Inorganica Chimica Acta, 90 (1984) 185–190 185

The Thermodynamics of Complex Formation of Cyclic Tetra-aza-tetracetic Acids

RITA DELGADO, J. J. R. FRAÚSTO DA SILVA and M. CÂNDIDA T. A. VAZ

Centro de Química Estrutural - Complexo I, Instituto Superior Técnico, Lisbon, Portugal

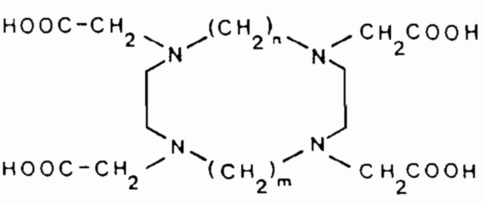
Received February 27, 1984

Enthalpy changes for the complexation of alkaline-earth and transition metals with three cyclic tetra-aza-tetracetic acids (cDOTA, cTRITA and cTETA) were obtained by continuous titration calorimetry. From these values and free energy data, the entropy changes for the same reactions were derived. The results show that these complexes are stabilised by both favourable enthalpy and entropy changes, except those of Mg^{2+} *and those of* Sr^{2+} *and* Ba^{2+} *with cTETA. Generally, the entropy changes for the reactions of the alkaline-earth metals are higher than for the reactions of the non cyclic polyaminocarboxylic acids, but for the reactions of the transition metals the entropy changes are comparable for the cyclic and non cyclic ligands. These results are discussed in terms of a model of 'cage' coordination of the metals.*

The enthalpy changes decrease with the increase in size of the tetra-aza ring (except in the case of Cu^{2+}*) but no specific cavity size effect is noticeable. Consideration of the temperature-dependent and temperature-independent contributions to* ΔH *supports the idea that the number of coordinated nitrogen atoms and carboxylate groups vary along the series.*

Introduction

In a previous paper [1] we reported the result of a study of the complexation properties of a series of cyclic tetra-aza-tetracetic acids corresponding to the general formula I.



I

a) m = 2, n = 2:
1,4,7,10-tetra-azacyclododecane-N,N′,N″,N‴-tetracetic acid ([12]aneN$_4$·4ac) or cDOTA.
b) m = 2, n = 3:
1,4,7,10-tetra-azacyclotridecane-N,N′,N″,N‴-tetracetic acid ([13]aneN$_4$·4ac) or cTRITA.
c) m = 3, n = 3:
1,4,8,11-tetra-azacyclotetradecane-N,N′,N″,N‴-tetracetic acid ([14]aneN$_4$·4ac) or cTETA.

These ligands form stable complexes with both the alkaline-earth and the transition metal ions, particularly cDOTA which had been previously reported to give the most stable Ca^{2+} complex known in aqueous solution [2].

This was confirmed in our study, in which we have also shown that the stabilities of the complexes of the alkaline-earth ions decrease abruptly with the increase in the size of the tetra-aza ring of the ligands, but the same is not found for the complexes of the transition metal ions studied, whose stability constants are very close (except in the cases of the Co^{2+} and the Zn^{2+} complexes of cTETA), in contrast with what happens with the complexes of the parent amines [3a]. On the other hand, the stability constants of the complexes of cDOTA with the alkaline-earth metals are exceptionally high, but those of the complexes of the transition metals ions compare with those of common non-cyclic complexones such as EDTA [1]. This was interpreted as implying that for the alkaline-earth metal ions all nitrogen atoms and carboxylate groups of cDOTA are involved in coordination (a situation which probably is different for cTRITA and cTETA), whereas the transition metals might be interacting with two or three of its donor nitrogen atoms and carboxylates. The increase in the size of the tetra-aza ring does not substantially alter the number and the strength of the bonds formed with each ligand. This would explain the similarity of the values of the stability constants of the transition-metal complexes of these ligands with non-cyclic complexones with less coordinating potentialities [1]. A spectral study of the complexes of Co^{2+} and Ni^{2+} with a closely similar cyclic ligand (meso-5,12-dimethyl-1,4,8,11-tetra-aza cyclotetradecane-N,N′,N″,N‴-tetra-acetic acid) also supports the idea that not all possible donors of this compound are involved in coordination [4].

0020-1693/84/$3.00

Crystallographic and ^{13}C NMR spectroscopy studies of the complexes formed by another related compound (1,4,7,10-tetra-(2-hydroxyethyl)-1,4,7,10-tetra-aza cyclododecane) [5–7] and the results of NMR studies of some lanthanide complexes of cDOTA [8–10] and cTRITA [10] have subsequently shown that these ligands are quite rigid (particularly cDOTA), that the four acetate groups seem to be all on one side of the tetra-aza ring, and that the four nitrogen atoms are completely shielded, on the opposite side, by the hydrocarbon chains which connect them [7].

These findings are now completed by a thermodynamic study of the complexation reactions of cDOTA, cTRITA and cTETA with some alkaline–earth and transition metals.

Experimental

Reagents

All ligands were synthesised and purified in our laboratories [1]. cDOTA and cTRITA were initially crystallised with 2 mol of KCl, but were later purified by passing their aqueous solutions, at pH 12–13, through an anion exchange resin, eluting with dil. HCl and concentrating the solutions until crystallisation occurred.

Analytical grade metal nitrates were used; the metal content of the solutions was checked by titrating with EDTA, except in the case of Ba^{2+}, which was determined gravimetrically as sulphate. Potassium and tetramethylammonium hydroxide titrating solutions were prepared as described in previous papers [1]; tetramethylammonium nitrate, necessary for the work with cDOTA, was prepared and purified by neutralising the hydroxide with HNO_3.

Equipment and Procedure

The calorimetric determinations were carried out in a TRONAC model 450 titration calorimeter coupled to an 'Advance digital multimeter DMM2' and to a potential *vs.* time recorder. A 100 ml glass vacuum Dewar was used as titration vessel. A 2 ml burette was used and the rate of addition of titrant was 0.383 ± 0.003 ml min^{-1}. This rate proved to be adequate since the complexation reaction of both the alkaline-earth and the transition metals with the cyclic tetra-azatetracetate ligands are relatively fast at high pH, the rate constants for the monoprotonated macrocyclic compounds being only 5–10 fold smaller than for $H(EDTA)^{3-}$ [19] and the same is probably true for the completely deprotonated ligands. The thermostat was kept at 298.000 ± 0.003 K with a TRONAC model 40 precision temperature controller. The thermometric titration curves were all linear.

The accuracy of the determinations was checked by determining the heat of neutralisation of nitric acid by potassium hydroxide, the heats of protonation of ethylenediaminetetracetic and of nitrilotriacetic acids and the enthalpy of complexation of Cu^{2+} with these two ligands. The results obtained compared favourable with those reported in the literature [3b].

The determination of the heats of protonation of the ligands, corresponding to the reactions

$$L^{4-} + H^+ \rightleftharpoons LH^{3-} \qquad \Delta H_1$$

$$LH^{3-} + H^+ \rightleftharpoons LH_2^{2-} \qquad \Delta H_2$$

was carried out by titrating 50 ml of 5.0×10^{-3} or 1×10^{-2} *M* nitric acid with 0.25 *M* or 0.50 *M* solutions of the deprotonated ligand (adding the equivalent amount of KOH or Me_4NOH). The ionic strength was kept at 0.10 *M* KNO_3 (or Me_4NNO_3).

The heats of complexation were determined by adding 0.25 *M* or 0.50 *M* solutions of the deprotonated ligand to the solutions of the metals (50 ml of 2.5×10^{-3} or 5×10^{-3} *M*) keeping the ionic strength constant to 0.10 *M*.

The values of ΔH_{ML} refer to the reaction

$$L^{4-} + M^{2+} \rightleftharpoons ML^{2-}$$

Corrections were made by taking into account the heat of dilution of the ligands and the effects due to secondary reactions, namely the hydrolysis of L^{4-} and LH^{3-} which occur simultaneously. The formation of protonated complexes, MHL, was also taken into account but can be disregarded since the error is negligible. Computer programs were developed to calculate the distribution of the species at each stage.

Results and Discussion

The results obtained are summarized in Table I. The ΔG° values were calculated from the values of stability constants of proton and metal complexes reported in [1]; ΔH° values were determined by continuous calorimetric titrations of metal solutions with the ligands and were corrected for dilution, protonation of the ligands and non-chemical effects. ΔS° values were obtained from $T\Delta S^\circ = \Delta H^\circ - \Delta G^\circ$.

Inspection of the values in Table I shows that the majority of the metal complexes are stabilised by favorable enthalpy and entropy changes; the only exceptions are the Mg^{2+} complex of cDOTA (and, certainly, of the other ligands) and the Sr^{2+} and Ba^{2+} complexes of cTETA, for which the enthalpy changes are positive.

For both the alkaline-earth metals and the transition metals, the entropy changes on complex forma-

TABLE I. Thermodynamic Functions for Proton and Metal Complexes of Cyclic Tetra-azatetracetic Acids. T = 25.0 °C; $\mu = 0.10$ ($(CH_3)_4NNO_3, KNO_3$), $\Delta G°, \Delta H°$, –kJ mol^{-1}; $\Delta S°$, – JK^{-1} mol^{-1}.[a]

Ion	cDOTA			cTRITA			cTETA		
	$\Delta G°$	$\Delta H°$	$\Delta S°$	$\Delta G°$	$\Delta H°$	$\Delta S°$	$\Delta G°$	$\Delta H°$	$\Delta S°$
H^+	–69.0	–35.1	113	–64.8	–33.5	105	–61.1	–34.3	92
	–55.2	–33.0	75	–55.6	–29.3	88	–57.7	–27.2	105
Mg^{2+}	–68.2	+7.9	255	–	–	–	–	–	–
Ca^{2+}	–98.3	–48.9	167	–69.0	–25.5	146	–47.7	–8.8	130
Sr^{2+}	–87.0	–43.9	146	–56.9	–14.6	142	–32.6	8.8	138
Ba^{2+}	–73.6	–35.6	125	–47.7	–13.0	117	–22.2	10.5	109
Co^{2+}	–115.1	–55.6	201	–114.6	–34.3	268	–94.6	–19.2	255
Ni^{2+}	–114.2	–55.2	197	–118.8	–41.0	259	–113.8	–37.7	255
Cu^{2+}	–126.8	–59.8	226	–123.0	–56.9	222	–123.4	–54.0	233
Zn^{2+}	–120.1	–44.4	255	–110.9	–35.1	255	–92.9	–15.5	259

[a]The average standard deviation of the ΔH and ΔS values, calculated from a series of six titrations using EDTA as model ligand, are, respectively, ±0.8 kJ mol^{-1} and 1.5 J K^{-1} mol^{-1}.

TABLE II. Entropy Changes for Metal Complexes of H_2O and Various Polyaminocarboxylic Acids: $\Delta S°$, J K^{-1} mol^{-1}.

Ion	H_2O	EDTA	PDTA	BDTA	CDTA	DTPA	cDOTA
Mg^{2+}	–238	213	247	238	218	222	255
Ca^{2+}	–184	113	113	96	146	121	167
Sr^{2+}	–163	109	–	–	142	84	146
Ba^{2+}	–130	80	–	–	121	67	125
Co^{2+}	–264	251	259	276	285	234	201(268[a])
Ni^{2+}	–276	247	251	234	264	222	197(259[a])
Cu^{2+}	–247	243	251	238	280	218	226
Zn^{2+}	–243	247	259	238	247	226	255

[a]Values of cTRITA. Data from references [3a] and [18].

tion do not vary much for the same ion along the series of ligands, even if some exceptions are conspicuous, such as those of the Co^{2+} and Ni^{2+} complexes with cDOTA.

Furthermore, the $\Delta S°$ values for the complexes of the transition metals compare with those found for the corresponding complexes of hexadentate non-cyclic complexones of the n-alkanediaminetetracetic acid type, such as diaminoethane, diaminopropane, diaminebutane and cyclohexanediamine-tetracetic acids (EDTA, PDTA, BDTA and CDTA) and also with those of the complexes of diethylenetriamine-pentacetic acid (DTPA), a potentially octadentate ligand –see Table II. This is not the case for the complexes of the alkaline–earth metals, for which the entropy changes are higher in the case of the cyclic complexones.

The observations are coherent with a 'model' for the structure of the complexes based in the findings of the crystallographic and NMR studies [5–10]. Indeed, if the four acetate groups are all located on one side of the tetra-aza ring (similarly to what happens with other N-substituted tetra-aza macrocycles [5–7, 11] the configuration is such that the metal ions will tend to be encapsulated within a kind of 'cage' when the complexes are formed [7]. This 'cage' is quite rigid for the first member of the series (cDOTA) and less so for the last (cTETA), but to fit inside it the metal ions must be stripped off their hydration shells before coordinating to the nitrogen and carboxylate donors.

The alkaline earth metal ions and the majority of the transition metal ions, fit well inside the 'cage', as can be seen using molecular models; this was confirmed by the determination of the metal–nitrogen distances in the complexes of the lanthanides [8, 10] and is reflected in the fact that the stability constants of the Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+} complexes decrease monotonically from cDOTA to cTETA, *i.e.* none is particularly favoured by an increase in the size of the internal cavity of the ligands. As a consequence, all metal ions will probably lose their hydration shells more or less completely and the entropy changes on complex formation will be fairly constant and close to the entropy changes on hydration of the corresponding gaseous ions (but of opposite sign), corrected for the configurational entropy changes mainly due to the four acetate groups, which are likely to be small.

The same should happen for the transition metal ions when forming complexes with other ligands which satisfy completely their specific coordination requirements, as is the case of the hexadentate non-cyclic complexones (higher coordination numbers are possible and frequent for some metals, but not for those considered here).

Since for the alkaline-earth metals the bonding is predominantly ionic and non-directed, it is expected that the 'encapsulation' of the ions brings about a higher entropy change, corresponding to the complete dehydration of the ion, whereas complex formation with 'open' ligands may leave room for some bonded water molecules. Indeed, it has recently been shown that the solid EDTA complex of Ca^{2+} has two coordinated water molecules and that of NTA still has three coordinated water molecules [12]; the same situation seems likely in aqueous solution.

Table II shows that these forecasts are indeed verified; the small differences found in the ΔS° values for the complexes of the metals with the cyclic complexones and for the hydration of the gaseous metal ions confirm that changes in configurational entropies are small.

The case of the Co^{2+} and Ni^{2+} complexes of cDOTA appears anomalous and raises doubts on the correction of the determinations. An error in ΔG° (log K) might be possible since the equilibria between cDOTA and these ions are relatively slow to establish at low values of pH, but the determinations have been repeated and gave reproducible values; on the other hand, batch experiments were also carried out in which mixtures of the metal and the ligand were left to equilibrate for more than 7 days and the results were again close to those obtained before. In any case the difference to be accounted for is of the order of 19 kJ mol^{-1} (63 J K^{-1} mol^{-1} in ΔS°), corresponding to an increase of about 3 log units in log K, with which the Co^{2+} and Ni^{2+} complexes of cDOTA would become more stable than those of Cu^{2+}, a very unlikely event.

An error in the determination of ΔH° is also possible but unlikely, not only because the values obtained are reproducible and the differences too high to be due to experimental errors, but because a decrease of 19 kJ mol^{-1} in the enthalpy changes on formation of the complexes of Co^{2+} and Ni^{2+} with cDOTA would make ΔH° less favourable than for the corresponding complexes of cTRITA and even cTETA (in the case of Co^{2+}), opposite to the general trend.

The most likely hypothesis is that the complexes of Co^{2+} and Ni^{2+} with cDOTA may still have some remaining coordinated water molecules, hence a structure different from that of cTRITA and of the cTETA complexes of the same ions, thus justifying the smaller entropy changes on their formation. Although it is not clear why this should happen, it is a possibility worth exploring in future work.

The enthalpy changes on complex formation may also be interpreted in terms of the proposed coordination model. Generally, ΔH° decreases considerably as the size of the tetra-aza ring of the ligands increases, both for the alkaline earth and for the transition metals, but the differences in the cases of the Ni^{2+} complexes of cTRITA and cTETA and the Cu^{2+} complexes of the three ligands are relatively small – less than 6 kJ mol^{-1}. The progressive fall along the series in the stability of the Co^{2+} relatively to the Ni^{2+} complexes, due to less favourable enthalpy changes in the case of Co^{2+}, is worth noting. The same is true for the Zn^{2+} complexes, which behave just like those of Co^{2+}.

From the results obtained, it seems that there is no cavity size effect; indeed, even the larger Ba^{2+} ion can fit inside the 'cage' of the ligands and a decrease in absolute value of ΔH° along the series due to the increase in the distances between the metal and the donor atoms is to be expected. However, this effect alone is insufficient to account for decreases of the order of 21–29 kJ mol^{-1} from one ligand to the next in the case of the alkaline-earth metals – note that the change in ionic radius on going from Ca^{2+} to Sr^{2+} and Ba^{2+} for the complexes of the same ligand causes differences of only about 8 kJ mol^{-1} in ΔH°. Hence, the main source of the decrease in ΔH° for the complexes of these metals may be a less favourable orientation of the lone-pair electrons of the nitrogen atoms (and of the corresponding dipole moments) for cTRITA and cTETA [13]. This may also be the case for the Co^{2+} and Zn^{2+} complexes, in which covalent rather than ionic bonds are involved, and in these cases one can more properly speak of changes in the number of nitrogen atoms bonded.

For the Cu^{2+} and Ni^{2+} complexes the values of ΔH° are fairly constant (except for the value corresponding to the complex of Ni^{2+} with cDOTA), and this supports the idea that these ions are coordinated to possibly just two or three of the nitrogen atoms of the ligands which are maintained along the series for Cu^{2+} and also for Ni^{2+} in the cases of cTRITA and cTETA.

The separation of the temperature-dependent (mainly ionic) and temperature-independent (mainly covalent and structural) components of the overall ΔH° [14–17] helps the discussion at this stage.

TABLE III. 'Covalent' (ΔH_c) and 'ionic' (ΔH_e) Contributions to the Overall $\Delta H°$ Calculated from Amine and Carboxylate Complexes of Some Transition Metal Ions. Units: kJ mol^{-1}.

Metal	$\Delta H_c^{NH_3}$	$\Delta H_e^{NH_3}$	$\Delta H_c^{-COO^-}$	$\Delta H_e^{-COO^-}$
Co^{2+}	−15.9	2.5	−1.4	5.4
Ni^{2+}	−19.2	2.5	−2.3	5.0
Cu^{2+}	−25.9	2.9	−4.2	5.9
Zn^{2+}	−14.2	3.3	−1.7	5.4

TABLE IV. ΔH_c and ΔH_e Contributions to the Overall $\Delta H°$ for the Complexes of cDOTA, cTRITA and cTETA of Some Transition Metal Ions. Units: kJ mol^{-1}.

Metal	cDOTA		cTRITA		cTETA	
	ΔH_c	ΔH_e	ΔH_c	ΔH_e	ΔH_c	ΔH_e
Co^{2+}	−74.1	18.4	−58.2	23.8	−41.8	22.6
Ni^{2+}	−73.2	18.0	−64.0	23.0	−60.2	22.6
Cu^{2+}	−80.3	20.5	−77.0	20.1	−75.0	21.0
Zn^{2+}	−66.9	22.6	−55.7	22.6	−38.4	23.0

In Table III we summarize the values of ΔH_c and ΔH_e calculated for amine and carboxylate complexes of Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} [15, 17] For the amine complexes we have used the only available series of constant values obtained at an ionic strength of 2 *M* H_4NNO_3 [3, 15]; for the acetate complexes the data are even scarcer, hence we prefer to adopt average ΔH_e values derived from the enthalpy changes on going from glycinate to iminodiacetate and nitrilotriacetate complexes [17], with ΔH_c values calculated from these and Gibbs energy values obtained from the determined stability constants at 0.1 *M* $NaClO_4$ or $\mu = 0$, corrected to 0.1 *M* [3]. From these values and from the calculated ΔH_c and ΔH_e contributions for the overall $\Delta H°$ in the complexes of cDOTA, cTRITA and cTETA (Table IV) one can estimate the probable number of nitrogen atoms and carboxylates interacting with the metal ions.

The results are summarized in Table V and should be regarded only as rough indications, even though figures close to the expected sets of likely integers were obtained: the Co^{2+}, Ni^{2+} and Zn^{2+} complexes seem to change firstly from a ($4N + 2COO^-$) to a ($3N + 3COO^-$) coordination sphere, and than to a ($2N + 3COO^-$) in the cases of Co^{2+} and Zn^{2+}, whereas the Cu^{2+} complexes seem to maintain the same coordination sphere all along the series: ($3N + 2COO^-$). This could explain why the Co^{2+} and Zn^{2+} complexes drop in stability on going from cTRITA to cTETA but the Ni^{2+} and Cu^{2+} complexes are only slightly affected. The difference is of enthalpic origin and can indeed be due to the removal of one coordinate nitrogen atom when the hydrocarbon chain of the tetra-aza cycle of the ligands increases by one $-CH_2$ unit.

TABLE V. Probable Number of Nitrogen Atoms and Carboxylate Groups Interacting with the Transition Metals in the Complexes of cDOTA, cTRITA and cTETA.

Metal	cDOTA		cTRITA		cTETA	
	N	$-COO^-$	N	$-COO^-$	N	$-COO^-$
Co^{2+}	4	2	3	3	2	3
Ni^{2+}	4	2	3	3	3	3
Cu^{2+}	3	2	3	2	3	2
Zn^{2+}	4	2	3	3	2	3

Various questions do however remain unanswered, *e.g.* the reason for the lower entropy changes in the Co^{2+} and Ni^{2+} complexes of cDOTA and the reason why there is not a more pronounced effect in $\Delta H°$ in the Ni^{2+} and Cu^{2+} complexes on going from cTRITA to cTETA if the metals are indeed bonded to three nitrogen atoms. Note, however, that the estimation of the probable number of coordinated nitrogen and carboxylate groups ignores the 'structural' factors [15] and a similar approach (*i.e.* in terms of ΔH_c and ΔH_e) using the combined effects of *e.g.* ethylenediamine and 2 glycinates affords equally 'acceptable' values for a set of $2N + 3COO^-$ groups coordinated to Cu^{2+}, which may be a better proposal and overcomes the question of small differences in the enthalpy changes along the series of complexes of this metal.

Further work (mainly crystallographic) is necessary to elucidate these problems and other doubts, but the difficult and lengthy procedures to synthesise the ligands, particularly cTRITA, constitutes a major obstacle.

References

1 Rita Delgado and J. J. R. Fraústo da Silva, *Talanta, 29,* 815 (1982).

2 H. Stetter and W. Frank, *Angew. Chem. Int. Ed. Engl., 15,* 686 (1976).

3 A. E. Martell and R. M. Smith, 'Critical Stability Constants', a) Vol. 5, Plenum Press, New York, 1982; b) Vol. 1, Plenum Press, New York, 1974.

4 H. Häfliger and Th. A. Kaden, *Helv. Chim. Acta, 62,* 683 (1979).

5 P. Groth, *Acta Chem. Scand., A37,* 71 (1983); *A37,* 283 (1983).

6 S. Buøen, J. Dale, P. Groth and J. Krane, *J. Chem. Soc., Chem. Commun.,* 1172 (1982).

7 D. S. B. Grace and J. Krane, *J. Chem. Res. (M)*, 1646 (1983).

8 J. F. Desreux, *Inorg. Chem.*, *19*, 1319 (1980).

9 J. F. Desreux, M. F. Loncin, M. R. Spirlet and J. Rebizant, *Inorg. Chim. Acta*, *94*, 43 (1983).

10 J. R. Ascenso, Rita Delgado and J. J. R. Fraústo da Silva, to be published.

11 E. K. Barefield and F. Wagner, *Inorg. Chem.*, *2*, 2435 (1973);
B. S. Nakani, J. J. B. Welsh and R. D. Hancock, *Inorg. Chem.*, *22*, 2956 (1983).

12 B. L. Barnett and V. A. Uchtman, *Inorg. Chem.*, *18*, 2674 (1979).

13 N. F. Curtis, in G. A. Melson (ed.), 'Coordination Chemistry of Macrocyclic Compounds', Plenum Press, 1979, p. 227.

14 R. W. Gurney, 'Ionic Processes in Solution', McGraw–Hill, New York, 1953.

15 G. Degischer and G. H. Nancollas, *J. Chem. Soc. (A)*, 1125 (1970).

16 G. Anderegg, *Helv. Chim. Acta*, *51*, 1856 (1968).

17 M. Cândida T. A. Vaz and J. J. R. Fraústo da Silva, *J. Inorg. Nucl. Chem.*, *43*, 1573 (1981).

18 D. Wright, J. Holloway and C. Reilley, *Anal. Chem.*, *37*, 884 (1965).

19 S. Kasprzyk and R. G. Wilkins, *Inorg. Chem.*, *21*, 3349 (1982).