MAGNETIC RESONANCE IN CHEMISTRY, VOL. 35, 691–696 (1997)

Structural and Conformational Study of Macrocyclic Polyethers by NMR Spectroscopy and Molecular Modeling

A. Philippon,[1] M. Laguerre,[2] M. Petraud[3] and I. Pianet[3]*

[1] Laboratoire de Chimie Organique et Organometallique URA CNRS 35, 351 Cours de la Libération, 33405 Talence Cedex, France

[2] Centre de Recherche Paul Pascal, UPR CNRS 8641, Avenue Albert Schweitzer, 33600 Pessac, France

[3] CESAMO, Université de Bordeaux 1, 351 Cours de la Libération, 33405 Talence Cedex, France

Two macrocyclic polyether isomers were obtained by radical cyclization of (*E*)-8-iodo-3,6-dioxaoctyl-3-ethoxycarbonylpropenoate and separated by liquid–solid chromatography over silica gel. They were characterized, for the first time, by two-dimensional NMR; notably, the HMBC experiment gave access to the assignment of the two isomers through coupling via the carbonyl oxygen belonging to the macroheterocycle. The determination of the $^3J_{HH}$ coupling, associated with Monte Carlo simulation, gave information on the conformational space of these two isomers and showed that 85 conformers for one isomer and 29 conformers for the other were in equilibrium in the solution mixture. These results are discussed with regard to the complexing properties of these macrocyclic polyethers. © 1997 John Wiley & Sons, Ltd.

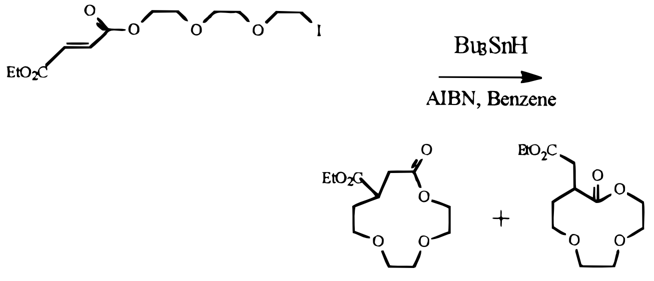
Magn. Reson. Chem. **35**, 691–696 (1997) No. of Figures: 5 No. of Tables: 3 No. of References: 16

Keywords: NMR; ^{1}H NMR; ^{13}C NMR; macrocyclic polyethers; molecular modeling

Received 19 January 1997; revised 7 May 1997; accepted 14 May 1997

INTRODUCTION

Since their discovery by Pedersen,[1] macrocyclic ethers have been extensively used as complexing agents for metallic cations.[2] The various routes developed for their synthesis involve ionic processes.[3] Recently, some macrocyclic polyethers have been synthesized by free radical cyclization, using the intramolecular addition of a primary alkyl radical to a carbon–carbon double bond activated by electron-withdrawing groups.[4,5] These radicals were generally generated from the reaction of tributyltin hydride with the corresponding halogen compound, with azobis(isobutyronitrile) in benzene at reflux. In this way, the treatment of the tributyltin hydride with (*E*)-8-iodo-3,6-dioxaoctyl-3-ethoxycarbonylpropenoate leads to two isomeric cyclic compounds, by *endo* and *exo* cyclization, with an overall yield of 70%:



Isomer 1 Isomer 2

These two isomers were separated by liquid–solid chromatography over silica gel and were identified, for the first time, by using a set of two-dimensional NMR spectra obtained by methods such as COSY, HMQC and HMBC. Coupling constants $^3J_{HH}$ were measured from 1D proton spectra in order to have access to conformational data. Using these results, molecular modeling of these two isomers was performed. These experimental and theoretical results are presented here.

EXPERIMENTAL

NMR experiments

The 1D and 2D NMR experiments were performed on a Bruker DPX400 spectrometer at 400.13 and 100.6 MHz for ^{1}H and ^{13}C experiments, respectively, equipped with an inverse 5 mm broadband probe and B_0 gradients. All the spectra were recorded using *ca.* 10 mg of both isomers dissolved in 0.7 ml of $CDCl_3$ in a 5 mm tube at ambient temperature (20 °C). Chemical shifts in ppm are given relative to TMS.

1D spectra

The ^{1}H spectra were recorded, for both isomers, with a spectral width of 2395 Hz and a pulse width of 7 μs

* *Correspondence to*: I. Pianet. E-mail: i.pianet@cesamo.u-bordeaux.fr.

CCC 0749–1581/97/100691–06 $17.50

(which corresponds to a nutation angle of 90°). A scan number of 16 and an interpulse delay of 16.84 s (6.84 s for the acquisition time and 10 s for the relaxation delay) were used. Processing, which was done without any multiplication, was carried out with 16K data points.

The proton decoupled ^{13}C spectra of the two isomers were recorded with a spectral width of 31 847 Hz with 64K data points and a pulse width of 9.5 μs (90° nutation angle). A scan number of 600 and an interpulse delay of 2 s (1 s each for the acquisition time and the relaxation delay) were used. Exponential weighting with a line-broadening factor of 1 Hz was applied before Fourier transformation.

2D spectra

The ^1H–^1H shift correlated two dimensional (COSY) spectra[6] of both isomers were obtained using the COSY-90 pulse sequence. For each t_1 increment, 16 scans were accumulated. The F_1 and F_2 spectral widths were 2395 Hz and the initial (t_1, t_2) matrices of 256×1024 real data points were zero-filled to 1024×1024 to give a final resolution of 2.3 Hz per point.

The one-bond ^1H–^{13}C chemical shift correlation (HMQC) spectra were obtained for both isomers according to the Bax sequence[7] using B_0 gradient pulses for the selection of ^1H coupled to ^{13}C carbons. For each t_1 increment, 32 scans were accumulated. The F_1 and F_2 spectral widths were 21 935 and 2395 Hz, respectively. The initial (t_1, t_2) matrices of 256×1024 real data points were zero-filled to 1024×1024 to give a final resolution of 21.4 Hz per point in the ^{13}C dimension (F_1) and 2.3 Hz per point in the ^1H dimension (F_2).

The ^1H detected heteronuclear multiple bond correlation (HMBC) spectra were recorded using the pulse sequence proposed by Bax and Summers[8] involving a low-pass *J*-filter (3.8 ms) and a delay in order to observe the long-range couplings (60 ms). As in the HMQC experiment, B_0 gradient pulses were applied in order to select ^1H coupled to ^{13}C nuclei. Except for the sequence, all the parameters were the same as in the HMQC experiment.

Simulation of ^1H spectra

All the simulation experiments were done using the gNMR c 1995 ivory soft software, version 3.6, using a 486 DX 66 PC as a calculator.

Molecular modeling

Calculations were performed on an SGI Indy 4400 SC workstation running Macromodel version 5.0 (Columbia University, New York). Conformational minima were found using the modified MM2* (1987 parameters) or MM3* (1991 parameters) force fields as implemented and completed in the Macromodel program.[9] Built structures were minimized to a final rms gradient $\leqslant 0.005$ kJ Å^{-1} mol^{-1} via the truncated Newton conjugate gradient (TNCG) method (1000 cycles). Coupling constant calculations were performed as done previously[10] and implemented in Macromodel.

Monte Carlo-style conformational search

This search is implemented in Macromodel.[11,12] The automatic setup was selected, i.e. single bonds variable, chiral centers set and flexible ring opened. In order to insure convergence, 3000 steps were made per input structure, in an energy range of 15 kJ mol^{-1} (solution accessible conformations). Each conformer was fully minimized (1000 cycles, TNCG method, rms ≤ 0.005 kJ Å^{-1} mol^{-1}, MM2* or MM3* force field). The least-used structures were used as starting geometries only if their energies were within the energetic window (15 kJ mol^{-1} of the lowest energy structure yet found). In all cases the extended cutoff option was used (VdW = 8 Å, electrostatic = 20 Å and H-bond = 4 Å).

Following the Monte Carlo search, a cluster analysis was performed with Xcluster 1.1.[13]

RESULTS AND DISCUSSION

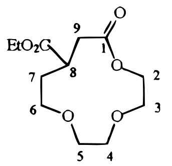
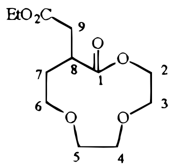
Proton and carbon-13 assignments

The classical NMR experiments (COSY, HMQC and HMBC) were used in order to determine all of the proton and carbon-13 resonances of the two isomers. The results are reported in Table 1. The two isomers are identified without ambiguity in the HMBC experiment (Fig. 1): the C-1 and C-10 carbonyls are assigned by the mean of the long-range correlation between H-2 and C-1 and H-11 and C-10. Isomer **1** also shows a correlation between H-7 and C-10 when isomer **2** exhibits a long-range correlation between H-7 and C-1.

Determination of the proton–proton coupling constants, $^nJ_{HH}$

Some proton coupling constants ($^2J_{HH}$ and $^3J_{HH}$) are measurable directly from the proton spectra with the help of a simulation software. This is the case for all the coupling constants between protons 2 and 3 and 7, 8 and 9. Iteration software was used in order to optimize all the chemical shifts and the $^2J_{HH}$ and $^3J_{HH}$ proton–proton coupling constants. Figure 2 represents, as an example, (A) the experimental and (B) the calculated expanded region of the proton spectrum of isomer **2**. This figure demonstrates the good agreement between the measurement of chemical shifts and proton–proton coupling constants with regard to the experimental expanded region containing the resonances of protons 7, 7′, 8, 9 and 9′. However, the coupling constants between protons 4, 4′, 5, 5′, 6 and 6′ are not measurable since their chemical shifts are very close and induce a coupling pattern that is difficult to interpret: all the resonances of the six protons have a chemical shift between 3.2 and 3.6 ppm for both isomers. $^2J_{HH}$ coupling constants are reported in Table 2 and $^3J_{HH}$ measured and calculated coupling constants in Table 3.

Table 1. ^{1}H and ^{13}C assignments of isomers 1 and 2

	 Isomer **1**		 Isomer **2**	
Carbon	δ_H (ppm)	δ_C (ppm)	δ_H (ppm)	δ_C (ppm)
1	—	172.3	—	175.8
2	4.21; 4.37	63.3	3.95; 4.47	65.8
3	3.67; 3.69	69.3	3.80; 3.82	70.3
4	3.61; 3.55	71.4	3.64; 3.56	71.3
5	3.51; 3.42	70.1	3.46; 3.49	73.1
6	3.50; 3.53	69.2	3.39; 3.64	70.0
7	1.97; 1.83	31.0	1.83; 1.84	33.3
8	3.11	39.3	2.84	41.2
9	2.81; 2.46	37.1	2.75; 2.34	37.0
10	—	175.1	—	172.1
11	4.11	61.2	4.06	61.1
12	1.22	14.6	1.18	14.6

Molecular modeling

The two compounds were built within Macromodel and submitted to a conformational search using a Monte Carlo technique with MM2* and MM3* force fields (see Experimental for details).

Table 2. Estimation of $^2J_{HH}$ coupling constants (Hz) of isomers 1 and 2

$^2J_{HH}$	Isomer **1**	Isomer **2**
2–2′	−11.8	−12.0
3–3′	−11.3	−12.2
4–4′	−12.0	−13.6
5–5′	−11.6	−11.3
6–6′	−10.8	−10.3
7–7′	−14.9	−14.4
9–9′	−15.1	−16.6

With MM2*, isomer **1** leads to 162 unique conformers within a 15 kJ mol^{-1} energy range (106 within exactly 3 kcal mol^{-1}; 1 kcal = 4.184 kJ) whereas isomer **2** leads to only 69 conformers within the same energy range (41 within exactly 3 kcal mol^{-1}).

Under the same conditions but using the MM3* force field, isomer **1** leads to 215 conformers within a 15 kJ mol^{-1} energy range (85 within exactly 3 kcal mol^{-1}) and isomer **2** leads to 112 conformers within the same energy range (29 within exactly 3 kcal mol^{-1}).

Since it is very difficult to detect NMR resonances from conformers whose ground-state free energies are more than 2 kcal mol^{-1}, above the minimum energy conformation it is interesting to know how many conformations would remain: using MM2* calculations 53 and 11 conformers are found for isomers **1** and **2**, respectively; the number of conformers falls to 31 and 7 for isomers **1** and **2**, respectively, using MM3* calculation.

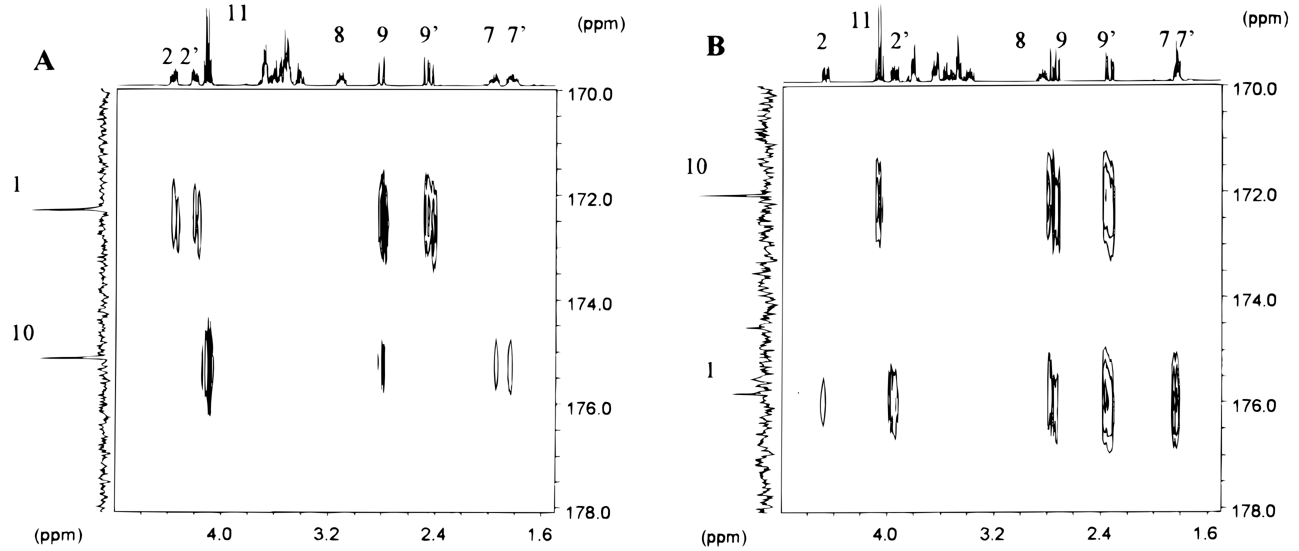


Figure 1. Part of the HMBC spectra showing the correlations between the carbonyl groups and the different protons of (A) isomer **1** and (B) isomer **2**.

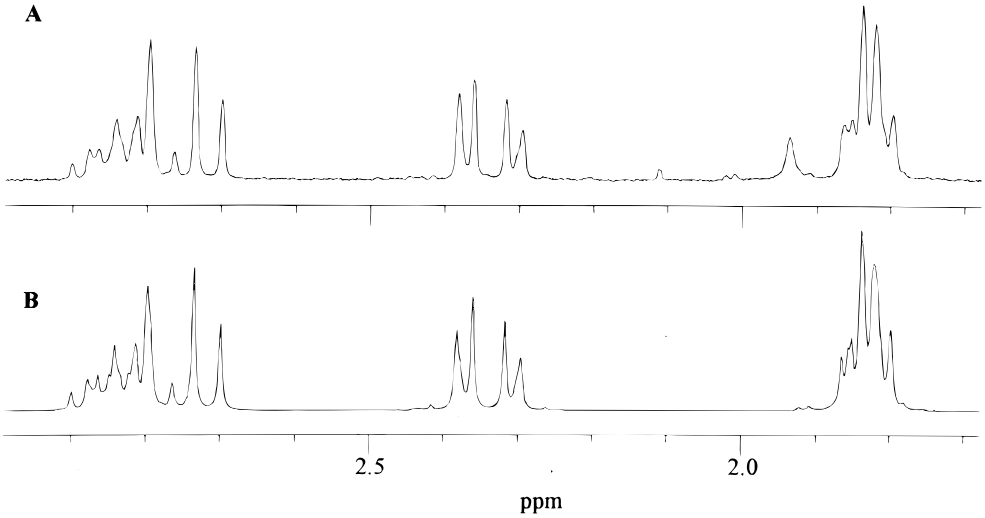


Figure 2. Expanded region (1.5–3 ppm) of (A) the experimental and the (B) calculated spectrum of isomer **2** comprising protons 7, 7′, 8, 9 and 9′. The experimental spectrum was acquired at 250 MHz.

The conformer files were analyzed using the Xcluster 1.1 program implemented in Macromodel.[13] For this purpose, we used a distance criterion selection as the rms difference between corresponding all heavy atoms in pairs of structures. This approach leads to a set of clusters, each of them being a family of conformers. In Xcluster, a conformer belongs to a cluster if it lies within the threshold distance of any component of this cluster and at more than this threshold distance of all components of all other clusters. Under these conditions and with MM2*, for isomer **1** at the best separation ratio level (level 199, rms = 0.58 Å) 17 clusters remain (seven clusters only within 3 kcal mol^{-1}) (Fig. 3); under the same conditions for isomer **2** (level 100, rms = 0.66 Å) 13 clusters remain (10 clusters only within 3 kcal mol^{-1}) (Fig. 4).

In order to compare the conformers found by the Monte Carlo search with the experimental data via the $^3J_{\mathrm{HH}}$ coupling constants, a second cluster analysis was performed using torsional H—C—C—H angles as a distance criterion. This analysis proved to be long and tedious as there are 20 coupling constants in the two compounds. In fact, it was not possible to find a cluster fitting exactly the eight ^3J measured constants. As these two compounds present a large number of possible conformers, a large part of them being separated by less than 0.2 kJ mol^{-1}, we made the hypothesis that at ambient temperature there is a rapid interconversion between all these conformers on the NMR time-scale. To test this hypothesis, ^{13}C spectra were acquired at -50 °C. At this temperature, no coalescence phenomena were observed, suggesting that the intercon-

Table 3. $^3J_{\mathrm{HH}}$ coupling constants (Hz) between protons, measured directly from the proton spectra with the help of simulation software (measured, first column) and/or determined from the molecular modeling of the two isomers; in the latter case, the values expressed are the Boltzmann means using the MM2* or MM3* method (calculated, second column)

		Isomer **1**			Isomer **2**	
		Calculated			Calculated	
$^3J_{\mathrm{HH}}$ [a]	Measured	MM2*	MM3*	Measured	MM2*	MM3*
2–3	6.7	4.6	4.8	1.5	2.5	1.3
2–3′	2.7	3.9	2.4	5.4	4.6	3.7
2′–3	2.8	3.5	2.4	8.8	6.3	8.4
2′–3′	6.3	6.3	6.8	1.4	2.6	1.3
4–5	2.1	3.3	2.0	1.5	2.1	1.7
4–5′	7.5	5.6	7.3	3.8	3.5	3.1
4′–5	5.3	5.4	4.5	0.9	3.6	1.8
4′–5′	1.7	3.3	2.0	8.9	8.8	8.8
6–7	2.5	2.7	3.6	2.8	3.6	2.6
6–7′	9.2	7.6	6.7	4.9	3.8	4.2
6′–7	6.2	6.6	7.0	8.7	10.2	10.9
6′–7′	2.7	2.9	3.5	2.1	2.0	1.2
7–8	6.4	4.6	6.2	10.3	11.5	11.7
7′–8	6.6	7.7	5.7	2.6	2.5	2.5
8–9	2.6	2.5	2.4	9.1	11.0	9.0
8–9′	10.8	9.0	11.1	5.8	4.2	5.9

[a] The convention used is that the more shielded atom has a prime.

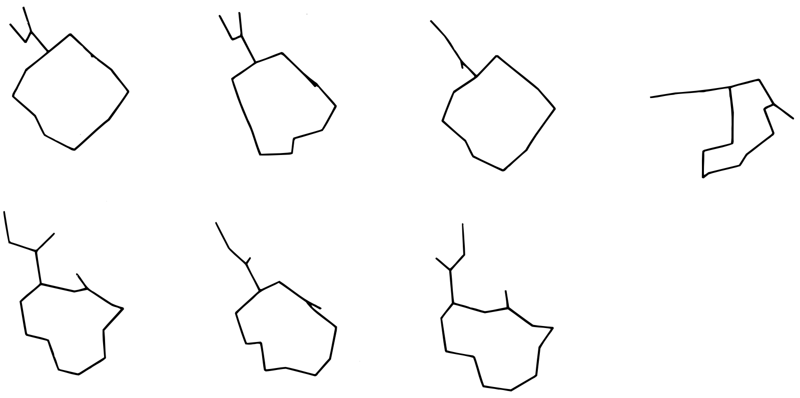


Figure 3. Isomer **1**: different families within 3 kcal mol^{-1} (heavy atoms only).

version barriers are too low to be measured by NMR. Then, as this option is implemented in Macromodel, we calculated the average coupling constants. Using the file containing only low-energy conformers, we performed a Boltzmann averaging. The results are reported in Table 3.

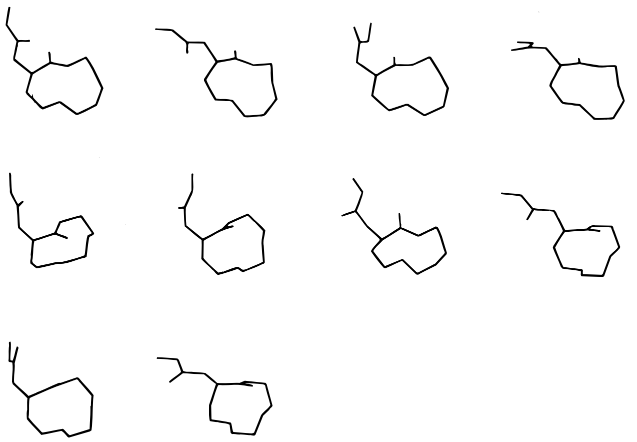


Figure 4. Isomer **2**: different families within 3 kcal mol^{-1} (heavy atoms only).

As already noted with compounds containing only C, H and O, the results found with MM3* are marginally better than those found with MM2*.

Calculated spectra

Since we could observe a good correlation between $^3J_{HH}$ coupling constant measurements and calculations obtained from the Boltzmann mean of the 85 and 29 conformers of minimum energies for isomers **1** and **2**, respectively (see Table 3) for protons 2, 3, 7, 8 and 9, we tried a second time to measure the coupling constants for protons 4, 5 and 6. We used, as a starting point, the experimental chemical shifts determined with precision in the HMQC spectra, the $^3J_{HH}$ values calculated from MM2* and MM3* calculation and $^2J_{HH}$ coupling constants commonly observed for vicinal coupling (between −10 and −17 Hz). An iteration procedure was then applied to the obtained calculated spectra in order to have a good estimate of these coupling constant values. As shown in Fig. 5, which represents the experimental and the calculated expanded regions containing the resonances of protons 3′, 4, 4′, 5, 5′, 6 and 6′ of isomer **1**, the coupling pattern obtained is very similar to that

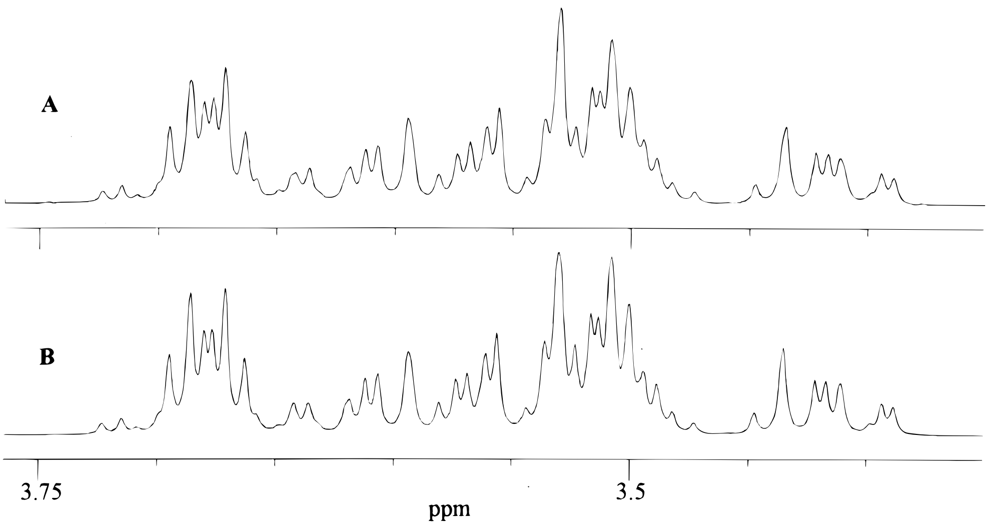


Figure 5. Expanded region comprising protons 3′, 4, 4′, 5, 5′, 6, 6′ of isomer **1**. (A) Experimental and (B) calculated spectrum. The values used for the calculated spectrum are those reported in Table 1 for chemical shifts, in Table 2 for $^2J_{HH}$ coupling constants and in Table 3 for $^3J_{HH}$ coupling constants.

observed in the experimental spectrum. The coupling constants obtained are reported in Table 2 for $^2J_{HH}$ and in Table 3 for $^3J_{HH}$.

CONCLUSION

The results presented in this paper show that NMR results are in good agreement with the molecular modeling findings, that is, the $^3J_{HH}$ coupling constants reflect well the Boltzmann mean of the 85 and the 29 conformers found by the molecular modeling calculation for isomers **1** and **2**, respectively. On the other hand, we showed that molecular modeling can be of great help for the measurement of $^3J_{HH}$ coupling constants with coupling patterns that are difficult to interpret. Finally, the measured $^3J_{HH}$ coupling constants agree better with the MM3* than with the MM2* calculation, confirming that, in such compounds, the former mode of calculation is better adapted. Such results suggest that, even for small molecules, NMR analysis and molecular modeling are complementary methods which can give information about the chemical properties of the studied molecule. Indeed, with regard to the results obtained here, it will be of interest to study the complexing properties of each isomer. On the one hand, isomer **1** presents a larger ring, capable of receiving a metallic cation, whereas isomer **2** has a longer arm containing an ethoxycarbonyl function, able to facilitate fixation of the metallic cation.[3–16] On the other hand, isomer **2** being less mobile than isomer **1**, access of the cation would be easier. Such complexation studies will be performed in order to combine structural data with the properties of these macroheterocycles.

REFERENCES

1. C. J. Pedersen, *J. Am. Chem. Soc.* **89**, 2495, 7017 (1967).
2. G. W. Gokel, *Crown Ethers and Cryptands*. Royal Society of Chemistry, Cambridge (1991), and references cited therein.
3. B. Dietrich, P. Viout and J. M. Lehn, *Aspect de la Chimie des Composés Macrocycliques*. Interéditions et Editions du CNRS, Paris (1991), and references cited therein.
4. A. Philippon, Thesis, University of Bordeaux 1 (1996).
5. A. L. J. Beckwith, K. Drok, B. Maillard, M. Degueil-Castaing and A. Philippon, *Chem. Commun.* 499 (1997).
6. W. P. Aue, E. Bartholdi and R. R. Ernst, *J. Chem. Phys.* **64**, 2229 (1976).
7. A. Bax and S. Subramanian, *J. Magn. Reson.* **67**, 565 (1986).
8. A. Bax and M. F. Summers, *J. Am. Chem. Soc.* **108**, 2093 (1986).
9. F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrikson and W. C. Still, *J. Comput. Chem.* **11**, 441 (1990).
10. C. V. Altona, C. A. G. Haasnoot and F. A. A. M. de Leew, *Tetrahedron* **36**, 2783 (1980).
11. G. Chang, W. C. Guida and W. C. Still, *J. Am. Chem. Soc.* **111**, 4379 (1989).
12. M. Saunders, K. N. Houk, Y. D. Wu, W. C. Still, M. Lipton, G. Chang and W. C. Guida, *J. Am. Chem. Soc.* **112**, 1419 (1990).
13. P. S. Shenkin and D. Q. McDonald, *J. Comput. Chem.* **15**, 899 (1994).
14. G. W. Gobel, in *Crown Ethers and Cryptands*, edited by J. F. Stoddart, pp. 111–113. Royal Society of Chemistry, Cambridge (1991).
15. S. Buoen, J. Dale, P. Groth and J. Krone, *J. Chem. Soc.* 1172 (1982).
16. G. Shoham, D. W. Christianson, R. A. Bartsch, G. S. Heo, U. Olsher and W. N. Lipscomb, *J. Am. Chem. Soc.* **106**, 1280 (1984).