Journal of Inclusion Phenomena and Molecular Recognition in Chemistry **13**: 361–367, 1992.

Synthesis, Characterization, NMR Study and Clathration Ability of *N*,*N*′,*N*″,*N*‴-Tetratosyl-8,11,21,24-tetramethyl-2,5,14,17,-tetraaza-[6.6]-paracyclophane

SALVATORE FAILLA and PAOLO FINOCCHIARO*
Institute of Chemistry, Faculty of Engineering, University of Catania, Viale A. Doria 6, 95125 Catania, Italy

(Received: 11 March 1992; in final form: 25 May 1992)

Abstract. The title macrocycle **1** was synthesised in good yield (66%) by a one-pot condensation process from 2,3-bis(chloromethyl)-*p*-xylene and *N*,*N*′-ditosylethylendiamine. The macrocycle was found to undergo isomerization processes at elevated temperature on the NMR time scale ($\Delta G^{+} = 87.8$ kJ mol^{-1}) and acts as a suitable host only for toluene. The FAB-MS spectra of **1** is rich, and full of interesting and very diagnostic fragmentation pathways.

Key words. Isomerization processes, FAB-MS spectra, selective clathration.

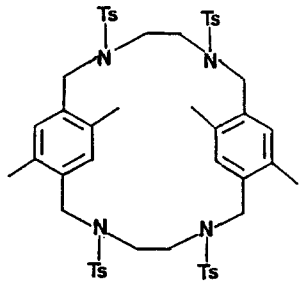
1. Introduction

In the past few years we have investigated in some detail the one-pot condensation of a tosylamide sodium salt with bis(halomethyl)-aromatic compounds which offers a practical route to symmetrical *N*-tosyl azamacrocycles [1]. The interest in some of the compounds investigated resides in their ability to selectively bind transition metals [1, 2]; furthermore, detosylation of these materials affords bifunctional aminomacrocycles which have proved to be suitable matrices for structurally defined polymeric compounds [3, 4].

Unfortunately, most of the azamacrocycles so far synthesized show an internal cavity which is too small to accommodate neutral organic molecules, and, in some cases, their stereochemical rigidity prevents measurements of the isomerization processes [5]. Thus, with the aim of enlarging the internal cavity of our aza-cyclophanes in order to thus broaden the potential of these compounds to act as hosts, and with the hope of detecting stereochemical non-rigidity on the NMR time-scale, we synthesized *N*,*N*′,*N*″,*N*‴-tetratosyl-8,11,21,24 -tetramethyl-2,5,14,17,-tetraaza-[6.6]-paracyclophane (**1**).

In addition, cyclophane **1**, after detosylation, can be viewed as a suitable macrocycle susceptible of undergoing functionalization on the trivalent nitrogen in order to improve its water solubility or its ability to complex metals.

* Author for correspondence.



1

2. Experimental

2.1. GENERAL

2,5-bis(chloromethyl)-*p*-xylene, solvents and chemicals used, were high purity commercial products (Aldrich) which were recrystallised before use.

Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected.

^{1}H-NMR spectra were recorded at ambient temperature in $CDCl_3$ with Me_4Si as internal reference using a Bruker AC-250 instrument operating at 250 MHz. The variable temperature measurements were performed in $C_6D_5NO_2$ as solvent, with TMS as internal standard, and the spectra were recorded on a Bruker WP-80 NMR spectrometer operating at 80 MHz.

Mass spectra were obtained using a double focusing Kratos MS 50S instrument equipped with a standard FAB source and a DS 90 data system. 3-Nitro-benzyl-alcohol was used as a matrix.

2.2. SYNTHESIS OF AZA-MACROCYCLE 1

To a stirred suspension of anhydrous K_2CO_3 (30.7 g, 0.22 mol) in anhydrous DMF (500 mL) at 80°C a solution of *N,N'*-ditosyl ethylendiamine [6] (14.5 g, 0.039 mol) and a solution of 2,5-bis(chloromethyl)-*p*-xylene (8.0 g, 0.039 mol) in DMF (500 mL in total) were added dropwise and at equal rate, over a period of 10 h, from two different separatory funnels. After the addition was completed, the reaction mixture was stirred overnight at room temperature. The reaction mixture was then warmed again at *ca.* 100°C, filtered when hot, and the filtrate was concentrated to about 200 mL. White crystals were formed, on standing, and were collected by filtration and washed several times with water, in order to yield a white powder. The solid was recrystallised from DMF in order to give **1** (13.0 g, 66%) as minute white needles which are solvated with a very limited amount of DMF, as judged by NMR integration. Recrystallization from different solvents ($CHCl_3$, dioxane) yielded pure **1** (64%), m.p. > 320°C; ^{1}H-NMR ($CDCl_3$) δ: 1.99 (*s*, $ArCH_3$, 12 H), 2.45 (*s*, $TsCH_3$, 12 H), 2.13 and 3.55 (two *t*, $J = 12.2$ Hz, NCH_2, 8 H), 4.03 (*AB* quartet, $J = 15.2$ Hz, $ArCH_2$, 8 H), 6.24 (*s*, ArH, 4 H), 7.31 (*d*, $J = 8.1$ Hz, TsH, 8 H) and 7.69 (*d*, $J = 8.1$ Hz, TsH, 8 H), irradiation of the peak

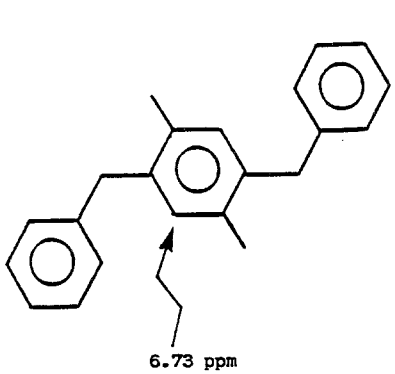
at $\delta = 3.55$ ppm causes coalescence into a singlet of the peak at $\delta = 2.13$ ppm; FAB-MS: *m/z* 997 MH^+. *Microanalysis* (%) *found* (*required*) for $C_{52}H_{60}N_4O_8S_4$: C 62.85 (62.62), H 6.01 (6.06), N 5.70 (5.61).

3. Results and Discussion

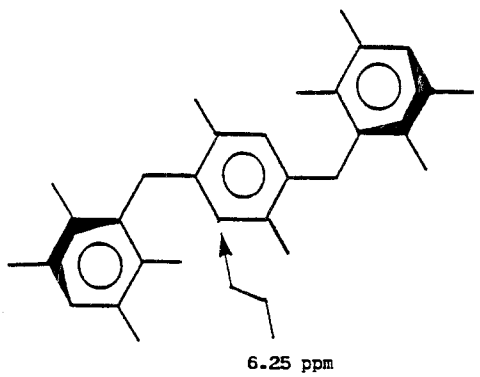
3.1. NMR SPECTRA

The ^{1}H-NMR spectrum of **1** in $CDCl_3$ at ambient temperatures, besides confirming the cyclic structure of our compound, allows us to extract some interesting conformational information.

First of all, the xylyl aromatic protons resonate at $\delta = 6.24$ ppm, a value which is quite up-field for a sym-tetramethyl substituted benzene (*ca.* 6.8 ppm) indicating that such protons should experience an up-field shift due to the ring current effect of a benzene nucleus. In order to interpret such an effect, the chemical shift of the xylyl protons in compounds **2** and **3**, both measured at ambient temperatures in $CDCl_3$ as solvent, are reported below.



2



3

In a previous work [7] we rationalized the difference in chemical shifts between compounds **2** and **3**, in terms of a preferred conformation for compound **3** which experiences a double-tri-ortho-substitution forcing the molecule to adopt a 'perpendicular' conformation in which the xylyl protons reside, for steric reasons, under the shielding cone of the durene ring.

Following such an interpretation we can suggest for compound **1** the existence of a preferred conformation A (see Figure 1) in which the aromatic nuclei of the tosyl groups lie above the xylyl protons, causing such a long-range up-field shift.

Furthermore the ^{1}H-NMR spectrum of **1** at ambient temperatures reveals an AB quartet for the methylene hydrogens attached to the xylyl ring. This pattern is indicative of restricted rotation of the aromatic rings: on increasing the temperature, the AB quartet broadens significantly and finally coalescence phenomena are observed in $C_6D_5NO_2$ at $T = 391$ K.

By employing the Gutowski–Holm approximation [8] a $\Delta G^{\neq}$ value of 87.8 kJ mol^{-1} was calculated for the isomerization process, which should occur via π-radian rotation of one xylyl ring with respect to the other one.

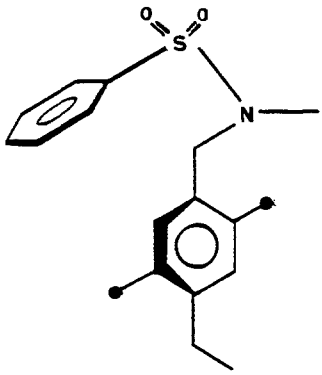
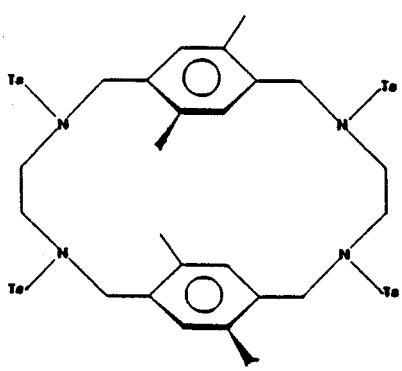


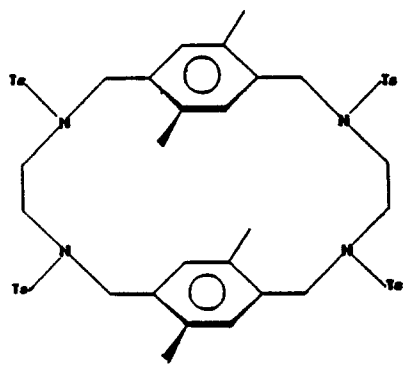
Fig. 1. Schematic representation of conformation A for macrocycle **1**.

Thus, considering the restricted rotation of the aromatic rings with respect to one another, two inconvertible diastereomeric tetramethyl-2,5,14,17-tetraaza-[6.6]-paracyclophanes **1a** and **1b** can be expected from the condensation reaction used.

The symmetry point groups of isomer **1a** and **1b** reveals that **1a** is a chiral macrocycle, as it contains only C_2 symmetry elements (torsional dissymmetry), whereas **1b** is meso. Considering that the ^{1}H-NMR spectrum of the isolated material reveals only one sharp signal for the xylyl methyl groups at ambient temperatures in all solvents investigated, we can conclude, in the absence of accidental isochronies, that our isolated macrocycle is a pure diastereomer. On the basis of the NMR spectrum alone it is quite impossible to decide which isomer was isolated; further studies will clarify this stereochemical problem.



1a (D_2)



1b (C_{2h})

3.2. MASS SPECTRA

Generally, tosylazacyclophanes are high melting compounds which often do not volatilize on EI-MS. In fact, it is well known [9], that for a series of tosylazacyclophanes with relatively low molecular weights, the mass spectra at 18 eV of such

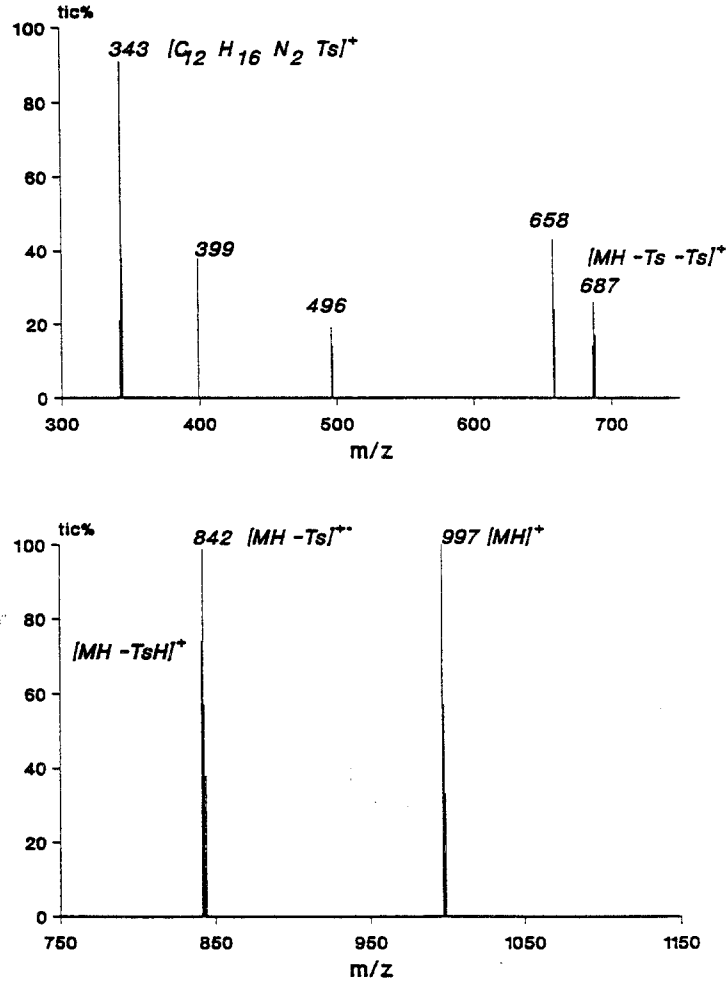
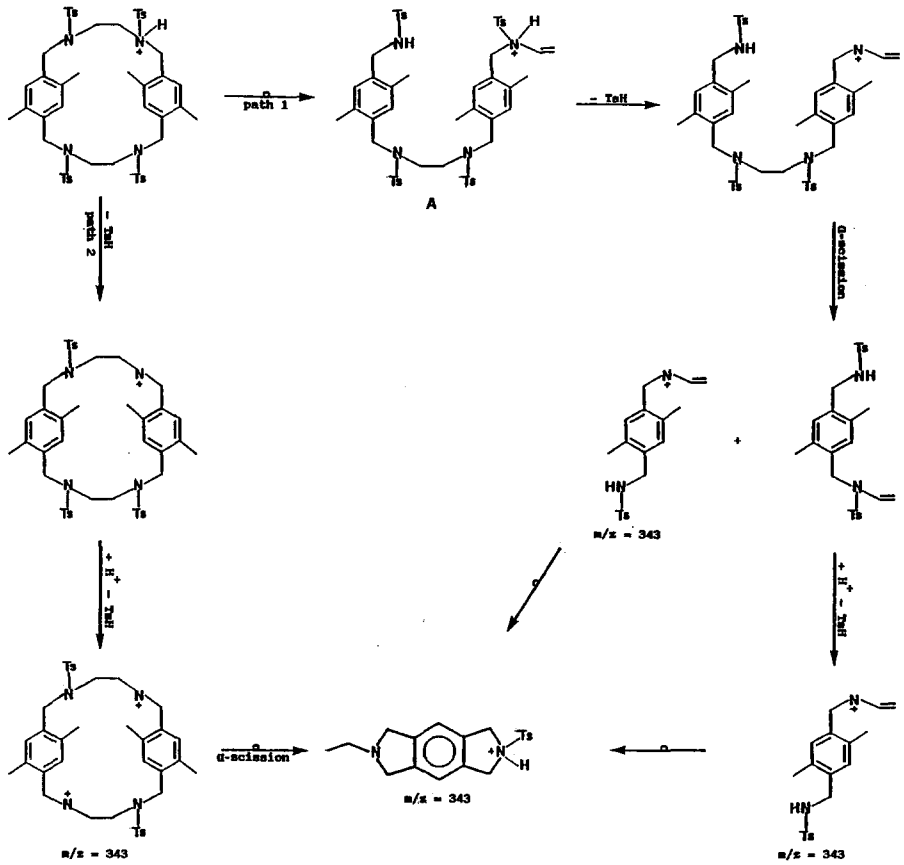


Fig. 2. FAB-MS spectrum of **1**, after subtraction of the contribution from the matrix (2-nitrobenzylalcohol) and normalized with respect to the peak at 997 D $[MH]^+$. The peak at 496 D is the adduct between the fragment at $m/z = 343$ and the matrix.

a family of compounds show the absence of a molecular peak, or, if present, it has a very low intensity. In such a case the diagnostic peak for the determination of the molecular weight is the ion $[M - Ts]^+$, which, in general, constitutes the base peak of the mass spectrum.

In this respect, the FAB-MS technique is much more sensitive and soft, since it allows a simple and rapid determination, via the molecular peaks, of the dimension of the cyclic oligomers formed in a step-wise reaction of macrocyclization [10], because, in general, the FAB-MS spectra of cyclic oligomers are very simple and clear, due to the lack of extensive fragmentation patterns. Despite this general trend, the FAB-MS spectrum of macrocycle **1** is rich in interesting and very diagnostic fragmentation pathways.

Inspection of Figure 2 and Scheme 1 reveals that the molecular ion $[MH]^+$ at $m/z = 997$ constitutes the base peak. The fragment ion $[MH - Ts]^{+\bullet}$ at $m/z = 842$



Scheme 1

is also very intense, owing to the easy loss of a tosyl group (155 a.u.) from the molecular ion. This latter peak is accompanied by the peak at $m/z = 841$, corresponding to $[MH - TsH]^+$, probably generated by the loss of *p*-toluensulphinic acid from the molecular ion. According to Newkome *et al.* [11] this fragment may originate through a five-membered cyclic transition state, by a benzylic hydrogen transfer to the sulphonyl oxygen.

The peaks at $m/z = 687$ and $m/z = 686$, corresponding to the fragments $[MH - Ts - Ts]^{+\cdot}$ and $[MH - Ts - TsH]^+$, respectively, are present in lower intensities, and they originate as a consequence of other concomitant decomposition processes.

The region at relatively low masses is characterized by the presence of the peak at $m/z = 343$, which is the third peak in relative intensity (91%). This fragment may originate from the molecular ion by a loss of two tosyl groups as *p*-toluensulphinic acids; an α-scission on this double charged ion and subsequent rearrangement gives the hypothesized [9] heterocyclic structure at $m/z = 343$ (path 2 of Scheme 1).

Alternatively, skeletal rearrangement prior to fragmentation of the molecular ion to the linear structure A (path 1), generates by the loss of one TsH, a fragment which, by α-scission followed by a rearrangement through a six-centre cyclic

transition state, affords two species: one rearranges directly to the peak at $m/z = 343$, whereas the other one, through a protonation process and loss of another TsH fragment, rearranges again to the same peak at 343 Dalton (Scheme 1).

3.3. HOST PROPERTIES OF 1

Recrystallization of pure **1** from DMF has revealed, by NMR analysis, that this solvent is included in a very limited amount, and in a non-stoichiometric ratio, in the cavities present in the crystal structure of **1**. Therefore, we decided to investigate such behaviour in more detail, selecting different solvents from which **1** could be recrystallized.

Of the various solvents chosen, only toluene was found to be included in a molar ratio 1 : 1. The ^{1}H-NMR chemical shifts of the clathrate with toluene do not differ significantly from those of the pure components: this finding may indicate that the adduct is formed only in the solid state, whereas in solution each molecule is free with respect to one another.

Other solvents, such as benzene, ethylacetate, chloroform, 1,3,5-trimethoxybenzene and *p*-methylanisole were not found to form clathrates with **1**. Recrystallization of **1** from a mixture of benzene : toluene (10 : 1 molar ratio) shows that only the latter is preferentially included and therefore this finding could be utilized in order to extract toluene from a mixture of solvents.

4. Conclusions

From the foregoing we can conclude that macrocycle **1** is easily formed in good yield by a one-pot condensation reaction. Compound **1** is stereochemically non-rigid at elevated temperatures on the NMR time scale and acts as a suitable host for toluene.

References

1. F. Bottino, M. Di Grazia, P. Finocchiaro, F. R. Fronczek, A. Mamo, and S. Pappalardo: *J. Org. Chem.* **53**, 3521 (1988).
2. S. Pappalardo, F. Bottino, P. Finocchiaro, A. Mamo, and F. R. Fronczek: *J. Incl. Phenom.* **5**, 153 (1987).
3. S. Pappalardo, F. Bottino, P. Finocchiaro, and A. Mamo: *J. Polym. Sci. Polym. Chem. Ed.* **25**, 1793 (1987).
4. A. Mamo, P. Finocchiaro, F. Bottino, and S. Pappalardo: *J. Polym. Sci. Polym. Chem. Ed.* **28**, 2237 (1990).
5. P. Finocchiaro, A. Mamo, S. Pappalardo, W. Weissensteiner, and M. Widhalm: *J. Chem. Soc. Perkin Trans.* **2**, 449 (1991).
6. J. von Meisenheimer: *Lieb. Ann. Chem.* **438**, 217 (1924).
7. G. Montaudo, P. Finocchiaro, S. Caccamese, and F. Bottino: *J. Am. Chem. Soc* **93**, 4208 (1971).
8. H. S. Gutowsky and C. H. Holm: *J. Chem. Phys.* **25**, 1288 (1956).
9. S. Pappalardo: *Org. Mass. Spectrom.* **24**, 258 (1989).
10. S. Failla and P. Finocchiaro: *J. Chem. Soc. Perkin Trans.* **2**, 701 (1992).
11. R. Newkome, V. K. Gupta, and S. Pappalardo: *Org. Mass. Spectrom.* **19**, 590 (1984).