# CONFORMATIONAL ANALYSIS OF Eu(III)-(ETHYLENEDINITRILO)-TETRAKIS(METHYLPHOSPHONATES) (EDTMP)

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*Dedicated to Professor Rudolf Zahradník on his special Birthday; with words of admiration for his life achievements and with the best wishes for years to come.*

The optimal geometries obtained from DFT calculations are presented for Eu(III)-EDTMP (the parent system) and cages associated with the water molecules and carbonate and hydroxide ions. The numerical results demonstrate the existence of two conformers of each cage, which might explain the observation of two spectroscopic lines previously assigned to the electric dipole transition $^7F_0 \leftrightarrow {}^5D_0$ of $Eu^{3+}$. It is also found that the water molecules are associated with the chelate via hydrogen bonds with the oxygens of the phoshonate arms, while the carbonate and hydroxide ions are chelated with the lanthanide ion due to strong electrostatic interactions between the negatively charged oxygen atoms and positively charged metal ion. The analysis is illustrated by the qualitative comparison of the energies and is concluded with the relative stability of various chelates and energetically favorable, hypothetical reactions.
**Keywords**: Lanthanides; EDTMP; DFT calculations; Conformers; Europium.

The title of a paper published in 2006 by L. Moro et al.[1]: "Europium-154 Contamination Levels in Samarium-153-EDTMP for Radionuclide Therapy" was the inspiration for our research presented here. The motivation for this research is very well described by the first sentence of this very paper: "$^{153}$Sm-EDTMP, a useful non toxic bone seeking isotope in the palliative radionuclide therapy for bone metastases ... ." These scientifically sounding quotations become personalized when realizing that the compound discussed is the medicine Quadramet® approved in the U.S.A. in 2005 for clinical application as a radiopharmaceutical. It is used for patients with advanced breast and prostate cancers, since the spread of carcinoma causes very painful bone metastases. H. Fischer et al.[2] in the report on the results

of their research performed in Vienna, Austria and devoted to the role of radiopharmaceuticals wrote: "Once these patients have developed bony metastases, pain control becomes difficult and most patients die within 6–12 months of inanition with narcotic use and immobility". This means that replacing the standard methods of palliative treatment, such as radiation therapy from an external beam or application of strong opiates like morphine, by the radiopharmaceuticals does not have only an impact upon the comfort of the life of patients, but also prolongs their survival. On a popular Web page www.virtualcancercentre.com it is stated "Once concentrated in areas of bone metastases, Quadramet helps relieve the pain they cause. The mechanism by which it achieves this is unknown." This statement is a challenge and, most of all, a demand for additional research, following the words of Maria Skłodowska-Curie: "Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less."

Quadramet® is a chelate of (ethylenedinitrilo)tetrakis(methylphosphonate) (EDTMP) coordinated with the radioactive isotope $^{153}$Sm, one of the members of the lanthanide family. Its short half-life of about 46 h and its radiation of medium-energetic β rays with the penetration range of 0.83 mm in water, make the samarium isotope an optimal source of local radiation. $^{153}$Sm is obtained by the neutron bombardment of a target made of $^{152}$Sm$_2$O$_3$, and, in the final step of Quadramet production, almost complete complexation is achieved (more than 99%) in the chelation of the isotope with the EDTMP.

The chelates of EDTMP are addressed to bone tissue, because even though absorbed by various tissues and organs when administered intravenously, they accumulate only in the bone. Unfortunately during the production of $^{153}$Sm, several isotopes of Eu are also obtained. In particular, $^{154}$Eu is produced, which is radioactive with a half-life of more than 8 years. This means that there is additional radiation provided than expected, but more important is its relatively long half-life, because of this multiple treatments can lead to a undesired build-up in the bone of the long-lived, radioactive $^{154}$Eu [1,2].

Sm$^{3+}$ and Eu$^{3+}$ are neighboring ions in the lanthanide series with the electronic configurations of 4f$^5$ and 4f$^6$ in addition to their xenon-closed shells, respectively. However in the case of the Sm$^{2+}$, its valence shell consists of 6 equivalent 4f electrons, as does Eu$^{3+}$, and both ions have the ground energy state of the $^7F_0$ symmetry. Not only from these two ions, but also from all the lanthanide ions, the Eu$^{3+}$ ion is chosen for theoretical analysis of the spectroscopic properties of newly investigated chelates. This is be-

cause of its rather simple energy scheme and clear spectroscopic spectra, which provide additional data about the properties of newly synthesized compounds. Therefore the analysis presented here is performed for the Eu(III) chelated with EDTMP.

It was observed by Mondry and Janicki[3] that in the spectrum of Eu(III)-EDTMP there are two peaks assigned to the electric dipole transition $^7F_0 \leftrightarrow {}^5D_0$. The energy levels identified by $J = 0$ are non-generate (each consists of one component), therefore the presence of these two spectroscopic lines in the spectrum might suggest that at least two diastereomeric conformers of Eu(III)-EDTMP exist simultaneously. The situation is similar to the case of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid)[4–7] and DOTP (1,4,7,10-tetraazacyclododecane $N,N',N'',N'''$-tetrakis-(methylphosphonic) acid)[8] chelates coordinated with the Eu(III) ion, where DFT calculations have provided evidence for the presence of two diastereomeric conformers of each chelate (results of calculations are in preparation for publication). However it is noted that while two diastereomeric conformers have been observed for the DOTA complexes, this is yet not the case for those of the DOTP complexes.

Although the numerical results presented here are obtained for the chelate coordinated with the $Eu^{3+}$ ion, the similarity between Eu and Sm allows one to extend all conclusions drawn here to the geometrical and energetic properties of the chelate containing the $Sm^{3+}$ ion. This is supported by the results of the analysis based on the DFT calculations performed for DOTA [6] coordinated with all lanthanide(III) ions. They show that changes in the optimal geometries for various ions across the series are minimal, and the trends and overall properties are almost independent of the number of equivalent electrons in the 4f shell. This conclusion is especially true for the neighboring ions. To confirm that this is also the case for the EDTMP chelate, a comparison of the results obtained for EDTMP chelates of $Eu^{3+}$ and $Sm^{3+}$ is presented.

## COMPUTATIONAL DETAILS

The calculations were carried out with the program Gaussian 03 [9] using the DFT method (B3LYP functional) and 6-31G* basis set[10] for all atoms except for the lanthanides. For the lanthanide(III) ions the quasi-relativistic effective core potential (ECP) of Dolg and the related (5s4p3d)-GTO valence basis sets were applied[11]. This means that for the tripositive lanthanides $46 + 4f^N$ electrons are included in the core, and the remaining electrons are treated explicitly. In all cases, full geometry optimizations were performed

and the resulting geometries were confirmed to be minima on the potential surface by the computation of the second derivative of the energy (all positive eigenvalues of the Hessian). All energies quoted include zero-point energy corrections obtained from unscaled frequencies.

### OPTIMAL GEOMETRY OF CONFORMERS OF Eu(III)-EDTMP

Calculations were performed for a total of 12 $Eu^{3+}$ chelates, two of which are the parent conformers of Eu(III)-EDTMP (**I** and **II**), and the remaining ones are the original cages coordinated with the $Eu^{3+}$ ion, associated in addition with two water molecules ($H_2O(2)$), one water molecule ($H_2O(1)$), the hydroxide ion (OH), and the carbonate dianion ($CO_3(2)$ and $CO_3(1)$). The number in parentheses indicates the number of additional oxygen atoms coordinated with the central ion. The optimized Chem3D structures for conformer **I** of all the chelates obtained with the DFT method are shown in Fig. 1
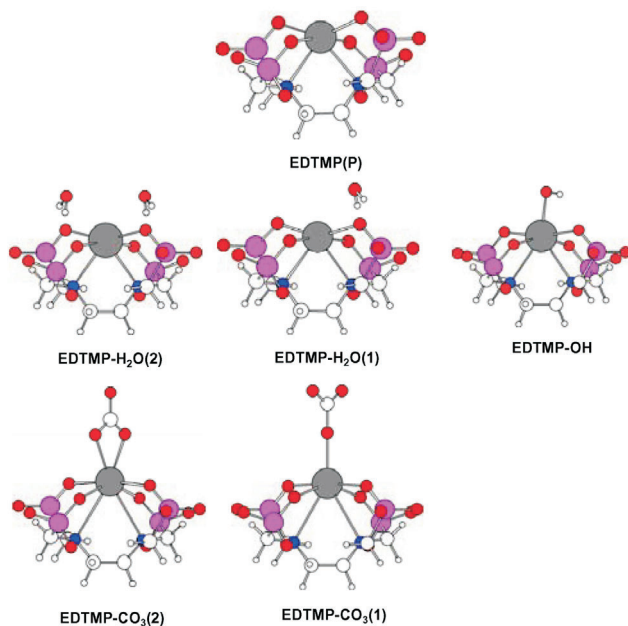


Fig. 1

Structures (conformer **I**) for which DFT calculations were performed. Oxygen atoms are red, phosphorous atoms in magenta, nitrogen atoms in blue

### *Parent Chelates*

The overall charge of the parent chelates is 5–. With the exception of Eu(III)-EDTMP-$H_2$O(1) and Eu(III)-EDTMP-OH, which has $C_1$ symmetry, all structures possess $C_2$ symmetry, and by computation of their frequencies (all real) were found to be minima. Figure 1 indicates that each cage has four oxygens of the phosphonate groups and two nitrogens of the basal plane coordinated with the $Eu^{3+}$ ion. The basal plane of EDTMP is determined by the zigzag, which is built of two nitrogen atoms connected via the C–C bond.

Inspired by the observation of two atomic-like lines attributed to the electric dipole transitions $^7F_0 - ^5D_0$ of $Eu^{3+}$ ion in Eu(III)-EDTMP [3] we undertook a search for two conformers of the parent system. Although the basal planes of EDTMP, DOTA [6] and DOTP [8] are indeed different, the similarity of their capping planes, which are determined in all cases by the four chelated oxygen atoms of the phosphonate (acetate in DOTA) arms, suggested the possible existence of at least two conformers in the case of Eu(III)-EDTMP.

In Fig. 2, the two conformers found for the parent system of Eu(III)-EDTMP, **I** and **II**, are shown. It is seen from these two views that they differ by the "twist" angle, which is defined by the line connecting the two oxygen atoms of opposite phosphonate arms ($O_1$ and $O_2$) coordinated with $Eu^{3+}$ ion (which is aligned with the *y* axis) and the bond between the two carbon atoms (yellow) connecting the nitrogen atoms (blue) of the basal plane of the cage. The consequences of the difference of more than 63° between two twist angles are seen in the lower part of the figure where the

TABLE I
Distances (in Å) of the coordinated atoms from Eu for the parent systems **I** and **II** (for the numbering of atoms see Fig. 2)

| Distance, Å | Eu(III)-EDTMP (**I**) | Eu(III)-EDTMP (**II**) |
|---|---|---|
| Eu–$O_{1(3)}$ | 2.345 | 2.331 |
| Eu–$O_{2(4)}$ | 2.367 | 2.352 |
| Eu–$N_{1(2)}$ | **2.595** | **2.595** |
| $C_1$–$C_2$ | 1.541 | 1.555 |
| $\angle(O_1O_2$–$C_1C_2)$ | 52.6 ° | –10.8 ° |
| $\Delta E$(**II**-**I**)[a] | –7.7 kcal/mol | |

[a] Difference in energy of the two conformers.

superposition of both cages is shown. Distances obtained from the DFT optimal geometry are given in Table I.

Although the result of the calculations should be treated qualitatively rather than quantitatively, the energy difference for both conformers suggests that the chelate with the arrangement of atoms in the structure of **II** is more stable than the cage with the geometry of **I**. However, at the same time, this difference is small enough to let one expect the presence of both conformers in the experimental samples. It is striking when inspecting the results presented in Table I that apart from all the changes seen in Fig. 2, the distances between Eu and the nitrogen atoms are the same in both cases (bold numbers). This means that the "zigzag" formed by these two nitrogen atoms and the two connecting carbon atoms, which define the basal plane
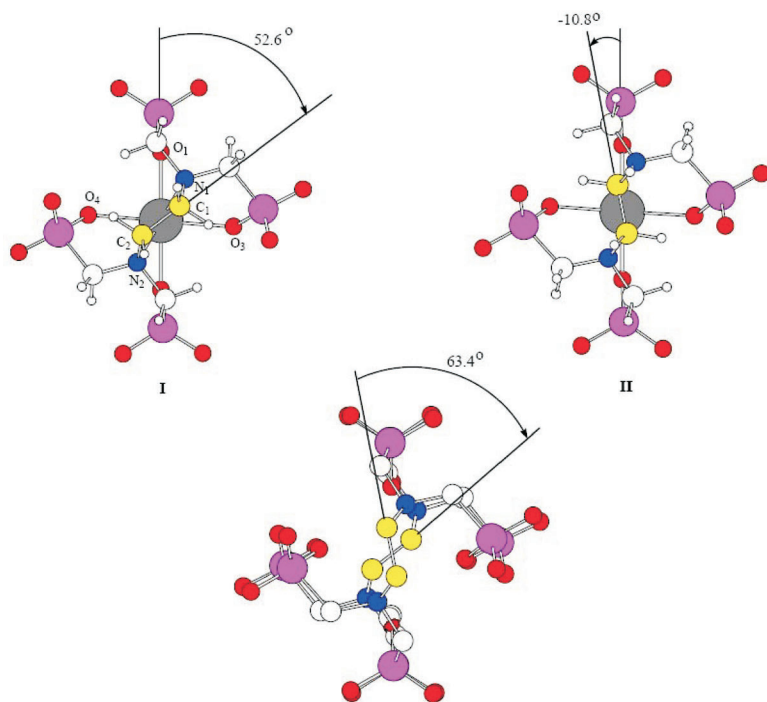


FIG. 2
Structures of the parent chelates Eu(III)-EDTMP(**I**) and Eu(III)-EDTMP(**II**) with the "twist" angles; the lower drawing shows the superposition of both conformers. Oxygen atoms are red, phosphorous atoms in magenta, nitrogen atoms in blue and carbon atoms in yellow

of the cage, adjust to keep the Eu–N distance the same with the change of the twist angle. This is a measure of strength of the coordination (chelating bond, since it is of a purely electrostatic origin) between the tripositive central ion and the negatively charged nitrogen atoms (each with the lone electron pair pointing towards the $Eu^{3+}$ ion). However, the stiffness (or rather firmness) of these parts of the chelates results in changes of the angles between the coordinated oxygen atoms of the phosphonate arms, as well as by the differences of their distances from the central ion. The two parent conformers are illustrated from another view in Fig. 3 to also show the angles between the Eu–N chelating bonds. The strength of the chelating bond between the $Eu^{3+}$ ion and nitrogen atoms permits the latter only to slide on the surface of a "sphere" while maintaining the same distance from the central ion. To compensate for the possible strain in the cage caused by this replacement of the nitrogen atoms, the C–C bond of the zigzag is twisted, as seen in Fig. 3

*Chelates Modified by $H_2O(2)$, $H_2O(1)$, OH, $CO_3(2)$, $CO_3(1)$*

In order to mimic the experimental conditions of experiment (calculations are performed in the gas phase) and to find a possible correlation between the observed spectroscopic properties of the chelates[3] and their symmetry and, in particular, to determine the order of coordination with the central ion in each case, the DFT calculations were performed for the remaining systems shown in Fig. 1. These are the parent cages additionally coordinated with water molecule(s), and hydroxide and carbonate ions.
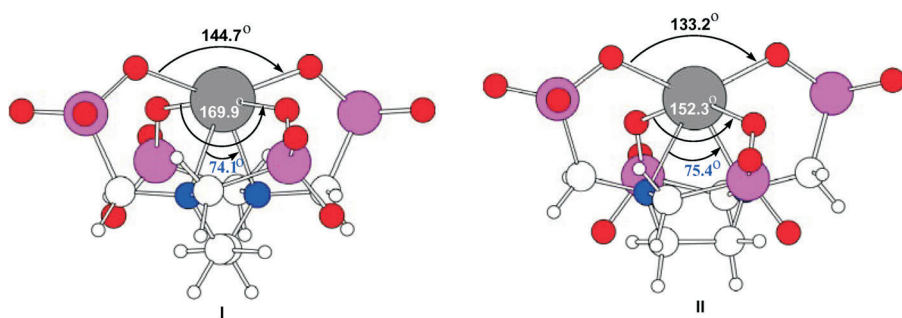


FIG. 3
Structures of both conformers **I** and **II** with the appropriate angles demonstrating their modification resulting from the change of the twist angle. Oxygen atoms are red, phosphorous atoms in magenta, nitrogen atoms in blue

The lanthanide(III) ion is responsible for the characteristic atomic-like lines observed in the spectra of the chelates. From a theoretical point of view these lines result from the electric dipole transitions between the energy levels of the lanthanide(III) ion. In the case of a free ion (in particular when the perturbing influence of the hyperfine interactions are neglected[12]), due to the Laporte parity selection rules, the electric dipole transitions are forbidden between the energy levels of the electronic configuration of equivalent electrons ($4f^N$ in the case of the tripositive lanthanide ions). When the ion is embedded in an environment of lower than spherical symmetry, the electric dipole transitions are visible in the spectrum and, from a theoretical point of view, they are forced. This is why the detailed analysis of the environment of the central ion in such systems as chelates plays a very important role. This becomes obvious when one realizes that any change or disturbance of the symmetry around the lanthanide(III) ion (including the coordination number) affects the crystal field potential, which in turn plays the dominant role in the theoretical description of the spectroscopic properties of lanthanide coordinated systems.

To gain the confidence in the results of the calculations, in Table II the distances from the $Eu^{3+}$ ion to the chelated atoms, and also the bond distances in the zigzag obtained from the DFT optimal geometries are compared with those from the X-ray structure of Eu(III)-EDTMP-$CO_3$(2) [3]. As

Table II
The DFT geometry of conformers **I** and **II** of Eu(III)-EDTMP-$CO_3$(2) compared with the X-ray structure[3]

| Distance, Å | X-ray | I | II |
|---|---|---|---|
| Cage: | | | |
| Eu–$O_{1(2-4)}$ | $2.372^a$ | 2.537 | 2.528 |
| Eu–$N_{1(2)}$ | $2.718^a$ | 3.213 | 3.155 |
| Zigzag: | | | |
| $C_1$–$C_2$ | 1.514 | 1.544 | 1.545 |
| $C_{1(2)}$–$N_{1(2)}$ | 1.489 | 1.460 | 1.464 |
| Attachment: | | | |
| Eu–$O_{1(2)}(CO_3)$ | 2.432 | 2.521 | 2.521 |

$^a$ Average of the two measured Eu–O bond distances, for the atoms from two opposite phosphonate arms; the same for the distance Eu–N. The calculated values are the same in each pair of distances because of the $C_2$ symmetry of the system.

mentioned above, (2) means that the carbonate ion is attached to the cage via two of its three oxygen atoms. The graphical comparison of the optimal structure calculated for the Eu(III)-EDTMP(**I**)-CO$_2$(2) and the X-ray structure (at the right-hand-side) is presented in Fig. 4

The analysis of all the results collected in Table II demonstrates that the symmetry and geometry of the cages are quite well reproduced by the calculations. While there are some differences in the distances between the metal ion and the coordinated oxygens and nitrogens, it is seen from this table that the over qualitative agreement between the computed and experimental structures is excellent. In both structures four phosphonate oxygens and two nitrogens are coordinated with the metal ion to form the cage. Furthermore, the conformations of the organic part of the structures are seen to be very similar. The biggest discrepancy between measured and evaluated distances, 18 and 16%, for **I** and **II**, respectively, is in the case of the coordination between the Eu$^{3+}$ ion and the nitrogen atoms, while the most accurate are the distances of the zigzag (reproduced with a relative error of 2%). This agreement lends credence to the computational method being used. However, again it should be pointed out that in the analysis presented here the tendencies in relative modifications and changes rather than the absolute numerical values (of energies, for example) are the source of the conclusions.

It is interesting to verify how the parent systems are changed when water and carbonate ions are present in close proximity. In Table III the results obtained for H$_2$O(2), CO$_3$(2) and CO$_3$(1) are presented. The latter two cases are distinguished by the coordination of the carbonate ion via one or two oxygen atoms.
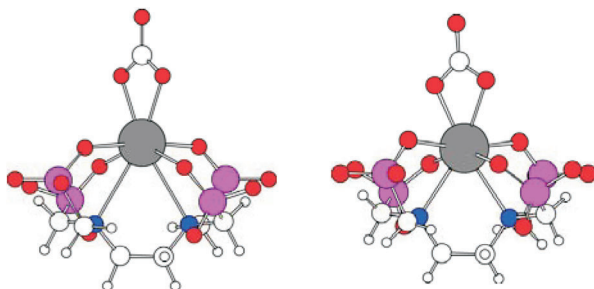


Fig. 4

Comparison of the optimized DFT geometry with the X-ray structure (right-hand side) of Eu(III)-EDTMP-CO$_3$. Oxygen atoms are red, phosphorous atoms in magenta, nitrogen atoms in blue

Inspection of the results presented in Table III allows one to derive the following conclusions:

*1.* the changes within each pair of conformers are comparable and in fact almost the same within the accuracy of the calculations,

*2.* for each cage the $C_2$ symmetry is preserved and the distances are the same for the pairs of appropriate atoms coordinated with the lanthanide(III) ion,

*3.* the distance of the chelated nitrogen from the Eu is not the same for both conformers (as it was for the parent cages) and in fact it varies the most from all the considered distances, while at the same time the C–C bond between the nitrogen atoms is practically constant for all chelates,

*4.* the presence of the carbonate ion in the vicinity of the $Eu^{3+}$ ion modifies the cage more than the presence of two water molecules; indeed the distances of the capping plane of the Eu(III)-EDTMP-$H_2O$(2) are almost the same as the counterparts for the parent systems (see also Table I),

*5.* the cage is most distorted when the carbonate ion is attached via two oxygen atoms,

*6.* the Eu(III)-EDTMP(**II**) conformer associated with the two water molecules is of lower energy than Eu(III)-EDTMP(**I**)-$H_2O$(2); the same relation is valid in the case of the carbonate ion attached via two oxygen atoms in Eu(III)-EDTMP-$CO_3$(2), while the situation is opposite for the Eu(III)-EDTMP coordinated with the carbonate ion via one oxygen atom, for which the energy of Eu(III)-EDTMP(**I**)-$CO_3$(1) is lower that the energy of Eu(III)-EDTMP(**II**)-$CO_3$(1). It is also interesting to note, that for both conformers

TABLE III
Changes in the structure of the cage when water and carbonate ions are associated with the parent chelates

| Distance, Å | I-$H_2O$(2) | II-$H_2O$(2) | I-$CO_3$(2) | II-$CO_3$(2) | I-$CO_3$(1) | II-$CO_3$(1) |
|---|---|---|---|---|---|---|
| Cage: | | | | | | |
| Eu–$O_{1(3)}$ | 2.398 | 2.379 | 2.513 | 2.507 | 2.447 | 2.417 |
| Eu–$O_{2(4)}$ | 2.405 | 2.390 | 2.560 | 2.548 | 2.512 | 2.524 |
| Eu–$N_{1(2)}$ | 2.683 | 2.671 | 3.213 | 3.155 | 3.177 | 3.135 |
| Zigzag: | | | | | | |
| $C_1$–$C_2$ | 1.534 | 1.542 | 1.544 | 1.545 | 1.542 | 1.542 |
| $\Delta E$(**II**-**I**)[a] | –4.7 kcal/mol | | 0.7 kcal/mol | | 1.2 kcal/mol | |

[a] difference in energy of the two conformers

the coordination with the carbonate ion via one oxygen atom is energetically preferable over the coordination via two oxygen atoms of $CO_3^{2-}$. However as before, these conclusions should be interpreted only in a qualitative way and in fact the simultaneous presence of both conformers is expected in practice.

The numerical results collected in Table III are illustrated in Fig. 5 where the optimal geometries of Eu(III)-EDTMP(**I**) coordinated with $CO_3(1)$, $CO_3(2)$ and $H_2O(2)$ are presented. This figure shows the relation between the distances and relative energies discussed above. Indeed, the central position of the carbonate ion chelated with the central ion via one oxygen atom is preferable, since the coordination via two oxygen atoms leads to a stronger pushing down of the phosphonate arms due to the repulsion between the negatively charged oxygen atoms. In addition, this Figure gives a basis for the most important conclusion about the coordination of the $Eu^{3+}$ ion by demonstrating that while carbonate ion is indeed chelated with the $Eu^{3+}$ ion due to the electrostatic interaction $Eu^{3+}$–$O^-_{CO_3}$, the water molecules are attached to the cage via the hydrogen bonding $H^+ \cdots O^-$; each water with one pair of the oxygens of the phosphonate arms (those which are simultaneously chelated with the $Eu^{3+}$ ion). This means that the calculated geometries of the chelates that contain water show the water molecules, which are in fact not coordinated but associated with the metal ion. As a consequence the coordination number of the $Eu^{3+}$ ion is 7, 8 and 6, respectively for $CO_3(1)$, $CO_3(2)$ and $H_2O$. This variation in the environment of the lanthanide(III) ion obviously has its consequences in the spectroscopic properties of these systems, and has a direct connection with the observed
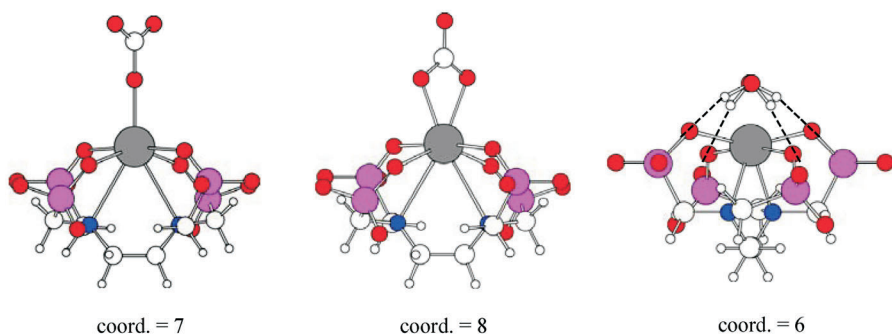


coord. = 7          coord. = 8          coord. = 6

Fig. 5

Coordination of the $Eu^{3+}$ ion in the case of the Eu(III)-EDTMP(**I**) with $CO_3(1)$, $CO_3(2)$ and $H_2O(2)$. Oxygen atoms are red, phosphorous atoms in magenta, nitrogen atoms in blue

spectra in each case. At this point it is interesting to learn which reaction, coordination with the carbonate or association with the water molecules, is energetically preferable; this issue is discussed below.

In the case of one water molecule, if its oxygen were coordinated with the metal, one would expect it to lie directly above the metal in a symmetrical position, as in the case of the oxygen atom of $CO_3(1)$. The results of DFT calculations show however that the oxygen atom of a single water molecule is moved to one side of the cage in order to be bonded by the hydrogen bridge with the oxygen atoms of two phosphonate arms as presented in Fig. 1

In Table IV the distances obtained for both conformers of the Eu(III)-EDTMP-$H_2O(1)$ are compared with those evaluated for Eu(III)-EDTMP-OH. It is seen from this table that the cages of both conformers, when associated with one water molecule or with the hydroxide ion, lose the approximate

TABLE IV
Dimension of cages of conformers **I** and **II** of Eu(III)-EDTMP-$H_2O(1)$ and Eu(III)-EDTMP-OH

| Distance, Å | Eu(III)-EDTMP-$H_2O(1)$ | | Eu(III)-EDTMP-OH$^-$ | |
|---|---|---|---|---|
| | **I** | **II** | **I** | **II** |
| Cage: | | | | |
| Eu–$O_1$ | 2.439 | 2.408 | 2.545 | 2.584 |
| Eu–$O_2$ | 2.328 | 2.323 | 2.447 | 2.416 |
| Eu–$O_3$ | 2.449 | 2.398 | 2.441 | 2.414 |
| Eu–$O_4$ | 2.331 | 2.322 | 2.458 | 2.458 |
| Eu–$N_1$ | 2.650 | 2.646 | 2.848 | 2.836 |
| Eu–$N_2$ | 2.630 | 2.618 | 2.875 | 2.843 |
| Attachment: | | | | |
| Eu–$\mathbf{O}^a$ | 2.770 | 2.891 | <u>2.307</u> | <u>2.316</u> |
| $H_1$–$O_1$ | **1.730** | **1.752** | 2.209 | 2.057 |
| $H_i{}^b$–$O_3$ | **1.756** | **1.822** | 3.896 | 3.978 |
| $O^a$–$O_1$ | 2.635 | 2.663 | 2.944 | 2.833 |
| $O^a$–$O_3$ | 2.670 | 2.732 | 3.695 | 3.978 |
| $\Delta E(\mathbf{II}\text{-}\mathbf{I})^a$ | –5.0 kcal/mol | | –2.0 kcal/mol | |

$^a$ Oxygen atom of water or hydroxide ion, respectively; $^b$ $i = 2$ for chelate with water and $i = 1$ for hydroxide ion.

$C_2$ symmetry, and the distances of respective atoms from the central ion are all different. The energy difference between the two conformers of both systems is again rather small, but qualitatively it may be concluded that the conformer with the smaller twist angle again is energetically preferable (if assuming, as before, that the error made in the calculations is the same for the pairs of conformers). Inspection of the distances collected in Table IV leads to the conclusion that there is a rivalry between the strengths of the hydrogen bonding between the hydrogens of water or hydroxide ion and the oxygens of the phosphonate arms, and chelating bond between the oxygens of these two attached species and the metal ion. The hydrogen bonding wins this rivalry in the case of the Eu(III)-EDTMP-$H_2O$(1), since the distance between the hydrogens $H_1$ and $H_2$, and the attached oxygens $O_1$ and $O_3$ is 1.7–1.8 Å (the bold numbers in Table IV) while the same distance in the cage with the $OH^-$ ion is 2.1–2.2 Å, for both conformers, respectively. The situation is reversed when the distances from the $Eu^{3+}$ ion of the oxygen atoms of both attachments are analyzed. Indeed, the oxygen of the $OH^-$ ion is situated closer to the central ion (underlined numbers in the Table IV) than the oxygen of the water molecule; the situation is illustrated in Fig. 6

In the case of the Eu(III)-EDTMP-$H_2O$(1) the electrostatic interaction between the inert oxygen of the water and the tripositive $Eu^{3+}$ ion is weaker than the strength of two hydrogen bonds with the $O_1$ and $O_3$. Therefore the water molecule is tilted towards the arms of the cage and there is little,
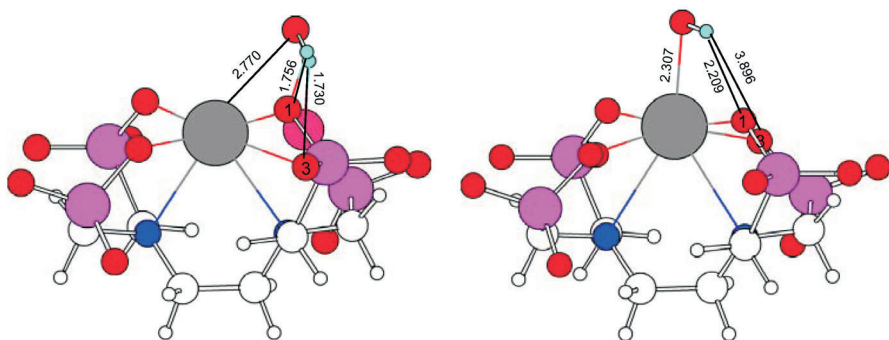


FIG. 6

Hydrogen bonds holding the water molecule in Eu(III)-EDTMP(**I**)-$H_2O$(1) (left-hand side) and chelating bond of $OH^-$ in Eu(III)-EDTMP(**I**)-OH. Distances shown are in Å. Oxygen atoms are red, phosphorous atoms in magenta, nitrogen atoms in blue, and hydrogen atoms of the hydrogen bonds in turquoise

if any, coordination with the central ion. In fact the distance of $O_{water}$ from the $Eu^{3+}$ ion, 2.770 Å, is shorter than 2.850 Å evaluated for Eu(III)-EDTMP-$H_2O$(2); this is likely the consequence of the repulsion between the oxygen atoms of the two water molecules in the latter case. As a result the coordination number of the metal ion in Eu(III)-EDTMP-$H_2O$(1) is six and is the same as in the case of the parent system of Eu(III)-EDTMP and Eu(III)-EDTMP-$H_2O$(2).

In Eu(III)-EDTMP(**I**)-OH the physical situation is different. Here the chelating bond obtains its strength from the strong electrostatic interaction between the tripositive lanthanide ion and the negatively charged oxygen atom of the hydroxide ion. The length of the chelating bond between them of 2.31 Å is even shorter than the bond between the singly coordinated $CO_3^{2-}$ ion in Eu(III)-EDTMP-$CO_3$(1) of 2.34 Å. However, as it is seen in Fig. 6, there is a certain force originating from a hydrogen bond with one of the oxygens of the arm since the $OH^-$ ion does not take a central position above the cage. It is interesting also to note that the hydrogen atom of the hydroxide ion is not placed between $O_1$ and $O_2$, but it is associated via the hydrogen bond with one of the oxygen atoms, $O_1$. This is the atom that is the most distant from all the other oxygens coordinated with the $Eu^{3+}$ ion (see Table IV) as a result of the repulsive interaction between the oxygen atoms coming close to one another. This analysis leads to the conclusion that the coordination of the metal ion in Eu(III)-EDTMP-OH is seven, the same as in the case of Eu(III)-EDTMP-$CO_3$(1).

### STABILITY OF THE Eu(III)-EDTMP CAGE COORDINATED WITH $H_2O$, $OH^-$ AND $CO_3^{2-}$

The energies obtained from the DFT calculations performed for all the systems are presented in Table V; however, it is impossible to derive any reliable conclusions from a direct comparison of the energies of the individual species. In general, only the relative magnitude obtained for the pairs of the two existing conformers of the same system leads to the conclusion which of them is more stable; these are the values of the energies underlined in Table V. It is seen that qualitatively in all cases but one, when the carbonate ion is coordinated via one oxygen atom, the second conformer (the one with the smaller twist angle) is more stable. Only for two particular cases presented in Table V, **5** ≡ Eu(III)-EDTMP-$CO_3$(2) and **6** ≡ Eu(III)-EDTMP-$CO_3$(1), it is possible to compare directly their energies, since they differ only by the spatial arrangement of the same atoms. Hence,

$$E(\mathbf{5_I}) - E(\mathbf{6_I}) = -0.0149 \text{ a.u.} = -9.4 \text{ kcal/mol}$$

$$E(\mathbf{5_{II}}) - E(\mathbf{6_{II}}) = -0.0119 \text{ a.u.} = -7.5 \text{ kcal/mol.}$$

This simple calculation shows that indeed the double coordination of the carbonate ion to the cage is energetically less favorable (by not more than 10 kcal/mol) over single coordination. It should be mentioned again that the conclusions derived from the results of the numerical calculations should be treated strictly as qualitative.

From the data given in Table V it is possible to compute the overall energy of reaction, $E_r$, of the parent system **P** with water, hydroxide ion and carbonate ion (the numerical symbols of the compounds are taken from Table V). The results of this analysis are presented in Fig. 7 where in each case the energy of the product of the reaction for the two conformers, **I** and **II**, of each system is given. Only for the cases of the association of the parent system **1** with water molecule(s), **2** and **3**, the reactions are favorable, since their energy changes are negative. It is interesting to note that the differences between the $\Delta E_r$ for the pairs of the conformers of a given type are very small, and they reflect minor variations in the geometries, which adjust to two possible twist angles, as discussed above.

TABLE V
Values of the energies obtained from the DFT calculations

| Complex | $-E$, a.u. | |
|---|---|---|
| | **I** | **II** |
| **1** EDTMP | 2648.4104 | 2648.4226[a] |
| **2** - $H_2O$(2) | 2801.2877 | 2801.2952[a] |
| **3** - $H_2O$(1) | 2724.8513 | 2724.8593[a] |
| **4** - OH | 2723.8017 | 2723.8044[a] |
| **5** - $CO_3$(2) | 2911.3084 | 2911.3095[a] |
| **6** - $CO_3$(1) | 2911.3233[a] | 2911.3214 |

$E(H_2O) = -76.3878$ a.u.

$E(CO_3) = -273.5729$ a.u.

$E(OH^-) = -75.7130$ a.u.
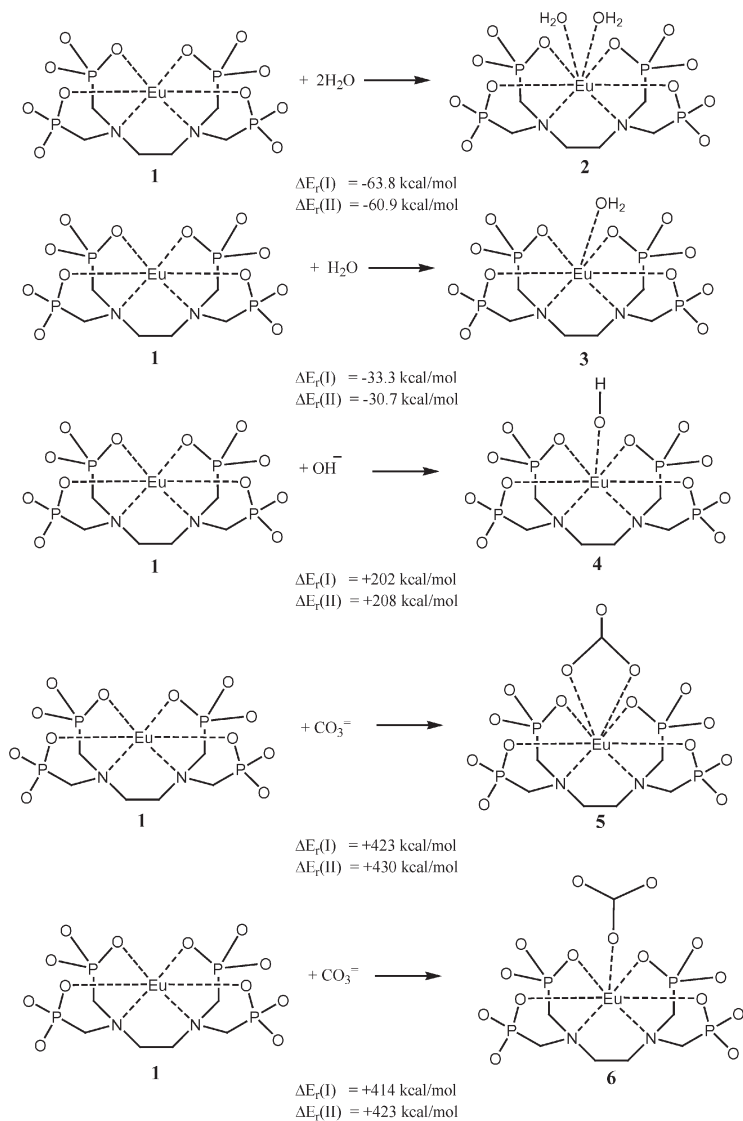
[a] The values of more stable energies.

**Fig. 7**
Energies of reaction of Eu(III)-EDTMP (parent) with water, hydroxide ion and carbonate ion; the optimal geometries of the conformer **I** (with the greater twist angle) are presented as an example. Charges in the complexes are omitted for clarity

The numerical results obtained for the products **4**, **5**, and **6** reflect the physical situation, which is present in all these cases. The strong electrostatic attraction between the negatively charged ions and the tripositive $Eu^{3+}$ ion is the physical origin of the chelating bonds, which form the cage. However there is also a strong repulsive force between the very same negatively charged $OH^-$ and $CO_3^{2-}$ ions, and the negatively charged phosphonate arms. Although the attachments are indeed chelated with the metal ion, due to the latter repulsion, the reactions are not energetically preferred, and their energies in all six cases are highly positive. It should be pointed out that Eu(III)-EDTMP-CO$_3$(2) has been isolated in the crystalline state as mentioned above[3], in spite of our high, positive calculated value of its heat of formation. The calculations presented here are performed for the gas phase and do not take into account the positively charged counter ions nor hydration waters present in the crystalline structure. Both of these factors of course help to stabilize the formation of a complex of the two highly negatively charged species. In fact some preliminary calculations demonstrated that the compensation of the total negative charge by attached hydrogen atoms to the phosphonate oxygens do not provide any qualitative changes in the optimal geometry and also the relative magnitude of appropriate energies. This has been verified for both the EDTMP chelate and its modification by the cyclohexyl group (both coordinated with the $Eu^{3+}$ ion). It was also determined that increasing the size of the basis set (diffuse functions on all oxygens) had an insignificant effect on calculated heats of formation of the carbonate complexes of Eu(III)-EDTMP.

With the evaluated energies of various cages it is possible to verify the conclusion derived above that the attachment of the water with the parent system is energetically preferable. In Fig. 8 the result of the numerical analysis of several hypothetical reactions are presented. In each case results for the two conformers are displayed below the respective scheme.

Taking the numerical results in a qualitative way it is impossible to judge which of the reactions below will occur more easily; in all cases, however, it is seen that the coordination of the parent cage with the water via the hydrogen bonding is energetically preferable. Indeed, in all cases replacement of the attached water by the carbonate or hydroxide ions results in an increase of the energy even though they would be chelated with the central ion. This is another manifestation of a strong repulsion between the attached spices and the phosphonate arms of the cage, since both subsystems are negatively charged.
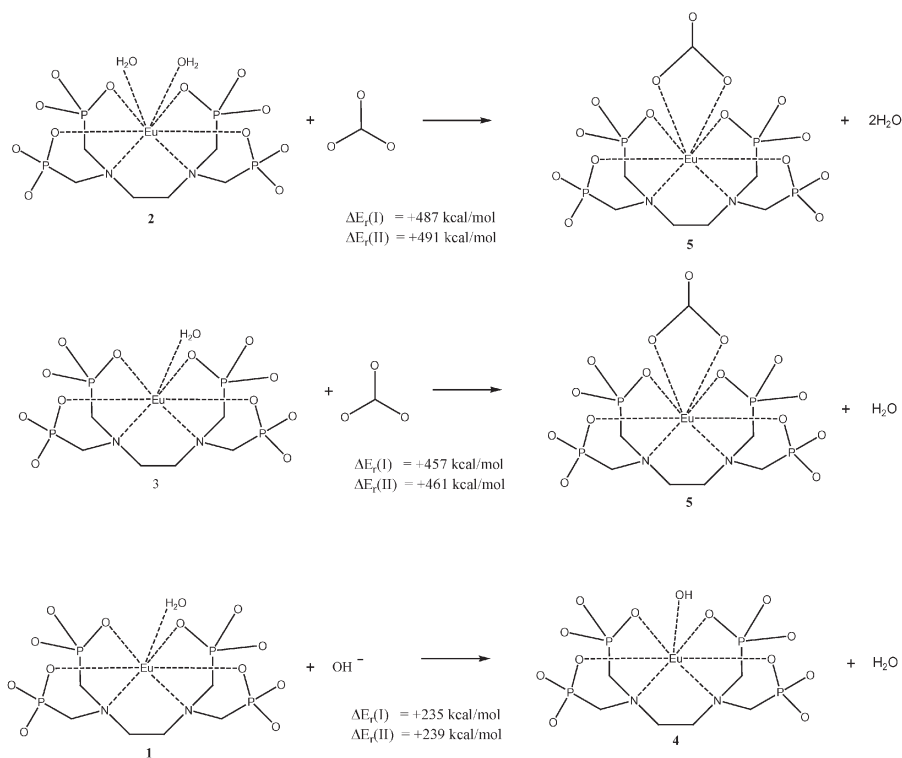
FIG. 8
Energy of reactions in which the water attached is replaced by the carbonate and hydroxide ions, respectively (two results for each case refer to two existing conformers). Charges in the complexes are omitted for clarity

### CONCLUSIONS

It has been found that Eu(III)-EDTMP complexes exist in two different conformers that are relatively close in energy. They arise from a 120 rotation about the C–C bond of the zigzag present in the basal plane of the ligand in the complex cage; this operation changes one staggered conformation into the other. It is important to note that the existence of two conformers of the Eu(III)-EDTMP cages might explain the spectra observed when the chelate is coordinated with the $Eu^{3+}$ ion.

The energy differences between two conformers of the parent system are only slightly affected by the additionally coordinated groups of hydroxide or carbonate anions or by the water molecules attached via hydrogen

bonds. A comparison of the calculated geometry with that from an X-ray structure of Eu(III)-EDTMP-CO$_3$(2) lends credence to the computational method used in the calculations presented here.

In order to verify that the overall structure of EDTMP chelates is not strongly changed by replacement of a central lanthanide(III) ion, calculations were carried out on the complex of the Sm$^{3+}$ ion (this is the major constituent of the medicine Quadramet). Again two diastereomeric conformers were theoretically identified, and like the two conformers of the parent Eu(III)-EDTMP, they differ in energy by 7 kcal/mol. The structures of the Sm(III)-EDTMP and Eu(III)-EDTMP chelates were found to be very similar. This is clearly demonstrated in Fig. 9 where the two calculated structures are superimposed.
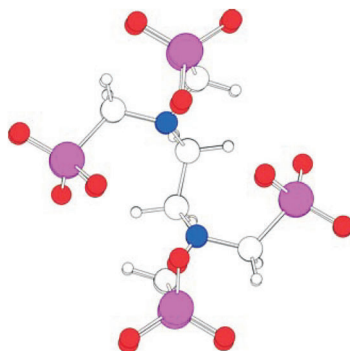


FIG. 9
Superimposed optimal geometries of Eu(III)-EDTMP(**II**) and Sm(III)-EDTMP(**II**) (the lanthanide(III) ions are removed from the figure for clarity). Oxygen atoms are red, phosphorous atoms in magenta, nitrogen atoms in blue

Although the results presented here are of a nature of basic research, their importance becomes clear in light of a remark of Maria Skłodowska-Curie:

"*We must not forget that when radium was discovered no one knew that it would prove useful in hospitals. The work was one of pure science. And this is a proof that scientific work must not be considered from the point of view of the direct usefulness of it. It must be done for itself, for the beauty of science, and then there is always the chance that a scientific discovery may become like the radium, a benefit for humanity.*"

Lecture at Vassar College, May 14, 1921

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