

Synthesis of ferrocenylketyl radicals by chromium(II) complexes

Zoran R. Ratkovic^{a,1}, László Somsák^b, Károly Micskei^{c,*}, Claudia Zucchi^d,
Gyula Pályi^d

^a Department of Chemistry, Faculty of Sciences, University of Kragujevac, R. Domanovica 12, PO Box 60, YU-34000 Kragujevac, Serbia, FR Yugoslavia

^b Department of Organic Chemistry, Faculty of Natural Sciences, University of Debrecen, Egyetem tér 1, PO Box 20, H-4010 Debrecen, Hungary

^c Department of Inorganic and Analytical Chemistry, Faculty of Natural Sciences, University of Debrecen, Egyetem tér 1, PO Box 21, H-4010 Debrecen, Hungary

^d Department of Chemistry, University of Modena, Via Campi, 183, I-41100 Modena, Italy

Received 12 April 2001; received in revised form 8 May 2001; accepted 8 May 2001

Abstract

Chromium(II)-imino-diacetate (IDA), -ethylenediaminetetra-acetate (EDTA) and -1,3-propanediamine-*N,N'*-diacetic-*N,N'*-dipropionate (PDADP) complexes were used as reagents in H₂O–DMF solutions at 5 < pH < 7 for the preparation of ferrocenylketyl radicals, which could be isolated in solid form under argon in very good yields. Under similar reaction conditions chromium(II)-amino acid (glycine, alanine) complexes selectively reduced ferrocenyl ketones to the corresponding alcohols. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Ferrocenes; Ketones; Radicals; Alcohols; Chromium complexes

1. Introduction

In the early 1960s, evidence was found for the existence of ferrocenyl radicals [1]. Ferrocenylalkyl and ferrocenylketyl radicals were prepared under anhydrous conditions using potassium metal [2] or potassium/sodium alloy [3]. Gamma irradiation in an adamantane matrix produced ferrocenylmethyl radicals [4], and ferrocenyl peroxy radicals could also be generated in an aqueous medium [5]. Despite only sporadic investigations on ferrocenyl radicals, practical applications of this species are widespread and have been discussed in detail (chapter 10 in Ref. [6]).

Ferrocenyl ketones and alcohols are key intermediates for various transformations of racemates of fer-

rocene derivatives with configurational (central) chirality. Enantioselective synthesis of ferrocenyl alcohols under mild conditions is questionable in many cases (chapter 4 in Ref. [6]). Simple syntheses of numerous non-commercial ferrocenyl ketones published earlier [7,8] facilitated preparation of the desired substrates for further transformations.

Chromium(II) compounds are widely used in organic synthesis [9] for selective reduction of various functional groups under mild conditions. Recently, we reported on applications of chromium(II)/alpha-amino acid complexes as reagents in a neutral aqueous medium using the so-called 'biomimetic' set-up in some organic syntheses [10].

In this paper we present a new method for the preparation of ferrocenylketyl radicals in a mild, neutral, aqueous/DMF medium in the reaction of ferrocenyl ketones with chromium(II) complexes. These conditions also open the possibility of obtaining enantioselective reduction of prochiral ferrocenyl ketones [11].

* Corresponding author. Tel.: +36-52-512900, ext. 2757; fax: +36-52-489667.

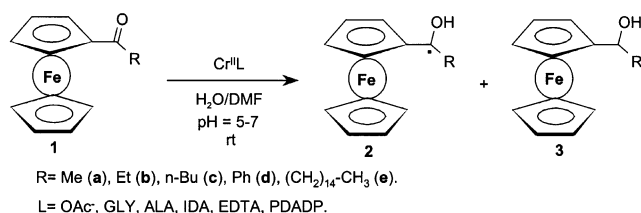
E-mail address: kmicskei@delfin.klte.hu (K. Micskei).

¹ Guest Professor at the University of Debrecen.

2. Results and discussion

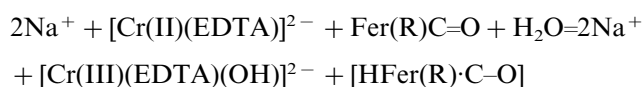
Ferrocenyl ketones **1a–e** were reacted (1) with Cr(II)L complexes (L = acetate (OAc); glycine (GLY); DL-alanine (ALA); imino-diacetate (IDA); ethylenediaminetetra-acetate (EDTA); 1,3-propanediamine-*N,N'*-diacetic-*N,N'*-dipropionate (PDADP)). Using the Cr(EDTA)²⁻ complex as a reagent (see entries 3, 6, 9, 14 and 18 in Table 1) we obtained an orange colour in the ethereal phase after work up, which indicated the formation of an unexpected species. We also found that the starting materials **1a–e** (usually red) could be recovered when we attempted at using Cr(OAc)₂ as the reducing agent (entries 1, 4, 7, 10 and 16).

Reacting the ketones **1a–e** with the Cr(GLY)⁺ complex, the corresponding alcohols **3a–e** (yellow) could be prepared (entries 2, 5, 8, 11 and 17).



The ethereal solution of the crude products were analysed by TLC. We observed different behaviour in

an argon atmosphere and under air. In oxygen-free atmosphere we observed a TLC spot, overlapping with that of the starting ketone (red), but with a distinctly different colour: orange. In air, the colour of this spot turned gradually to the red colour of the starting compound (**1a–e**). This gave us the first indication that the origin of the intense orange fraction could be the formation of an unexpectedly stable *radical species*. In preparative experiments, this orange substance could be extracted by using carefully deoxygenated diethyl ether; even after evaporation of the solvent, the orange colour persisted for a longer time (even weeks) until the sample came in contact with oxygen. Identification of the new species by elementary analysis could not be expected since the supposed elementary composition is very close to that of the ketones (**1**) and the alcohols (**3**). Analyses for metal ions (Na⁺, K⁺, Cr³⁺) gave negative results. Thus, we hypothesised the formation of a *neutral radical species*, according to the following stoichiometry:



UV–vis spectroscopic measurements provided additional evidence for the formation of the radicals (Fig. 1). The absorption at 360 and 465 nm are roughly the same for **1d** and **2d** but the molar absorption coeffi-

Table 1
Reactions of ferrocenyl ketones with Cr(II) complexes

Entry	1 (mmol)	Ligand L	Cr(II) (mmol)	Ligand (mmol)	V ^a (cm ³)	pH	Reactive complex	1 (%) ^b	2 (%) ^b	3 (%) ^b
1a										
1	0.5	OAc	2	4	20	5.0	Cr(OAc) ₂	89	–	–
2	0.5	GLY	1.25	5	40	7.0	Cr(GLY) ⁺	–	–	86
3	1	EDTA	2.5	3	40	5.5	Cr(EDTA) ²⁻	–	77	–
1b										
4	0.5	OAc	2	4	20	5.0	Cr(OAc) ₂	91	–	–
5	0.5	GLY	1.25	5	40	7.0	Cr(GLY) ⁺	–	–	82
6	1	EDTA	2.5	3	40	5.5	Cr(EDTA) ²⁻	–	85	–
1c										
7	0.5	OAc	2	4	20	5.0	Cr(OAc) ₂	92	–	–
8	0.5	GLY	1.25	5	40	7.0	Cr(GLY) ⁺	–	–	88
9	1	EDTA	2.5	3	40	5.5	Cr(EDTA) ²⁻	–	89	–
1d										
10	0.5	OAc	2	4	20	5.0	Cr(OAc) ₂	93	–	–
11	0.5	GLY	1.25	5	40	7.0	Cr(GLY) ⁺	–	–	85
12	0.5	ALA	1.25	5	40	7.0	Cr(ALA) ⁺	–	–	79
13	1	IDA	2.5	5	40	6.5	Cr(IDA)	–	84	–
14	1	EDTA	2.5	3	40	5.5	Cr(EDTA) ²⁻	–	91	–
15	1	PDADP	2.5	3	40	6.0	Cr(PDADP) ²⁻	–	89	–
1e										
16	0.5	OAc	2	4	20	5.0	Cr(OAc) ₂	96	–	–
17	0.5	GLY	1.25	5	40	7.0	Cr(GLY) ⁺	–	–	89
18	1	EDTA	2.5	3	40	5.5	Cr(EDTA) ²⁻	–	91	–

^a H₂O–DMF = 1:1.

^b Isolated yield.

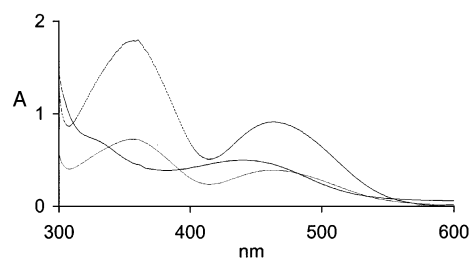


Fig. 1. UV-vis spectra of **2d** (—), $8.0 \times 10^{-4} \text{ mol dm}^{-3}$; **1d** (---), $1.4 \times 10^{-3} \text{ mol dm}^{-3}$; **3d** (- - -), $2.3 \times 10^{-3} \text{ mol dm}^{-3}$ in solution of diethylether at 25 °C.

coefficients are different ($\epsilon_{360} = 1.32 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$, $\epsilon_{360} = 9.8 \times 10^2 \text{ M}^{-1} \text{ cm}^{-1}$ respectively). Similar differences

(40–60%) were found while measuring ϵ of **1a–c,e** and **2a–c,e**. Strong interactions of the radical formed and d-orbitals of the ferrocene-iron can cause significant differences in ϵ values for these species.

$^1\text{H-NMR}$ spectra indicated the paramagnetic properties of the radicals formed. Increased proton relaxation rates as well as considerable line broadenings were observed in the $^1\text{H-NMR}$ spectra of **2d** (Fig. 2). Upon oxidation, the spectrum became identical with that of the starting ketone (**1d**), known from experience and literature [8].

EPR spectra (Fig. 3) provide an important qualitative support to the existence of the ferrocenylketyl radicals **2a–e** too. The EPR spectra of **2a** and **2d** at

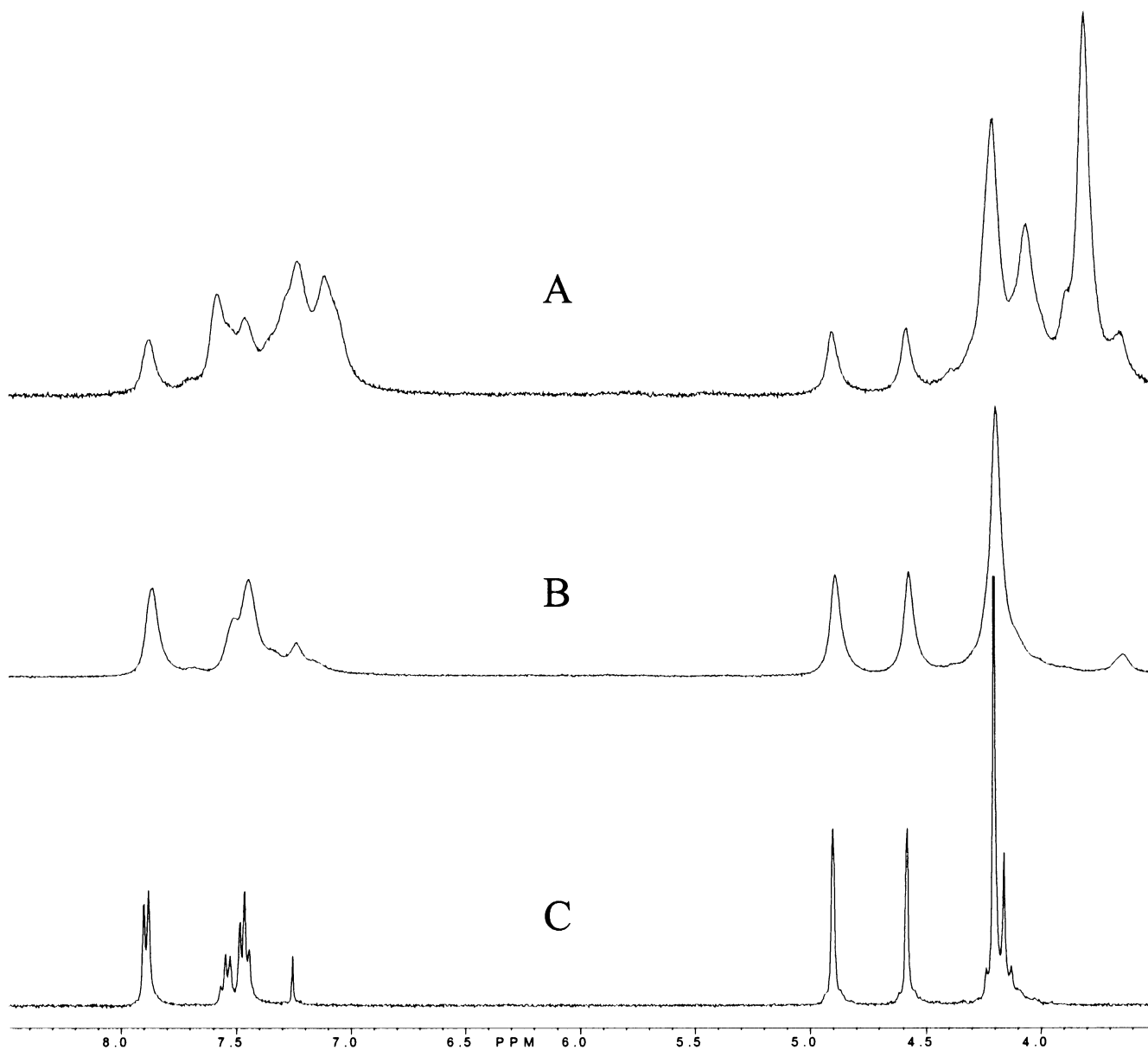


Fig. 2. $^1\text{H-NMR}$ spectra of the product formed in the reaction of **1d** with $\text{Cr}(\text{EDTA})^{2-}$ after: (A) 30 min; (B) 1 week; (C) oxidation by air.

room temperature are not so well resolved but for **2c,b** and **2e** spectra of sufficient quality were obtained.

Experiments with **1d** indicated the fundamental role of the coordinated ligand in the Cr(II) complexes. Alcohol **3d** was the only product detected, when the bidentate glycine or alanine were used as ligands in the reducing Cr(II) complex (Table 1, entry 12). By increasing the number of the donor groups in the coordination sphere of the metal ion as in Cr(IDA) and Cr(PDADP)²⁻, the radical **2d** could be prepared in good yields (entries 13 and 15).

The preparative, TLC, UV-vis, ¹H-NMR and ESR observations described above provide a consistent picture, all elements are in accord with the formation of stable, neutral ferrocenyl radicals (**2**) generated in an oxygen-free atmosphere by the reduction with Cr(II) complexes.

Our work also presents a new method for the synthesis of neutral ferrocenylketyl radicals in ethereal solution and solid form. Contrary to earlier findings, it was demonstrated that carefully deoxygenated, neutral aqueous conditions are applicable for the preparation

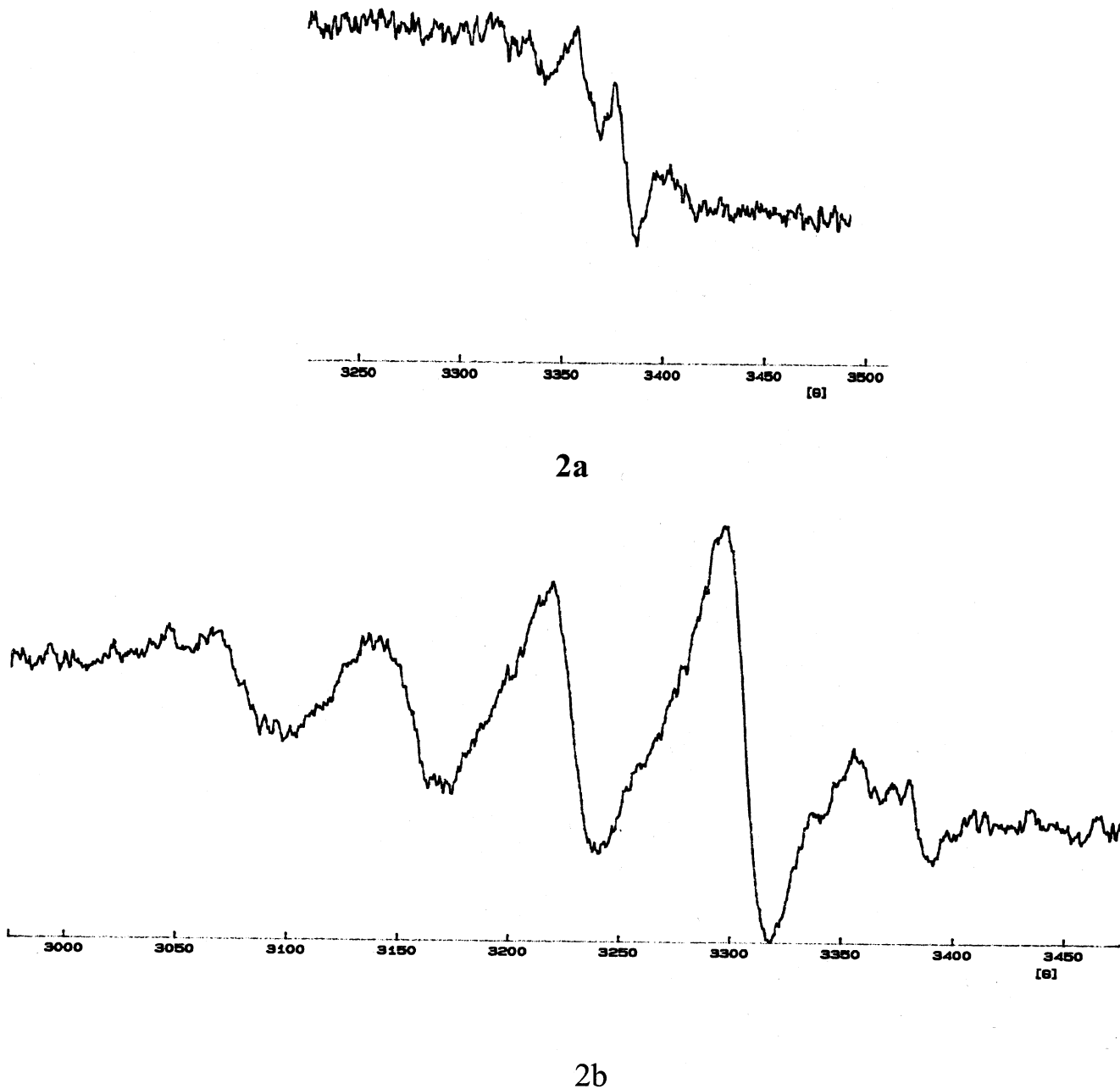
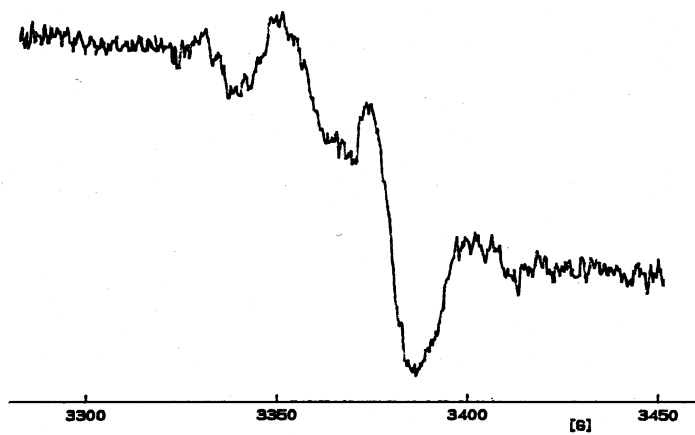
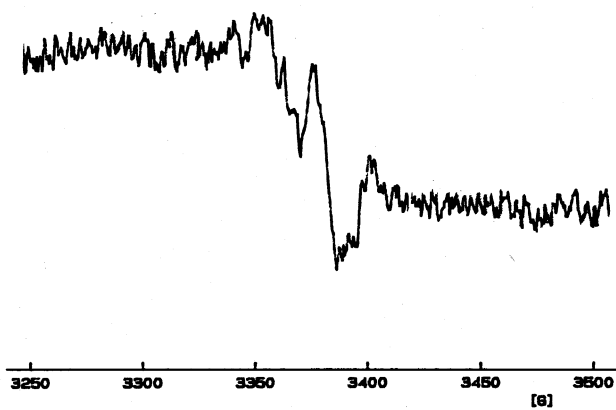


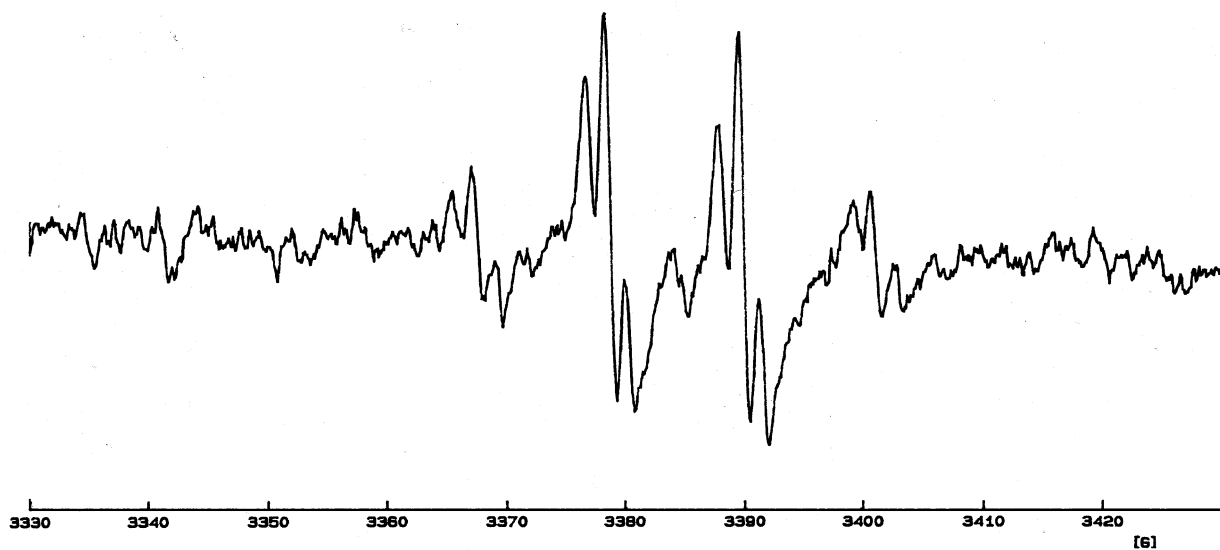
Fig. 3. X-band EPR spectra recorded at room temperature in toluene solution: **2a**, $5.0 \times 10^{-2} \text{ mol dm}^{-3}$; **2b**, $5.3 \times 10^{-2} \text{ mol dm}^{-3}$; **2c**, $5.3 \times 10^{-2} \text{ mol dm}^{-3}$; **2d**, $3.9 \times 10^{-2} \text{ mol dm}^{-3}$; **2e**, $4.0 \times 10^{-2} \text{ mol dm}^{-3}$.



2c



2d



2e

Fig. 3. (Continued)

of such species. The suitable selection of the coordinated ligand in the Cr(II)L reagents stops the reaction either at the radical stage or lets it proceed to form the alcohol.

Further studies are in progress in our laboratories to prepare additional new ferrocenylketyl radicals as well as to characterise them by using X-ray techniques.

3. Experimental

3.1. Chemicals

All ferrocenyl ketones used for reactions were prepared by a procedure described earlier [8]. Chromium(II) acetate hydrate $[\text{Cr}(\text{OAc})_2 \cdot \text{H}_2\text{O}]_2$ as well as the chromium(II) complexes were prepared by us using essentially the literature protocols [10d]. Ligands as glycine, DL-alanine, imino-diacetate and ethylenediaminetetra-acetate were purchased from Aldrich Chemical Company. The 1,3-propanediamine-*N,N'*-diacetate-*N,N'*-dipropionate was prepared at the Department of Chemistry, University of Kragujevac. All other reagents were purchased from Merck Company.

The amounts of reagents used for the preparation of the Cr(II)L complexes were calculated [12a], using the reported formation constants [12b] and considering the actual pH value.

3.2. Preparation of ferrocenylketyl radicals

Chromium(II) ethylenediaminetetra-acetate, $[\text{Cr}(\text{II})\text{-(EDTA)}]^{2-}$, was prepared from $\text{Na}_2\text{EDTA} \cdot 2\text{H}_2\text{O}$ (1.12 g, 3 mmol), KOH (2.46 mol dm^{-3} , 1.3 cm^3 , 3.2 mmol) and $[\text{Cr}(\text{OAc})_2 \cdot \text{H}_2\text{O}]_2$ (0.47 g, 2.5 mmol Cr(II)) in a mixture of H_2O (20 cm^3) and DMF (15 cm^3) (pH 5.5, checked by pH-potentiometry) under Ar using standard Schlenk technique at room temperature. The red chromium(II) acetate was completely dissolved only after the addition of the ligand, with blue colour. Ferrocenyl ketone (**1a–e**, 1 mmol) was dissolved in DMF (5 cm^3) and this solution after deoxygenation was added to the complex in one portion. The colour of the solution slowly (2–3 h) changed from blue to deep violet. The reaction vessel was then kept under a slight overpressure of Ar, and stirring was continued for 6 h. After this period the solution was extracted (3 \times 15 cm^3) with Et_2O under Ar atmosphere. The organic phase was washed (3 \times 10 cm^3) with deoxygenated water, then dried over anhydrous Na_2SO_4 , subsequently the solvent was evaporated under reduced pressure and an orange residue was obtained, which changed colour (to red) upon exposition to air. Yields are shown in Table 1.

3.3. Separations on TLC

The reaction mixtures were analysed by TLC (DC-Fertigplatten, Kieselgel 60 F254 (Merck-5719) under Ar

atmosphere; eluent Et_2O –hexane = 1:1(v/v)). The spots were evaluated at first under Ar taking into account the oxygen sensitivity properties of the radicals. Subsequently, the plates were oxidised by standing on air and visualised with UV light. The R_f values of the ketones and the radicals were roughly the same, but the colour of the spots was different. After oxidation the colour of the radicals (orange) changed to that of the ketones (red). The corresponding alcohols have a different colour (yellow) and R_f .

3.4. UV–vis measurements

A 1.00 cm quartz cell was closed by means of silicon-rubber caps and flushed with Ar, using hypodermic needles as inlet and outlet. Ethereal solutions of **2a–e** were added through a hypodermic needle from a specially designed storing vessel (similar to a Schlenk tube). The cell was then closed under a small overpressure of Ar and placed into the spectrophotometer (HP8453). After recording the spectra the solvent was evaporated and the residue was oxidised by air. After it the sample was dissolved in Et_2O and the spectra recorded again. These spectra were found identical to those of the ketones (**1a–e**). The samples were also checked by TLC and only the ketones could be detected.

3.5. $^1\text{H-NMR}$ measurements

$^1\text{H-NMR}$ spectra were recorded with a Bruker AM 360 spectrometer (^1H 360 MHz) in CDCl_3 . From the ethereal solution of **2a–e** the solvent was evaporated by an Ar stream and the residue was dissolved in CDCl_3 . (Slow decomposition of the radicals was observed in CDCl_3 in contrary to Et_2O .) All the samples showed strong paramagnetic line broadenings. After oxidation of the samples by air only the spectra of ketones **1a–e** were observed. No alcohols could be detected by TLC in these samples.

3.6. EPR measurements

X-band EPR spectra (9.50 GHz) were recorded at 298 K with a Bruker 200D SCR spectrometer. The ethereal solutions of **2a–e** were evaporated and the solid residues were dissolved in toluene. The purity of the samples was checked by TLC before and after the measurements.

Acknowledgements

Financial support of this work is provided by the Hungarian OTKA (contract No. T33130) and FKFP 0308/2000 Projects, as well as the (Italian) Ministry of University and Research (MURST). The János Bolyai Research Scholarship for K.M. is also acknowledged.

Also, travel by Z.R.R. was supported by Pharmacy Sveti Nikola (Kragujevac).

References

- [1] M. Rosenblum, *Chemistry of the Iron Group Metallocene*. Part 1, Wiley, New York, 1965.
- [2] G. Bigam, J. Hooz, S. Linke, R.E.D. McClung, M.W. Mosher, D.D. Tanner, *Can. J. Chem.* (1971) 1825.
- [3] J.J. McDonnell, G. Capen, R. Michaelson, *Tetrahedron Lett.* (1969) 4251.
- [4] R.A. Jackson, M. Scarmoutsos, A.K. Zarkadis, *J. Chem. Soc. Perkin Trans. 2* (1991) 809.
- [5] S.V. Jovanovic, I. Jankovic, L. Josimovic, *J. Am. Chem. Soc.* 114 (1992) 9018.
- [6] A. Togni, T. Hayashi (Eds.), *Homogenous Catalysts, Organic Synthesis, Material Science*, VCH, Weinheim, 1995.
- [7] R.D. Vukicevic, Z.R. Ratkovic, M.D. Vukicevic, S.K. Konstantinovic, *Tetrahedron Lett.* 39 (1998) 5837.
- [8] R.D. Vukicevic, Z.R. Ratkovic, M.D. Vukicevic, S.K. Konstantinovic, *Synlett* (1998) 1329.
- [9] (a) L.A. Wessjohann, G. Scheid, *Synthesis* 1 (1999) 1; (b) A. Fürstner, *Chem. Rev.* 99 (1999) 991.
- [10] (a) G. Kovács, J. Gyarmati, L. Somsák, K. Micskei, *Tetrahedron Lett.* 37 (1996) 1293; (b) G. Kovács, K. Micskei, *Tetrahedron Lett.* 38 (1997) 9055; (c) K. Micskei, J. Gyarmati, G. Kovács, S. Makleit, C. Simon, Z. Szabó, J. Marton, S. Hosztafi, H. Reinke, H.-J. Drexler, *Eur. J. Org. Chem.* (1999) 149; (d) G. Kovács, K. Tóth, Z. Dinya, L. Somsák, K. Micskei, *Tetrahedron* 55 (1999) 5253.
- [11] (a) T. Patonay, C. Hajdu, J. Jekő, A. Lévai, K. Micskei, C. Zucchi, *Tetrahedron Lett.* 40 (1998) 1373; (b) J. Gyarmati, C. Hajdu, Z. Dinya, K. Micskei, C. Zucchi, G. Pályi, *J. Organomet. Chem.* 586 (1999) 106.
- [12] (a) L. Zékány, I. Nagypál, in: D.J. Leggett (Ed.), *Computational Methods for the Determination of Formation Constants*, Plenum Press, New York, 1985, pp. 291–353; (b) K. Micskei, F. Debreczeni, I. Nagypál, *J. Chem. Soc. Dalton Trans.* (1983) 1335.