A study of complex formation between some aliphatic or heterocyclic amines and gadolinium(III) tetraphenylporphyrin

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Abstract

Complex formation between gadolinium(III) tetraphenylporphyrin, GdTPP(acac), and some amines has been investigated in toluene solution. GdTPP(acac) gives 1:1 complexes with morpholine, pyrimidine, imidazole and 1-methylpyrrolidine. 1:2 complexes are formed with the chain aliphatic amines like triethyl-, tributyl-, tripentyl- and trioctylamine. Spectrophotometric studies of the formation equilibria yield the values of the stability constants. An analysis of the experimental data strongly suggests that in the amine solutions of GdTPP(acac) additional coordination of the gadolinium ion takes place. CN increases from 6 to 8. GdTPP(acac)–amine adducts are very stable in solution, and prevent demetallation of the gadolinium porphyrin complex, which is usual in common solvents.

Introduction

The relevance of metalloporphyrin complexes in various chemical and biological systems is well known. The chemistry of lanthanide porphyrins since their first successful synthesis in 1976 [1] has been of continuing interest. Such compounds have been employed as non-destructive metal-centered probes incorporated into marcomolecules of biological importance [2–5]. Gadolinium porphyrins have attracted much interest due to the fact that in these compounds the tumor concentration ability of the porphyrins [6, 7] is combined with the special properties of the f^7 configuration of gadolinium(III), which may be useful as a paramagnetic contrast in NMR imaging processes [8]. Gadolinium porphyrins can also be applied as an EPR probe, inasmuch as Gd^{3+} is the only lanthanide ion which gives a strong EPR signal at room temperature. Complexes of gadolinium may be used as metal carriers into biological systems [9–11].

Many aspects of metalloporphyrin coordination chemistry have been investigated. However, lanthanide porphyrin coordination chemistry is a rather unexplored area, except for a study done by Hambright and co-workers [12–14] concerning the stability of these complexes in water and another by Berezin and co-workers about the kinetics of demetallation by mineral acids in organic and mixed solvents [15–17]. Complexes of lanthanide porphyrins in the crystalline form exist only with acetylacetone and –OH as axial ligands. They have not been described for typical axial ligands known for porphyrins of trivalent metals, like acetates or chlorides. Furthermore, LnTPP(acac) complexes with amines have not previously been investigated, in contrast to such studies widely done with transition metal porphyrins, especially those of cobalt and iron [18–23]. Horrocks and Hove used the imidazole melt method for lanthanide porphyrin synthesis, and from NMR studies of the crystals obtained, deduced that they were possibly LnTPP(acac)–imidazole complexes with stoichiometry 1:1 or 1:2 [24].

Research on lanthanide porphyrin coordination chemistry is difficult as complexes are unstable in the commonly used solvents. It is assumed that solutions of lanthanide porphyrins are either susceptible to light (which initiates photodemetallation processes) or they decompose as a result of lanthanide ion hydrolysis [25, 26], owing to the large ionic radius of lanthanide placed well out of the plane of the N_4 moiety.

In this paper we present our results of a study concerning the search for solvents in which spontaneous demetallation of lanthanide porphyrin does not occur, or at least, is slow. We investigate the possibility of complex formation between GdTPP(acac) (Fig. 1) and triethyl-, tributyl-, tripentyl- and trioctylamine (aliphatic), or heterocyclic amines such as pyridine, morpholine, pyrimidine, imidazole and 1-methylpyrrolidine. For our study we have chosen amines which are known

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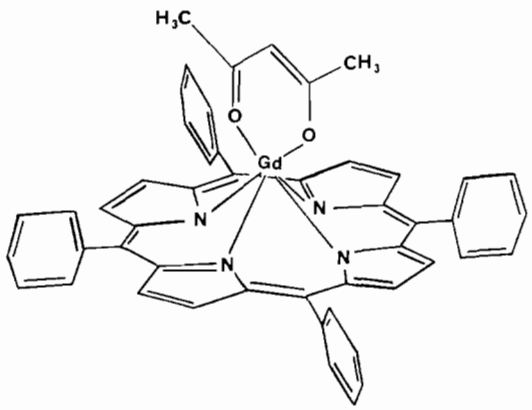

Fig. 1. Molecular structure of the GdTPP(acac) complex.

from the literature as uni- or bidentate ligands. The pK_a of chosen amines varies from 1.2 (pyrimidine) to 11.3 (1-methylpyrrolidine).

Experimental

Materials

5,10,15,20-Tetraphenyl-21*H*,23*H* porphyrin (Aldrich) was used without additional purification. Gadolinium(III)acetylacetonate hydrate was purchased from Strem Chemicals. Amines of highest available purity were purchased from Fluka and used without further purification. Neutral aluminium oxide (activity 90, 70–230 mesh, Merck) was used for column chromatography. All the solvents were certificated as purex for analysis grade (Solvants, Documentation, Syntheses – SDS) and were kept over 3 Å molecular sieves. The toluene was additionally dried by distillation over CaH_2.

Synthesis

The tetraphenylporphyrin complex of gadolinium Gd(III)TPP(acac), where H_2TPP = tetraphenylporphyrin, acac = acetylacetone, was prepared by the method described originally by Horrocks and Wong [1, 24, 27] and later modified by other authors [26, 28]. A mixture of hydrated $Gd(acac)_3$ (150 mg) and free base porphyrin (50 mg) in 1,2,4-trichlorobenzene was heated at reflux under argon for 4 h. After completion of the reaction, the 1,2,4-trichlorobenzene was removed by evaporation under reduced pressure. The residue was vacuum dried overnight, dissolved in CH_2Cl_2 and applied to an Al_2O_3 chromatography column. The unreacted H_2TPP was eluted first with toluene and then a mixture of toluene and MeOH (98:2, vol./vol.). The pure GdTPP(acac) was eluted with DMSO and then DMSO/H_2O (90:10, vol./vol.), followed by extraction of gadolinium porphyrin from the eluate with chloroform. The solvent was removed by vacuum evaporation. The final product was obtained as an amorphous powder. *Anal.* Calc. for GdTPP(acac)·8DMSO ($GdC_{65}H_{83}N_4O_{10}S_8$): C, 52.25; H, 5.59; N, 3.74. Found: C, 51.88; H, 5.80; N, 3.99%. UV–Vis (toluene) (λ_{max}, (log ϵ)): 421 (5.39), 515 (3.50), 555 (4.07), 593 (3.57). DMSO is strongly adsorbed on the gadolinium porphyrin polycrystalline powder, and we failed to remove it without partial demetallation. The IR spectrum was taken on a Nicolet 205FT-IR instrument using the KBr disk technique, and is in good agreement with literature data [29, 30], showing bands at 1520 and 1600 cm^{-1} characteristic of metalloporphyrin–acetylacetonate complexes.

Measurements

Absorption spectra were taken with a Perkin-Elmer Lambda 5 spectrophotometer, using 1 cm quartz cells to record in the near ultraviolet and visible region at a temperature of 21 ± 1 °C.

Methods

Equilibrium constants for amines binding to GdTPP(acac) were determined by the spectrophotometric titration procedure, in a spectrophotometric cell equipped with a magnetic stirrer. Neat amine or an amine solution in toluene were added in increments to a 2 ml toluene solution of GdTPP(acac) with a Hamilton syringe, until no further change in the spectrum was observed (except for dilution effects). Identical amounts of amine were added to the reference cell. Formation constants were calculated using the Benesi–Hildebrand law [31, 32]. Linearity of the plots was controlled with the Cricket-Graph program on a Macintosh computer.

Results and discussion

Gadolinium tetraphenylporphyrin is unstable in many common solvents like toluene, methylene chloride, chloroform or methanol. Figure 2 shows the modification of the absorption spectra of GdTPP(acac) toluene solution upon exposure to daylight. After 15 h, 30% of the GdTPP(acac) complex was demetallated. The process of spontaneous demetallation at first glance seems to be caused by light, but we found that it takes place even when precautions are taken to exclude light, although much more slowly. In methylene chloride, the process of demetallation is particularly fast, however it is slowed down when the solution is kept at a low temperature. Some preliminary experiments on neodymium, samarium and ytterbium porphyrins indicated that demetallation is faster for the lighter lanthanides with higher ionic radii, which are coordinated to porphyrin more 'out of the plane' formed by the porphyrin ring. We also noticed that decomposition of the

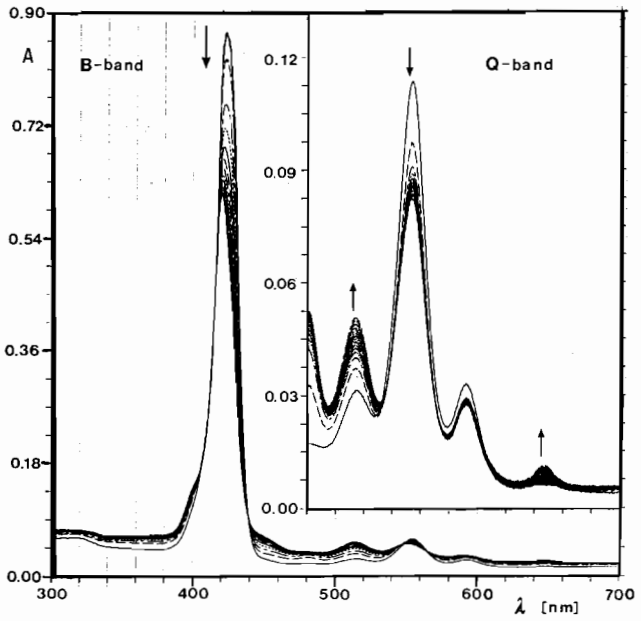

Fig. 2. Evolution of the GdTPP(acac) toluene solution absorption spectra upon 15 h exposure to daylight. Spectra were taken every hour. Solutions with different concentration were used to illustrate spectral changes of the B and Q bands ($c_M = 3.5 \times 10^{-6}$ and 1.0×10^{-5}, respectively).

GdTPP(acac) complex usually occurs in those solvents which can be considered as electron acceptors. Relatively fast demetallation in solvents which are Lewis acids suggests that this is the usual acidic demetallation process, only in our case induced by light.

It was interesting to study how the absorption spectrum of GdTPP(acac) alters with various solvents (Fig. 3) and compare these differences to changes of the spectrum of free-base porphyrin in the same solvents (Fig. 4). Every spectrum was taken of a solution with a concentration of about 10^{-6} M. The wavelength of the B and Q bands of GdTPP(acac) is seriously shifted in various solvents. In the literature this effect was considered to be a solvent effect only [27]. The solvents on Fig. 3 can be divided into two groups: the first (from cyclohexane to chloroform), may be considered as electron acceptors, the second (tetrahydrofuran to pyridine) as electron donors. The red shifts in electron donor solvents are remarkably high. This prompted us to check if complex formation occurs between amines (strong Lewis bases) and GdTPP(acac).

In Fig. 4 the band centers for H_2TPP in various solvents are presented. The shift of the bands is about 2 times smaller, and the arrangement of solvents is different compared to that for GdTPP(acac). These dissimilarities suggest that the gadolinium ion is involved in complex formation between gadolinium porphyrin and the Lewis base solvents. On the other hand the remarkable shift of the B and Q centers for H_2TPP in various solvents suggests that an electron charge transfer process between the porphyrin ring and the solvent cannot be entirely neglected. Such molecular donor–acceptor complexes in which the porphyrin ring may play either the role of the donor or the acceptor are described in the literature [33–35]. We have not found a direct correlation between band shifts and the Reichard empirical parameters of solvent polarity [36] either for GdTPP(acac), or for H_2TPP, but to a rough approximation we can say that the higher value of the parameter is connected with the bigger shift.

The stoichiometry and stability constants of the complexes formed were estimated using the Benesi–Hildebrand equation. All the gadolinium porphyrin solutions in toluene were prepared directly before measurements for a concentration range 10^{-7}–10^{-6} M. Such solutions follow the Beer–Lambert's law, and no spectral modifications were recorded up to these concentrations. The value of the absorbance was measured for exactly the same wavelength (an important requirement for the Benesi–Hildebrandt method). The stoichiometry and stability constants of the complexes formed between analysed amines and gadolinium porphyrin are presented in Table 1.

Complexes 1:1 are formed with morpholine, pyrimidine, imidazole and 1-methylpyrrolidine. As an example, the change in the GdTPP(acac) absorption spectrum upon pyrimidine titration is shown in Fig. 5. Upon evolution of the Q band only one isosbestic point can be observed. The binding of these amines to gadolinium porphyrin may be described by eqn. (1)

$$\mathrm{GdTPP(acac)} + \mathrm{Am} \overset{K_1}{\longleftrightarrow} \mathrm{GdTPP(acac)(Am)} \qquad (1)$$

The formation constants were calculated using the following expression

$$\frac{1}{A_0 - A_x} = \frac{1}{A_0 - A} + \frac{1}{A_0 - A} \times \frac{1}{K_1} \times \frac{1}{[\mathrm{Am}]} \qquad (2)$$

where A_0 is the absorbance when $[\mathrm{Am}] = 0$, A_x is the absorbance of the solution with amine concentration [Am] and A is the absorbance when the concentration of amine is very high, and we have practically only pure complex. The linear relation $1/A_0 - A_x$ versus $1/[\mathrm{Am}]$ confirms the existence of the mechanism corresponding to eqn. (1).

Complexes 1:2 are formed with other amines, but for triethyl- and tributylamine only one isosbestic point is observed upon Q band evolution. The following mechanism

$$\mathrm{GdTPP(acac)} + 2\mathrm{Am} \overset{K}{\longleftrightarrow} \mathrm{GdTPP(acac)(Am)_2} \qquad (3)$$

is confirmed by the linearity of eqn. (4)

$$\frac{1}{A_0 - A_x} = \frac{1}{A_0 - A} + \frac{1}{A_0 - A} \times \frac{1}{K_1} \times \frac{1}{[\mathrm{Am}]^2} \qquad (4)$$

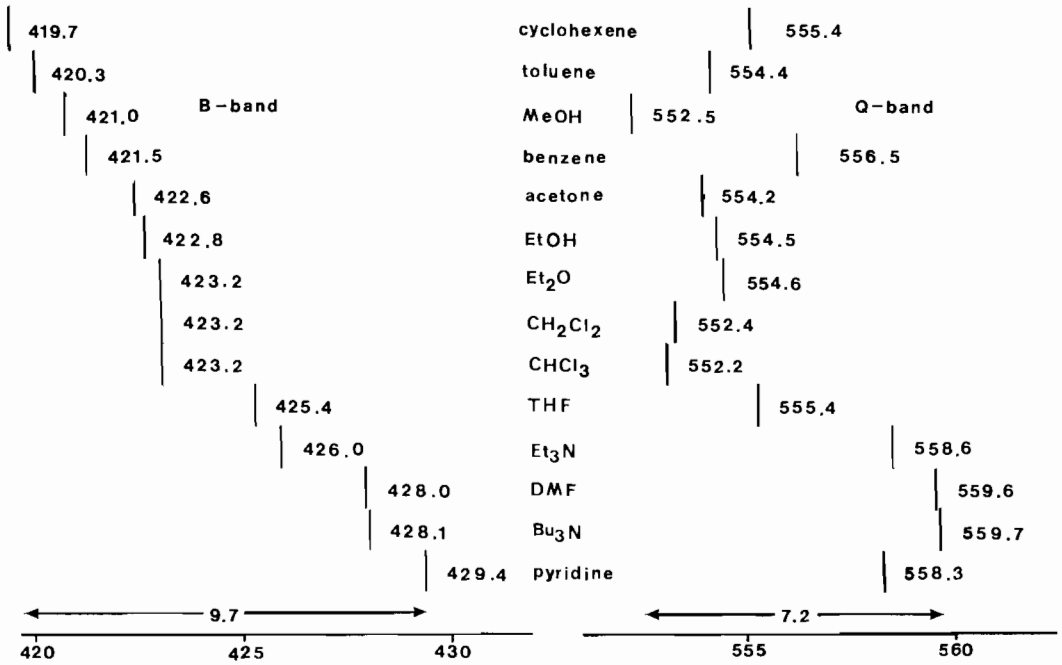

Fig. 3. Band centers (nm) from the absorption spectra of GdTPP(acac) in various solvents.

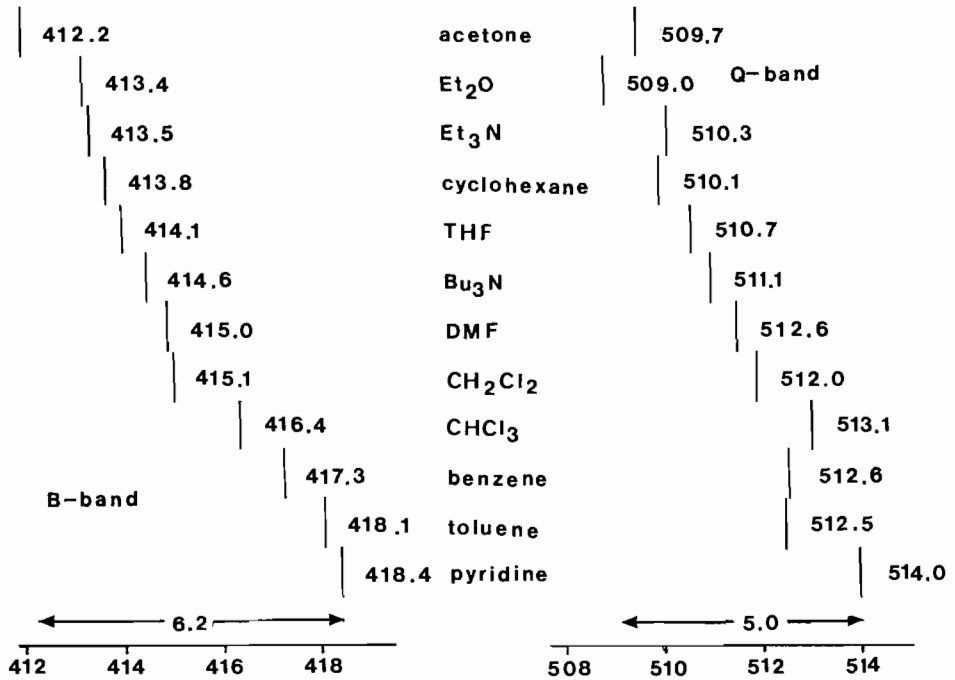

Fig. 4. Band centers (nm) from the absorption spectra of H_2TPP in various solvents.

For pyridine, tripentyl- and trioctylamine, the formation of 1:1 and 1:2 complexes is observed. Figure 6 shows an example of the evolution of the GdTPP(acac) absorption spectrum upon tripentylamine titration. The second isosbestic point appears when the concentration of the amine is increased. For the first step of complex formation reaction (1) can be proposed and K_1 was found by applying expression (2). Using the same equation for the second complex formation constant (K_2) according to the scheme

$$\mathrm{GdTPP(acac)(Am)} + \mathrm{Am} \overset{K_2}{\longleftrightarrow} \mathrm{GdTPP(Am)_2} \qquad (5)$$

is difficult, because it is not possible to estimate A accurately.

TABLE 1. Stoichiometry and formation constants of GdTPP(acac) complexes with some amines[a]

Compound	Stoichiometry	Log $K \pm E$	R
$[CH_3CH_2]_3N$ Triethylamine	1:2	3.96 ± 0.003	0.998
$[CH_3(CH_2)]_3N$ Tributylamine	1:2	5.67 ± 0.006	0.998
$[CH_3(CH_2)_4]_3N$	1:1	1.84 ± 0.009	0.997
Tripentylamine	1:2	3.20 ± 0.013	0.989
		$\log \beta = 5.04$	
$[CH_3(CH_2)_7]_3N$	1:1	265 ± 0.012	0.986
Trioctylamine	1:2	3.17 ± 0.015	0.982
		$\log \beta = 5.82$	
Pyridine	1:1	2.62 ± 0.006	0.997
	1:2	2.26 ± 0.011	0.995
		$\log \beta = 4.88$	
Morpholine	1:1	2.38 ± 0.009	0.998
Pyrimidine	1:1	2.25 ± 0.007	0.997
Imidazole	1:1	3.58 ± 0.004	0.999
1-Methylpyrrolidine	1:1	1.84 ± 0.004	0.999

[a]($E = \log(K + \text{deviation}/K)$, where deviation was estimated using the program Lotus 123; R = linear regression coefficient; $\log \beta = \log K_1 + \log K_2$.

For the K_2 calculation the following modification of the Benesi–Hildebrandt equation was applied

$$\frac{1}{A_\infty - A_x} = \frac{1}{A_\infty - A} + \frac{K_2[\text{Am}]}{A_\infty - A} \qquad (6)$$

where A_∞ is the absorbance of the GdTPP(acac)$(Am)_2$ complex [32]. The linearity of the $1/A_\infty - A$ versus [Am] plot is confirmed by the high value of the linear regression coefficient (Table 1). The same mechanism of two complexes formation probably occurs also for triethyl- and tripentylamine ligands but the kinetics of the first step may be so fast that it is not possible to observe the intermediate species.

Considering the stability constant values presented in Table 1 we can conclude that amines form relatively strong complexes with GdTPP(acac). The values of K_1 and K_2 are remarkably high. The stability of the compounds formed with the aliphatic amines increases slightly with the increasing number of CH_2 groups. There was no correlation with pK_a; the same observation was made for the amine adducts of cobalt porphyrin [37], in contrast to similar complexes of zinc, copper and nickel porphyrin [23]. However in the latter work only the derivatives of imidazole were used. It might be difficult to expect such a correlation for the large variety of ligands studied here.

If we try to answer the question about the nature of the GdTPP(acac)–amine complexes we have to take into consideration the following phenomena:

(i) Ligand exchange. The values of the formation constants are relatively high, but lower than the ones for the analogous complexes known for the cobalt and iron porphyrins [18–21]. Our attempts to isolate in the solid state the complexes with amines as axial ligands,

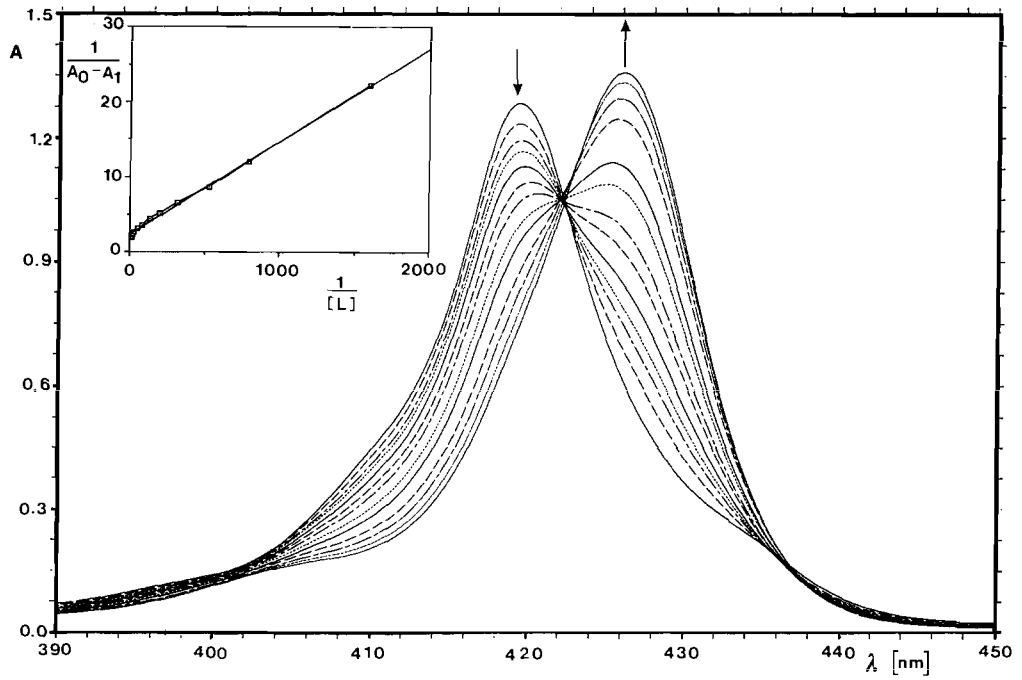

Fig. 5. Spectral changes on addition of 0.125 M pyrimidine solution in toluene to 5.2×10^{-6} M GdTPP(acac) solution in toluene. Plot of $1/A_0 - A_1$ vs. 1/[L] was done using the Cricket-Graph program.

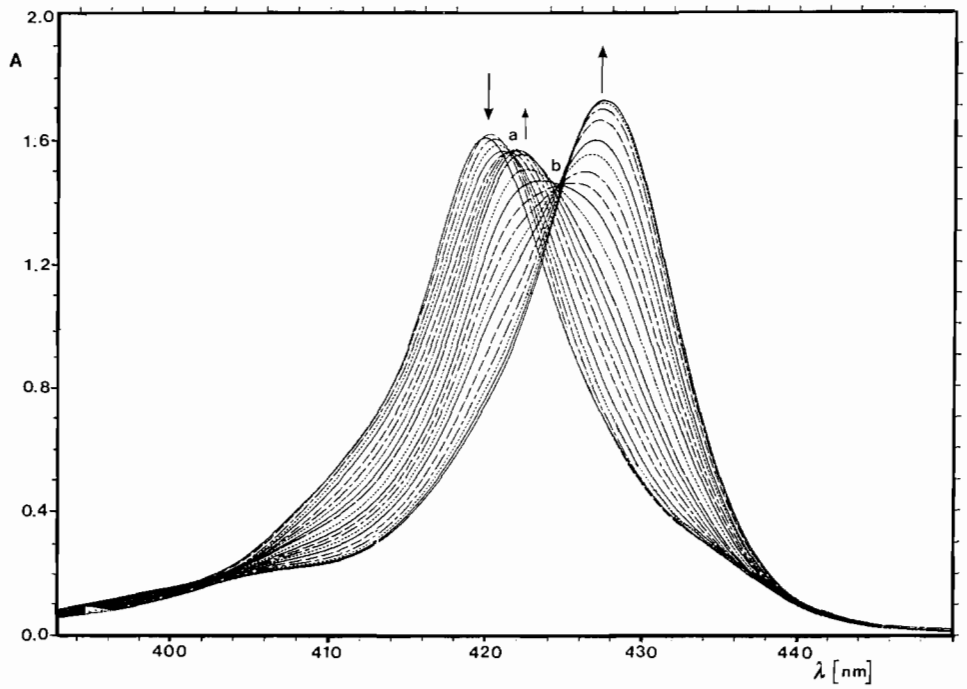

Fig. 6. Spectral changes on addition of 0.344 M tripentylamine solution in toluene to 6.5×10^{-6} M GdTPP(acac) solution in toluene.

using the common procedure [38], were unsuccessful. In every sample the presence of acetylacetone can be observed (by IR spectroscopy). We have also tried to separate such complexes on chromatography columns, but this leads either to the gadolinium porphyrin acetylacetonate complex, or to demetallation.

(ii) Electron charge transfer adduct formation. Although such compounds are not common for porphyrins, which are considered to be electron donors rather than acceptors [31], some contribution of this effect to complex formation cannot be neglected entirely. On the other hand the complex formation of free-base tetraphenylporphyrin with the same amines in toluene solution is not observed, despite red shifts in various solvents (Fig. 4). The last observation strongly supports the conclusion that gadolinium plays a dominant role in the formation of these amine adducts.

(iii) Additional coordination of gadolinium(III) ion. The possibility of the existence of coordination numbers larger than six is nothing extraordinary in the chemistry of the lanthanide complexes. It means that the coordination sphere of the Gd^{3+} ion may not be entirely saturated by the tetradentate porphyrin ring and the bidentate acetylacetone. Our results confirm that an additional coordination up to the coordination number eight, occurs with amines, which are strong Lewis bases. This conclusion is strongly supported by the fact that in our studies the ligands which can be considered as monodentate (aliphatic amines and pyridine) form complexes with stoichiometry 1:2, while bidentate amines form 1:1 complexes.

The increase of the gadolinium coordination number from six up to eight explains the stability of GdTPP(acac) in the amine solutions. The change of the absorption spectra of GdTPP(acac) in the triethylamine solution upon exposure to daylight is very small. Even after 24 h demetallation practically does not take place. The absorbance decreased only by about 3% and the shift of the bands is not observed.

Conclusions

(1) Solutions of GdTPP(acac) are stable in electron donor solvents (like amines), but are unstable in electron acceptor solvents.

(2) GdTPP(acac) forms 1:1 complexes with the amines which can be considered as bidentate ligands, but with monodentate amines forms complexes with a 1:2 stoichiometry. For pyridine, tripentyl- and trioctylamines it was possible to find two formation constants K_1 and K_2, while for triethyl- and tributylamine only overall constants were estimated.

(3) The increased stability of the GdTPP(acac)–amine complexes in solution is due to the different arrangement of the ligands surrounding the gadolinium ion. The coordination number is probably changing from six to eight.

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References

1 W. DeW. Horrocks and Ch-P. Wong, *J. Am. Chem. Soc., 98* (1976) 7157.
2 E. Knobbier, *Struct. Bonding (Berlin), 22* (1975) 1.
3 W. DeW. Horrocks, R. F. Venteicher, C. A. Spilburg and B. L. Vallee, *Biochem. Biophys. Res. Commun., 64* (1975) 317.
4 R. J. P. Williams, *Struct. Bonding (Berlin), 50* (1982) 79.
5 J. C. G. Buenzli and G. R. Choppin, *Lanthanide Probes in Life, Chemical and Earth Sciences,* Elsevier, Amsterdam, 1989.
6 J. Winkleman, G. Slater and J. Grossman, *J. Cancer Res., 27* (1967) 2060.
7 P. Hambright, R. Fawwaz, P. Valk, J. McRae and A. J. Bearden, *Bioinorg. Chem., 5* (1975) 87.
8 P. Marzola and S. Cannistraro, *Physiol. Chem. Phys. Medical NMR, 19* (1987) 279.
9 E. M. Stephens and C. M. Grisham, *Biochemistry, 18* (1979) 4876.
10 P. B. O'Hara and S. H. Koenig, *Biochemistry, 25* (1986) 1445.
11 O. Zak and P. Aisen, *Biochemistry, 27* (1988) 1075.
12 P. Hambright, C. Adams and K. Vernon, *Inorg. Chem., 27* (1988) 1660.
13 S. Haye and P. Hambright, *J. Chem. Soc., Chem. Commun.,* (1988) 666.
14 S. Haye and P. Hambright, *J. Coord. Chem., 22* (1991) 315.
15 T. N. Lomova, L. G. Andrianova and B. D. Berezin, *Zh. Fiz. Khim., 61* (1987) 2921.
16 T. N. Lomova, L. G. Andrianova and B. D. Berezin, *Koord. Khim., 14* (1988) 453.
17 L. G. Andrianova, T. N. Lomova and B. D. Berezin, *Koord. Khim., 14* (1988) 459.
18 F. A. Walker, *J. Am. Chem. Soc., 94* (1973) 1150.
19 F. A. Walker, E. Hui and J. M. Walker, *J. Am. Chem. Soc., 97* (1973) 2389.
20 E. Descalzo, H. R. Jimenez, J. M. Mortal and J. Faus, *Inorg. Chim. Acta, 108* (1985) 51.
21 T. Yoshimura, H. Toi, S. Inaba and H. Ogoshi, *Inorg. Chem., 30* (1991) 4315.
22 P. O'Brien and D. A. Sweigart, *Inorg. Chem., 21* (1982) 2094.
23 Y. C. Park, S. S. Kim and H. G. Na, *J. Korean Chem. Soc., 35* (1991) 512.
24 W. DeW. Horrocks and E. G. Hove, *J. Am. Chem. Soc., 100* (1978) 4386.
25 T. N. Lomova, L. G. Andrianova and B. D. Berezin, *Zh. Neorg. Khim., 34* (1989) 2867.
26 N. Suzuki, K. Saitoch and Y. Shibata, *J. Chromatogr., 504* (1990) 179.
27 Ch.-P. Wong, *Inorg. Synth., 22* (1983) 156.
28 S. Radzki, P. Krausz and C. Giannotti, *Inorg. Chim. Acta, 138* (1987) 139.
29 J. W. Buchler, G. Eikelman, L. Puppe, K. Rohbock, H. H. Schneehage and D. Weck, *Liebigs Ann. Chem., 745* (1971) 135.
30 W. Wenyun, Y. Yanheng and Z. Jie, *Chin. J. Appl. Chem., 3* (1986) 58.
31 R. Foster, *Organic Charge-transfer Complexes,* Academic Press, London, 1969.
32 P. Krausz and C. Giannotti, *J. Chim. Phys., 80* (1983) 299.
33 J. G. Heathcote, G. J. Hill, P. Rothwell and M. A. Slifkin, *Biochim. Biophys. Acta, 153* (1968) 13.
34 S. H. Mehdi, D. A. Brisbin and W. A. E. McBryde, *J. Sol. Chem., 4* (1975) 497.
35 W. G. Maslov, T. P. Prokofieva and A. N. Sidorov, *Zh. Fiz. Khim., 58* (1984) 381.
36 C. Reichardt, *Solvents and Solvent Effect in Organic Chemistry,* VCH, Weinheim, Germany, 1988, p. 408.
37 D. V. Stynes, H. C. Stynes, B. R. James and J. A. Ibers, *J. Am. Chem. Soc., 95* (1973) 1796.
38 H. Sugimoto, N. Ueda and M. Mori, *Bull. Chem. Soc. Jpn., 54* (1981) 3425.