s, C=C(CH$_3$)OH).

^{13}C NMR (50 MHz, $CDCl_3$) ppm: 23.0 and 24.7 (CH_2: β from C=O and CONH), 24.0 (CH_3), 37.0 (CH_2: α from CONH), 42.1 (CH_2: α from C=O), 114.8 (Ar–C), 118.7, 122.2, 126.5, 129.2 (CHar), 137.2, 138.6 (Car–C), 171.4 (CONH), 190.8 (C=O).

MS (DCI, NH_3^+ isobutane): m/z = 578 (M + 1); m/z = 536 (M – $COCH_3$ + 2).

Elemental analysis: calc for $C_{33}H_{40}N_2O_7$, 1/2H_2O: C = 67.67%, H = 7.05%, N = 4.78%; found: C = 67.65%, H = 7.08%, N = 5.07%.

■ *N,N'-Bis[3-(2,4-dioxopentan-3-yl)phenyl]benzene-1,3-dipentanamide.* M: 652.8 g mol^{-1} (**Ac$_4$**).

TLC (SiO_2; 94 CH_2Cl_2/6 ethyl acetate): R_f = 0.17; yield = 46%.

Mp = 52 °C.

IR (cm^{-1}): 3 511 (ν_{NH}), 3 297 (ν_{OH}), 3 058 (ν_{CHar}), 2 930–2 850 (ν_{CH}), 1 700–1 500 ($\nu_{C=O}$).

^{1}H NMR (200 MHz, $CDCl_3$) ppm: 1.28–1.50 (4H, m, CH_2: γ from Ar), 1.55–1.85 (8H, m, CH_2: β from CONH and Ar), 1.88 (12H, s, CH_3), 2.39 (4H, t, J = 7.4 Hz, CH_2: α from CONH), 2.60 (4H, t, J = 7.4 Hz, CH_2: α from Ar), 6.88–6.99 (5H, m, CHar), 7.13–7.51 (9H, m, CHar and CONH), 16.64 (2H, s, C=C(CH$_3$)OH).

^{13}C NMR (50 MHz, $CDCl_3$) ppm: 24.1 (CH_3), 25.3, 28.6, 31.0, 35.5, 37.6 (CH_2), 114.7 (Ar–C), 118.8, 122.3, 126.8, 129.4 (CHar from Ar–Acac), 125.8, 128.2, 128.6 (CHar from CH_2–Ar–CH_2), 137.7, 138.4 (Car from Ar–Acac), 142.4 (Car from CH_2–Ar–CH_2), 171.5 (CONH), 190.9 (C=O).

MS (EI): m/z = 653; m/z = 462 (M – [NH–Ar–C(COCH$_3$)$_2$]).

Elemental analysis: calc for $C_{40}H_{48}N_2O_6$, H_2O: C = 71.62%, H = 7.51%, N = 4.18%; found: C = 71.48%, H = 7.39%, N = 4.46%.

• *Synthesis of* **Ac$_5$**

Steps a), b), c) have previously been described [7] (fig 4). For steps d) and e), the same procedures as described above gave us respectively:

■ *1,3-Bis-[5-oxo-5-(2-thioxothiazolidin-3-yl)pentyl]-5-(methoxymethoxy)benzene.* M: 569 g mol^{-1} (**Y$_1$**); yield: 73%.

TLC (SiO_2; 8 CH_2Cl_2/2 ethyl acetate): R_f = 0.90.

IR (cm^{-1}): 3 020 (ν_{CHar}), 2 934–2861 (ν_{CH}), 1 707 ($\nu_{C=O}$).

^{1}H NMR (200 MHz, $CDCl_3$) ppm: 1.33–1.47 (4H, m, CH_2: γ from Ar), 1.55–1.78 (8H, m, CH_2: β from CON and Ar), 2.56 (4H, t, J = 7.5 Hz, CH_2: α from Ar), 3.24 (4H, t, CH_2: α from CON), 3.27 (4H, t, CH_2 thiazolidinethione), 3.48 (3H, s, CH_3–O–CH_2), 4.57 (4H, t, J = 7.5 Hz, CH_2 thiazolidinethione), 5.15 (CH_3–O–CH_2–O), 6.65–6.67 (3H, m, CHar).

^{13}C NMR (50 MHz, $CDCl_3$) ppm: 24.5, 28.2, 28.6, 31.0, 35.7 (CH_2), 38.3 (CH_2–S), 56.0 (CH_3–O), 56.0 (CH_2–N), 94.4 (CH_3–O–CH_2–O), 113.5 (CHar), 122.2 (CHar), 143.9 (Car–CH_2), 157.2 (Car–OCH_2), 174.7 (CON), 201.4 (C=S).

MS (EI): m/z = 568; m/z = 523 (M – CH_2OCH_3); m/z = 449 (M – thiazolidinethione); m/z = 404 (M – CH_2OCH_3 – thiazolidinethione).

■ *N,N'-Bis[3-(2,4-dioxopentan-3-yl)phenyl]-5-(methoxymethoxy)benzene-1,3-dipentanamide.* M: 712 g mol^{-1} (**6**); yield: 57%.

Mp = 45 °C.

TLC (SiO_2; 95 CH_2Cl_2/5 ethyl acetate): R_f = 0.13.

IR (cm^{-1}): 3 305 (ν_{NH}), 3 066 (ν_{CHar}), 2 934–2 851 (ν_{CH}), 1 700–1 500 ($\nu_{C=O}$).

^{1}H NMR (200 MHz, $CDCl_3$) ppm: 1.30–1.50 (4H, m, CH_2: γ from Ar), 1.55–1.90 (8H, m, CH_2: β from CONH and Ar), 1.89 (12H, s, CH_3), 2.34 (4H, t, J = 7.7 Hz, CH_2: α from CONH), 2.57 (4H, t, J = 7.3 Hz, CH_2: α from Ar), 3.47 (3H, s, CH_3–O), 5.14 (2H, s, CH_3–O–CH_2), 6.64 (1H, s, 1 CHar: α from Car–CH_2), 6.67 (2H, s, 2 CHar: α from Car–OMe), 6.88–6.92 (2H, d, CHar), 7.26–7.48 (8H, m, CHar and CONH), 16.65 (2H, s, C=COH(CH$_3$)).

^{13}C NMR (50 MHz, $CDCl_3$) ppm: 23.9 (CH_3), 25.2, 28.6, 30.7, 35.4, 37.2 (CH_2), 55.7 (CH_3–O), 94.1 (CH_3–O–CH_2), 113.4 (CHar: α from Car–CH_2), 114.8 (Ar–C), 122.0 (CHar: α from Car–CH_2), 118.8, 122.2, 126.4, 129.1 (CHar from Ar–Acac), 137.1, 138.5 (Car–NH and 2 Car–C(COCH$_3$)$_2$), 143.6 (Car–CH_2), 157.0 (Car–OMe), 172.0 (CONH), 190.7 (C=O).

MS (FAB$^+$, NBA): m/z = 713 (M + 1); m/z = 681 (M – OCH_3 – 1); (FAB$^-$; NBA): m/z = 711 (M – 1); m/z = 669 (M – CH_2–O–CH_3).

Elemental analysis: calc for $C_{42}H_{52}N_2O_8$: C = 70.76%, H = 7.35%, N = 3.93%; found: C = 70.74%, H = 7.33%, N = 3.99%.

■ *N,N'-Bis[3-(2,4-dioxopentan-3-yl)phenyl]-5-hydroxybenzene-1,3-dipentanamide.* M = 668.8 g mol^{-1} (**Ac$_5$**).

307 mg (0.43 mmol) of **6** in 30 mL of a THF/isopropanol mixture (2/1 in volume) and 53 μL (0.5 mmol) of HCl 37%

were stirred at room temperature for 4 h. **Ac_5** (195 mg) was obtained after silica gel chromatography of the crude oil; yield: 68%.

TLC (SiO_2; 8 CH_2Cl_2/2 ethyl acetate): R_f = 0.32.

Mp = 72 °C.

IR (cm^{-1}): 3 300 (ν_{OH} and ν_{NH}), 3 050 (ν_{CHar}), 2 931–2 857 (ν_{CH}), 1 662, 1 614, 1 595 ($\nu_{C=O}$).

^1H NMR (200 MHz, $CDCl_3$) ppm: 1.25–1.36 (4H, m, CH_2: γ from Ar), 1.45–1.78 (8H, m, CH_2: β from CONH and Ar), 1.86 (12H, s, CH_3), 2.34 (4H, t, J = 7.3 Hz, CH_2: α from CONH), 2.46 (4H, t, J = 7.1 Hz, CH_2: α from Ar), 6.47 (3H, s, 1 CHar: α from Car–CH_2 and 2 CHar: α from Car–OH), 6.89 (2H, d, J = 7.5 Hz, CHar), 7.25–7.51 (6H, m, 6 CHar), 8.04 (2H, s, 2 CONH), 16.62 (2H, s, C=COH(CH_3)).

^{13}C NMR (50 MHz, $CDCl_3$) ppm: 24.1 (CH_3), 25.4, 28.5, 30.7, 35.3, 37.5 (CH_2), 112.8 (CHar: α from Car–CH_2), 114.9 (Ar–C), 122.5 (CHar: α from Car–CH_2), 119.0, 20.7, 126.9, 129.4 (CHar from Ar–Acac), 137.5, 138.4 (Car–NH and Car–C($COCH_3$)$_2$), 143.8 (Car–CH_2), 156.0 (Car–OH), 172.2 (CONH), 191.0 (C=O).

MS (FAB$^+$, NBA): m/z = 669 (M + 1); m/z = 478 (M – NHArC($COCH_3$)$_2$); m/z = 287 (M – 2 NHArC($COCH_3$)$_2$); (FAB$^-$, NBA): m/z = 667.

Elemental analysis: calc for $C_{40}H_{48}N_2O_7$, 1/2 H_2O: C = 70.87%, H = 7.28%, N = 4.13%; found: C = 70.76%, H = 7.24%, N = 4.43%.

• *Iron(III) complexes of* **Ac_1** *to* **Ac_5** *ligands*

0.1 mmol of Fe(III) salt in MeOH (5 mL) was slowly added in 30 min to a solution of 0.1 mmol of ligand in CH_2Cl_2 (10 mL). A violet precipitate appeared on standing or after addition of diethyl ether. Yields ranged from 35 to 70%.

Elemental analysis:

– $FeAc_2$, NO_3, 2 H_2O, calc: C = 58.16%, H = 6.93%, N = 5.35%, Fe = 7.32%; found: C = 57.72%, H = 6.85%, Fe = 8.37%.

– $FeAc_4$, NO_3, H_2O, CH_2Cl_2, calc: C = 56.90%, H = 5.81%, N = 4.97%, Fe = 6.47%; found: C = 56.78%, H = 5.79%, N = 5.46%, Fe = 7.10%.

– $FeAc_5$, NO_3, 1.5 H_2O, calc: C = 59.19%, H = 6.08%, N = 5.18%, Fe = 6.88%; found: C = 58.81%, H = 6.21%, N = 5.24%, Fe = 7.05%.

IR: spectra of all the complexes (**$FeAc_1$** to **$FeAc_5$**) are very similar to the ones of the corresponding free ligands. For **$FeAc_5$**, the ν_{OH} vibration is not noticeably modified, showing that the phenolic group is not a ligand of Fe(III).

UV: characteristic LMTC bands of the complexes are summarized in table I.

References and Notes

1 Fontecave M, Mansuy D, *J Chem Soc Chem Commun* (1984) 879-881

2 Takai T, Hata E, Yamada T, Mukaiyama T, *Bull Chem Soc Jpn* (1991) 64, 2513-2518

3 Tohma M, Tomita T, Kimura M, *Tetrahedron Lett* (1973) 44, 4359-4362

4 Yamamoto T, Kimura M, *J Chem Soc Chem Commun* (1977) 948-949

5 Pelmont J, *Enzymes*, Presses Universitaires, Grenoble (1995)

6 Durham LJ, Mc Leod DJ, Cason J, *Org Synth Coll Vol IV* (1963) 555-557

7 Provent C, Chautemps P, Gellon G, Pierre J-L, *Tetrahedron Lett* (1996) 37, 1393-1396

8 Dell'Erba C, Novi M, Petrillo G, Tavani C, Bellandi P, *Tetrahedron* (1991) 47, 333-342

9 Oelschläger H, Schreiber O, *Liebigs Ann Chem* (1961) 641, 81-94

10 Bellamy FD, Ou K, *Tetrahedron Lett* (1984) 25, 839-842

11 Nagao Y, Seno K, Miyasaka T, Fujita E, *Chem Lett* (1980) 159-162

12 Nagao Y, Seno K, Kawabata K, Miyasaka T, Takao S, Fujita E, *Tetrahedron Lett* (1980) 21, 841-844

13 Vekey K, Zerilli L, *Org Mass Spectr* (1991) 26, 939-943

14 Murakami Y, Nakamura K, *Bull Chem Soc Jpn* (1966) 39, 901-909

15 Naruta Y, Maruyama K, *J Am Chem Soc* (1991) 113, 3595-3596

16 Robert A, Loock B, Momenteau M, Meunier B, *Inorg Chem* (1991) 30, 706-711

17 Ménage S, Vincent J-M, Lambeaux C, Fontecave M, *J Chem Soc Dalton Trans* (1994) 2081-2084