An ^{27}Al and ^{13}C N.M.R. study of the Complexes between Al^{3+} and Various Organic Molecules Containing the Amide Group in Concentrated Aqueous Solution

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Z. Naturforsch. **39a**, 1235 – 1241 (1984); received September 18, 1984

The complexation between Al^{3+} and urea, formamide, acetamide and their alkyl derivatives were investigated by ^{27}Al and ^{13}C N.M.R. spectroscopy. A fitting procedure allowed to obtain the populations of each bound and free form of Al^{3+}. From these data the equilibrium parameters were calculated in a direct way, and the results discussed in terms of substituent effects on the interaction phenomena. In this respect the steric hindrance, the polarization of the electronic charge and the hydrophobic character of the alkyl groups were considered as affecting factors.

Introduction

Various N.M.R. studies on aluminium complexes were performed providing information on the number of solvent molecules in the first coordination sphere of this metal ion in solution as well as on the symmetry of the aluminium-organic ligand complexes [1 – 7].

Among these, ^{27}Al N.M.R. spectroscopy was employed in a small number of investigations [8 – 10] on the complex formation between neutral organic ligands and Al^{3+} in aqueous solution. This very versatile metal ion occurs in a variety of organo-aluminium compounds exhibiting different affinities which were not often rationalized. On the other hand the knowledge of the molecular properties of the organic ligands affecting the interactions with Al^{3+}, may represent an interesting background in interpreting the observed bonding situations. In this connection a study on the interaction of Al^{3+} with imidazolidine-2-one $\underbrace{CH_2-NH-CO-NH-CH_2}$, a cyclic ligand provided with an amide function, was reported recently [11]. The results revealed that entropy is a driving factor in the formation of such adducts, and this was ascribed to a lowering of the order of water molecules around the metal ion in presence of the ligand. If accompained by a more systematic collection of data on the interaction mechanisms involved, these findings may contribute to a better knowledge of the amide complexes of Al^{3+} in aqueous solution.

Therefore, as part of a study on the formation of complexes between metal ions and organic ligands of biological interest [12 – 17], we have undertaken the present ^{27}Al and ^{13}C N.M.R. investigation on the interaction of Al^{3+} with different amide ligands of formula $R_1-CO-NR_2R_3$ (R_1=H, NH_2, CH_3 and R_2, R_3=H, CH_3 and C_2H_5).

Since Al^{3+} has been proved to be involved in many toxic processes because of its interaction with cellular components [18], the present investigation on the binding of Al^{3+} with the amide groups may be of interest in foreseeing the possible interactions of Al^{3+} with the peptide bonds of proteins, which are expected to exhibit binding properties similar to those of the simpler molecules here examined as structural models. The amide function of these compounds was gradually modified in order to gain more accurate information about the Al^{3+} interaction. Furthermore, these ligands were particularly suitable for our study because of their non-ionic binding sites which prevented the occurrence of dramatic electric field gradients around the Al^{3+} coordination sphere, thus allowing for fairly narrow resonances of the ^{27}Al N.M.R. spectra despite the nuclear quadrupole moment of 0.14988 of ^{27}Al.

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Since this metal ion exhibits long exchange times between free and bound forms in the N.M.R. time scale, the various complexes actually at equilibrium showed distinct resonances thus allowing an evaluation of the equilibrium parameters in a direct way.

Experimental

Materials: $Al(NO_3)_3 \cdot 9H_2O$ and D_2O (99.75%) were purchased from Carlo Erba and Merck, respectively. The organic ligands H_2NCONH_2, $H_2NCONHCH_3$, $(CH_3)_2NCON(CH_3)_2$, $HCONH_2$, $HCONHCH_3$, $HCON(CH_3)_2$, CH_3CONH_2, $CH_3CON(CH_3)_2$ and $CH_3CON(C_2H_5)_2$ were purchased from Fluka. Stock solutions were prepared by dissolving weighted amounts of the substances in D_2O; the $Al(NO_3)_3$ solution was acidified by nitric acid and titrated by the usual volumetric procedures.

N.M.R. Measurements: ^{27}Al and ^{13}C spectra were recorded on a Varian FT 80A spectrometer. The operating conditions for ^{27}Al were: frequency 20.7 MHz, 5 mm tubes, SW 500 Hz, AT 1.028 s, probe temperature 30 °C, PW 14 S, averaging over 256 FID, while the ^{13}C spectra observed at 20 MHz were ^{1}H decoupled by means of square wave modulation of the decoupler carrier, centered on the proton field. Because the equilibria were slowly reached, the spectra were recorded at least 12 h after preparation of the samples.

Calculations: In order to estimate the relative population of ^{27}Al contributing to any signal in the spectra, we have had to use a best fitting procedure. As a matter of fact most of the observed spectra presented a large superimposition of signals which did not allow their direct integration. Therefore they were analyzed as a sum of Lorentzian curves, by a non linear least squares procedure (Gauss-Newton method) with a BASIC program on a HP-85 Hewlett-Packard personal computer. This program allows a curve decomposition and optimizes the parameters (frequency, half-linewidth and intensity) of each component peak. Therefore it was been possible to estimate the relative populations of the various forms in all the solutions examined. The assignment of the ^{27}Al signals to complexes of different Al : ligand stoichiometries has been made on the basis of the occurrence of the signals with increasing ligand concentration.

The formation constants of every system for each examined solution were directly estimated from the relations $K_n = C_n \Big/ \left(C_{n-1} \left(L_T - \sum_{1}^{N} i\, C_i \right) \right)$, where L_T is the total concentration of ligand and C_n, the concentration of aluminium complexed with a $1:n$ Al : ligand stoichiometry, is obtained from the calculated populations by multiplying them with the total aluminium concentration; N is the greatest observed Al : ligand ratio. The K's relative to every examined ligand were obtained as a weighted mean value of the determinations taken individually. A weighting factor, which takes into account the standard deviations of the populations evaluated by the least squares method, was attributed to each determination. The precision in determining the population is strictly dependent on the degree of separation between the signals, and it therefore affects the precision in the final evaluation of the formation constants.

For each optimized spectrum 60 to 120 experimental readings, depending on the number of signals and on their amplitudes, were used.

Results and Discussion

Figures 1, 2 and 3 show some examples of ^{27}Al N.M.R. resonances in the octahedral coordination region with different amide derivatives added to aqueous solutions of $Al(NO_3)_3$. For comparison the ^{13}C N.M.R. spectra of the ligands observed in the same solutions are also reported in the figures. In addition to the resonances of the free forms, the appearance of new signals, both for the metal ion and for the ligands, gives evidence of adduct formation in all the studied systems. An apparent exception was the single signal exhibited by the ^{13}C spectrum of formamide (Fig. 2), which we attributed to the fact that the free and bound form signals coincided. Conversely, ^{27}Al and ^{13}C N.M.R. spectra of $Al(NO_3)_3$-tetramethylurea showed no changes with respect to the spectra of the free form, and therefore these are not reported.

The ^{27}Al N.M.R. results for urea and methylurea showed in this order the occurrence of three and two new resonances higher field shifted with respect to the signal of the hexaaquoaluminium ion A_0 (Figure 1). The sequence of the occurrence of these signals at increasing ligand concentrations led us to

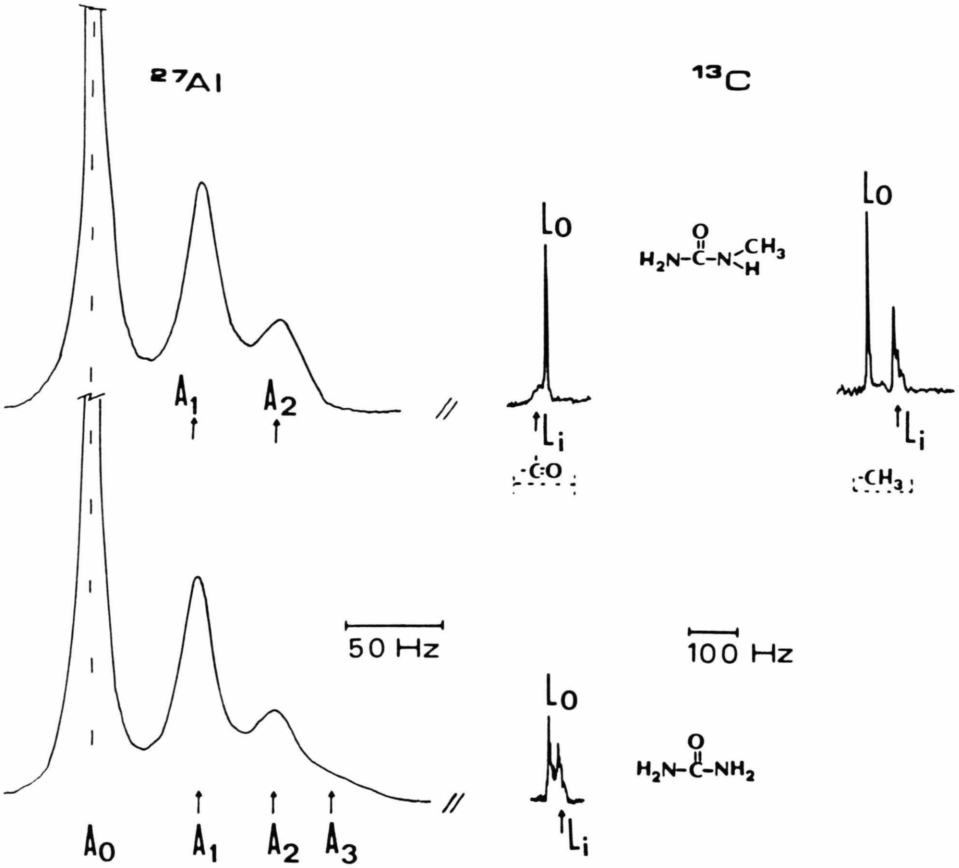
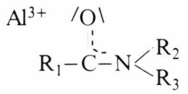


Fig. 1. ^{27}Al and ^{13}C N.M.R. spectra of $Al(NO_3)_3$ 1.5 M in aqueous solutions in presence of urea 3M and methylurea 3 M; for the resonances assignments see text.

assign peaks A$_1$, A$_2$ and A$_3$ to complexes with 1 : 1, 1 : 2 and 1 : 3 metal : ligand stoichiometries, respectively. When formamide derivatives are used, the signals of bound Al^{3+} were observed from the asymmetrical pattern of the resonances (Fig. 2) while acetamide derivatives showed the broadened signals illustrated in Fig. 3, as evidence of complexed Al^{3+}. The stoichiometries of these adducts, indicated in Figs. 2, 3, were obtained by means of a curve decomposition procedure, showing Al/ligand ratios from 1 : 1 to 1 : 2 (see later).

In the ^{13}C N.M.R. spectra of the various molecular systems, the signals due to the ligands L$_0$ in the bulk of the aqueous solvent and to the ligands L$_i$, $i = 1, 2, 3$ in the first coordination sphere of Al^{3+} are sufficiently distinguished (see Figs. 1, 2, 3). The resonances of each ^{13}C group of the free ligands were assigned by a comparison with the corresponding spectra of the alone ligands in aqueous solution. The remaining signals were then attributed to the bonded species on the basis of their relative signal areas compared with those of ^{27}Al N.M.R. resonances: the internal chemical shifts of carbonyl groups are reported in Table I, the remaining carbon atoms being neglected because often enveloped. The non equivalence of methyl and ethyl carbon atoms observed for the N-dimethyl and N-diethyl derivatives in the bound ligands suggests [18] that coordination is through the oxygen for the pertinent ligands, and this assumption was reasonably considered also for the remaining amide derivatives following the scheme



$$\overset{Al^{3+}\ /O\backslash}{R_1-C-N<^{R_2}_{R_3}}$$

The interpretation of these results in terms of affinity of aluminium toward amide function im-

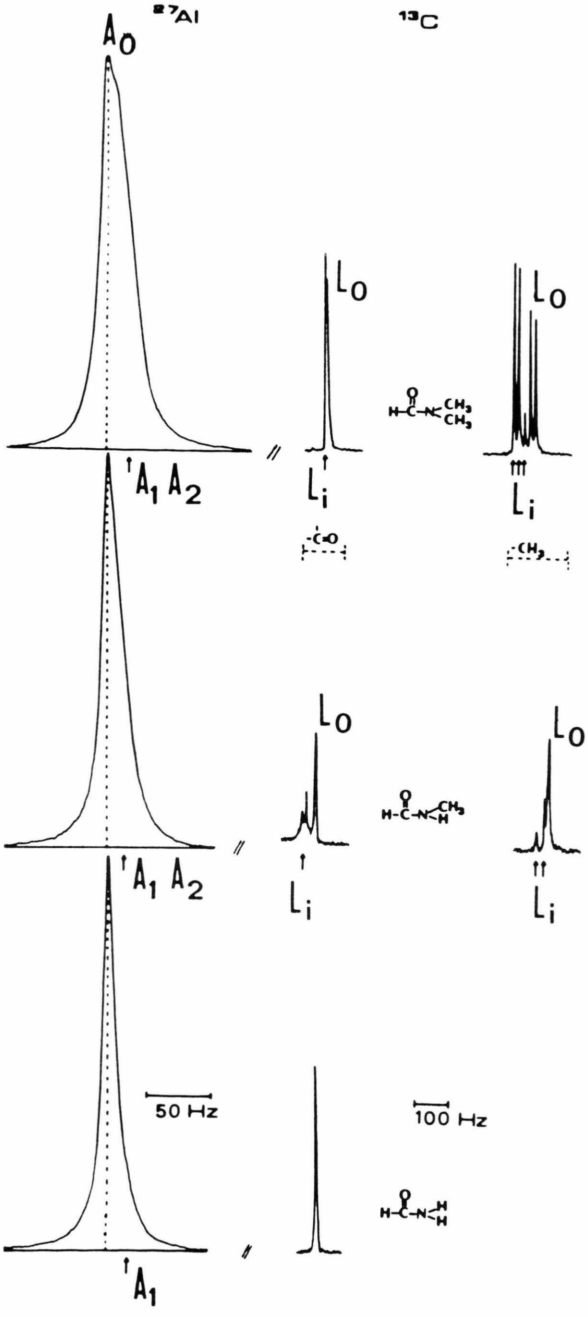


Fig. 2. ^{27}Al and ^{13}C N.M.R. spectra of Al(NO$_3$)$_3$ 1.5 M in aqueous solutions in presence of formamide 3 M, methylformamide 3 M and dimethylformamide 3 M; for the resonances assignments see text.

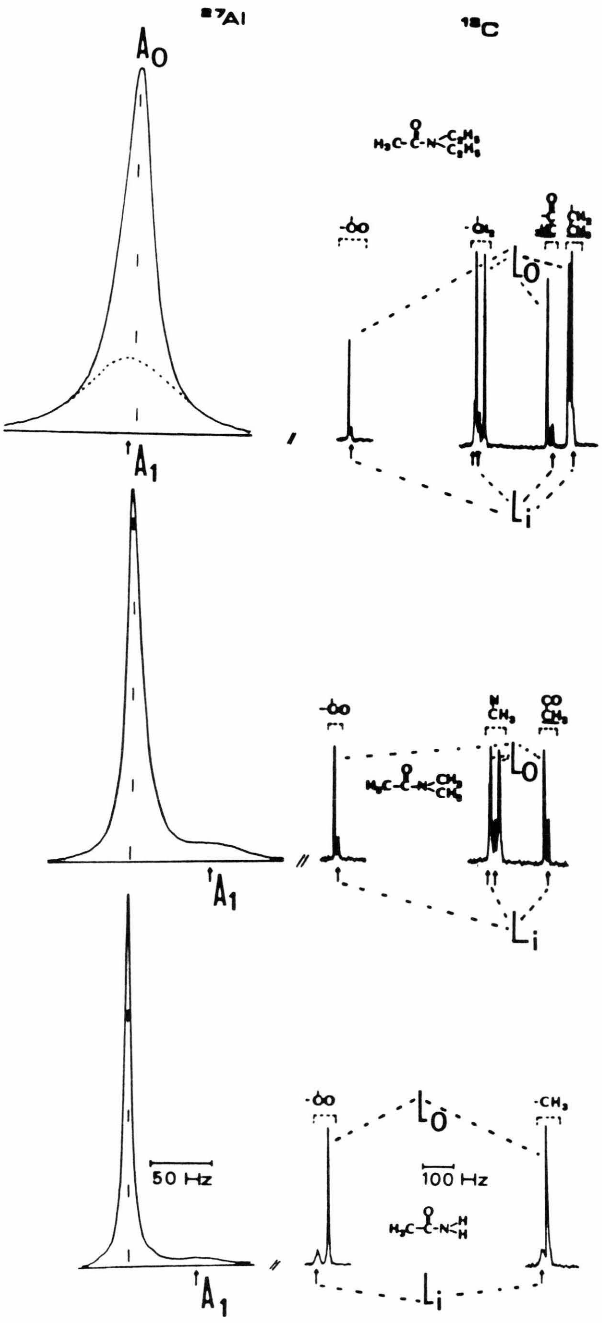


Fig. 3. ^{27}Al and ^{13}C N.M.R. spectra of Al(NO$_3$)$_3$ 1.5 M in aqueous solution in presence of acetamide 3 M, dimethylacetamide 3 M and diethylacetamide 3 M; for the resonances assignments see text.

Table 1. Equilibrium constants at 30 °C and internal chemical shift of bound species of Al^{3+} and of the carbonyl functions of urea, formamide, acetamide and related derivatives.

Ligand	K_1	K_2	K_3	δ_1	δ_2	δ_3	δ_{CO}
$HCON(CH_3)_2$	0.385	5.27	–	17.9	34.7	–	– 6.3
$HCONHCH_3$	0.498	1.13	–	14.1	33.1	–	40.4
$HCONH_2$	0.187	–	–	18.9	–	–	–
$CH_3CON(C_2H_5)_2$	0.35	–	–	0	–	–	– 10.1
$CH_3CON(CH_3)_2$	0.29	–	–	55.4	–	–	– 11.3
CH_3CONH_2	0.18	–	–	55.2	–	–	34.7
$(CH_3)_2NCO(CH_3)_2$	–	–	–	–	–	–	–
$H_2NCONHCH_3$	0.147	0.124	–	56.7	101	–	15.8
H_2NCONH_2	0.254	0.220	0.142	55.5	96.6	129	– 18.9
$\underline{CH_2NHCONHCH_2}$ [a]	0.224	0.296	0.114	44.0	77.2	102	–

The chemical shifts are in Hz from the signals of the pure compounds. –
[a] Data taken from [11].

plies both an evaluation of a stoichiometric model and of the relative association constants. Therefore, considering that ^{13}C N.M.R. signals are not suitable for quantitative studies [20], the data treatment was carried out on the ^{27}Al N.M.R. data. To evaluate the populations of the free and bound Al^{3+} resonances, the previously described program was employed.

Since a slow exchange between the bound and free forms of the ligands was clearly observed in the ^{13}C N.M.R. time scale, slow exchange conditions were given in the calculations of ^{27}Al N.M.R. data. In fact the ^{27}Al observing frequency $\nu^0_{(^{27}Al)}$ in our experimental conditions is greater than $\nu^0_{(^{13}C)}$ and the $|\delta_{free} - \delta_{bound}|$ value for ^{27}Al is not substantially different from the $|\delta_{free} - \delta_{bound}|$ value for ^{13}C and, as a consequence, the exchange processes between free and bonded Al^{3+} species are to be considered slow also in the ^{27}Al time scale [21]. Thus it can be stressed that the increased line-widths of the ^{27}Al N.M.R. signals observed for the various complexed forms are indicative of increasing distortion of the relative field of the Al^{3+} environment. In fact in the limit of fast motion the nuclear spin quadrupolar relaxation T_{1q} affects the line-widths according to the equation

$$1/T_{1q} = 1/T_1 = 1/T_2 = 3/40\,[(2I+3)/I^2\,(2I-1)] \cdot (1+\chi^2/3)\,(e^2 q Q/\hbar)\,Z c\,,$$

where T_1 and T_2 are the spin-lattice and spin-spin relaxation times, eq is the electric field gradient, χ gives the deviation of the electric field gradient from axial symmetry, and the remaining symbols have the usual meaning [6]. Therefore for constant correlation times τ_c, the electric field gradient configuration $(1+\chi^2/3)\,eq$ affects the quadrupolar relaxation and, as a consequence, the line width of the ^{27}Al resonances.

The stoichiometries of the adducts considered to be Al/ligand from 1:1 to 2:1 and 3:1 depending on the number of the observed bound signals were confirmed by the consistency of the equilibrium constant parameters calculated on the sets of solutions with very different [ligand]/[aluminium] ratios.

As an example of the good fit obtained in employing the curve decomposition procedure, the experimental points together with the calculated curves are reported in Fig. 4 for a number of ^{27}Al spectra with added dimethylformamide. The calculated association constants are reported in Table I as well as the frequencies of any complex species. It can be seen that urea and imidazolidine-2-one show a similar behaviour as far as regards stoichiometry and association constants, which are greatly reduced when a methyl group is introduced in urea, which fact seems to reflect the lower symmetry of this ligand. An apposite trend is given for formamide methylderivatives, dimethylformamide showing the largest affinity parameters.

On the basis of the overall findings, while the steric hindrance of methyl bound to the carbonyl group in acetamide and related derivatives seems to be the main cause of their low reactivity, which becomes not observable when two methyl groups are CO substituted, stabilizing effects arise from methyl groups when they are at the nitrogen atoms. These last are to be taken into account in order to be able to rationalize the increasing affinities observed on going from formamide to methyl- and dimethylformamide. On the other hand, the aptitude of the

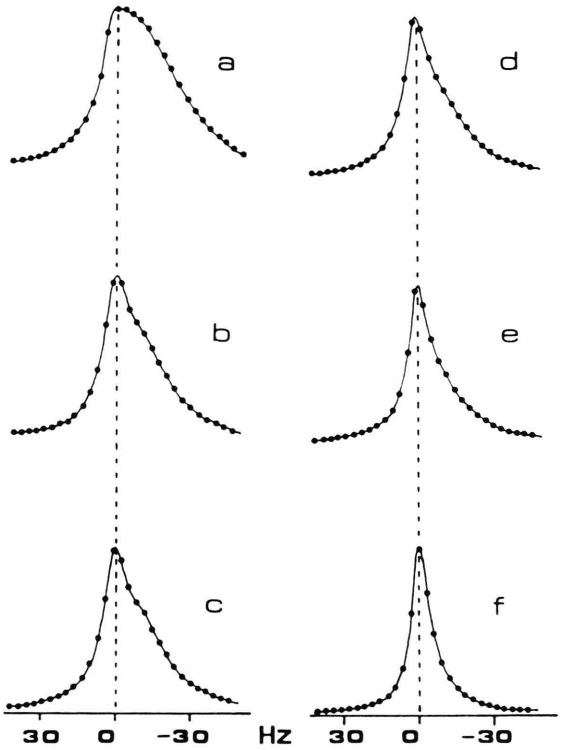


Fig. 4. ^{27}Al N.M.R. spectra obtained from solutions of Al(NO$_3$)$_3$ 1.5 M in aqueous solutions in presence of dimethylformamide at various concentrations: a) 2.7 M; b) 2.2 M; c) 1.7 M; d) 1.2 M; e) 0.7 M; f) 0.2 M; the chemical shifts are referenced to the free aluminium ion resonance.

methyl group in inducing polarization of the electronic charge in molecular systems with delocalized charge distribution is well documented [22], and this appears to be the case also with these amide derivatives. In fact, at our working temperature of 30 °C, the examined ligands are characterized by a delocalized structure of the electronic charge


$\overset{\displaystyle O}{\overset{\vdots}{-C\cdots N}}$,

as supported by the above mentioned presence of two distinct methyl signals in the ^{13}C N.M.R. spectra of N-bisubstituted compounds, due to the hindered rotation around the amide bond. Thus, considering coordination via oxygen, in accordance also with the relative energies of the σ and π orbitals associated with the C$\overset{\cdots}{-}$O group [23], and keeping in mind also that the interacting Al^{3+} binds the negative charge of the oxygen atom, the most polarized amide functions are expected to be the most reactive ones. Accordingly, the found increase in the affinities of the amide oxygen with respect to the metal ion following $\mathrm{HCONH_2 < HCONH(CH_3) < HCON(CH_3)_2}$ gives corroborating evidence of the correctness of the above considerations.

Moreover, the hydrophobic character of the methyl and ethyl groups when sufficiently apart from binding sites of the ligands plays an important role in favouring the complex formation through the contribution of entropy to the free energy of these complexes, as previously found for the imidazolidine-2-one-Al^3 system.

A better knowledge on the thermodynamic as well as kinetic parameters could be obtained from a variable temperature study. Unfortunately, in the examined ligands, the delocalized charge distribution of the amide moiety is lost on increasing the temperature, which fact produces the collapse of the alkyl signals. Thus, any attempt to study the effects of temperature on the complex formation may be invalidated by the alteration in the structure of the ligand.

Acknowledgement

This work has been partially supported by the C.N.R. and by the Credito Industriale Sardo.

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