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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 1597–1602

Cyclodextrins as NMR probes in the study of the enantiomeric compositions of *N*-benzyloxycarbonylamino-phosphonic and phosphinic acids

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Received 3 March 2004; accepted 30 March 2004
Available online 22 April 2004

Abstract—The inclusion complexes of α- and hydroxypropyl-γ-cyclodextrins with *N*-benzyloxycarbonyl protected α-aminophosphonic and α-aminophosphinic acids were studied by means of NMR spectroscopy. Cyclodextrins appear to be a useful tool for determining the enantiomeric excess of all the examined amino acid mimetics. Stoichiometry and geometry of selected complexes were investigated. 2D ROESY experiments and continuous variation methods indicated that there are three possible types of complexation: two of guest/host ratio being 1:1 and one of 1:2 stoichiometry. Molecular modelling studies confirmed the proposed modes of complexation.

1. Introduction

Aminophosphonic and aminophosphinic acids constitute a class of amino acid analogues in which a carboxylic group is replaced by a phosphonic or phosphinic acid moiety. These compounds attract considerable interest because of their diverse and useful biological activities, which usually originate from their competition versus amino acids for the active sites of enzymes or other cellular receptors. Therefore, they may be used in a wide spectrum of human activities ranging from agriculture to medicine.[1] The introduction of an aminophosphonate moiety into the peptide chain offers additional structural modifications and thus extends the potential biological relevance of these compounds. *N*-Benzyloxycarbonyl protected aminophosphonates and aminophosphinates are essential substrates for the synthesis of such phosphorus-containing peptidomimetics,[2] in which the phosphorus atom resembles a tetrahedral transition state of the amide bond hydrolysis.[3] Additionally, the organophosphorus fragment of these molecules is able to coordinate zinc ions present at the active sites of metalloproteases and to block their function in the hydrolysis process. Therefore their chemistry continues to draw significant attention as it provides a wide variety of potent inhibitors of proteases, particularly metallo-dependent.[4]

It is well recognised that the biological activity of organic compounds strongly depends on their three-dimensional structure. The preparation of individual, well defined phosphono and phosphino peptide stereoisomers may be achieved by the use of enantiomeric forms of *N*-benzyloxycarbonylamino-phosphonates or -phosphinates as substrates. In this respect, a simple and versatile method for the determination of the enantiomeric excess of these acids is highly desirable. The literature offers many useful methods concerning the enantiodifferentiation of aminophosphonates and their derivatives, which include high-performance liquid chromatography,[5] capillary electrophoresis[5a,h,6] and NMR spectroscopy.[7]

Herein we extend the application of ^{31}P NMR spectroscopy combined with the use of cyclodextrins as chiral selectors in the study of the enantiomeric compositions of *N*-benzyloxycarbonylaminoalkanephosphonic and -phosphinic acids. For a better understanding of the observed phenomenon, selected aminophosphonate-cyclodextrin complexes were studied in some detail, particularly when taking under the consideration stoichiometry and geometry of the inclusion complexes.

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doi:10.1016/j.tetasy.2004.03.037

2. Result and discussion

In order to a establish methodology for measuring the enantiomeric excess of *N*-benzyloxycarbonyl-aminophosphonic and -aminophosphinic acids, we have extended our previous studies on the use of cyclodextrins as chiral discriminators in ^{31}P NMR spectroscopy.[7k] This technique is a well established tool for determining the enantiomeric purity of organophosphorus compounds because of the large chemical dispersion and the simplicity of the broad band ^{1}H decoupled spectra.[8]

As described in the literature,[2b] the investigated compounds exhibit limited conformational flexibility in solution and exist in two additional stereomeric forms due to restricted rotation around the C-N bound of their carbamate moiety (Fig. 1). This effect is also visible in ^{31}P NMR spectra as two separated resonance signals of nonequal intensity. Since the *trans*-isomers are predominant (usually over 80%), the results herein are focused on their behaviour.

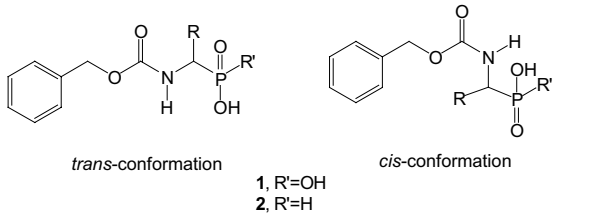

Figure 1. Conformations of *trans*- and *cis*-*N*-benzyloxycarbonyl-aminophosphonic and aminophosphinic acids.

The ^{31}P NMR determination of the enantiomeric composition of both racemic as well as enantiomerically pure *N*-benzyloxycarbonyl derivatives of aminophosphonates using α- and hydroxypropyl-γ-cyclodextrins as chiral selectors were carried out using a 10:1 cyclodextrin to guest molar ratio following the optimal conditions found earlier.[7k] The results presented in Table 1 clearly demonstrate that enantiodifferentiation depends on both the type of cyclodextrin used as well as on structure of the studied compound. Although significant signal resolution was achieved in all cases, it is difficult to draw any fundamental relationship between the structures of the guest versus chemical shift differences ($\Delta\delta$).

The main point of our study was to analyse the predominating conformer of the examined aminophosphonates; however, attempts to differentiate the enantiomers of the minor component were also undertaken. Such enantiodifferentiation of the minor isomer was not observed in case of α-cyclodextrin application, probably due to the inability of inclusion of the compact conformation characteristic for *cis*-isomers by this cyclodextrin. Therefore, hydroxypropyl-γ-cyclodextrin, which has a bigger inner cavity, was applied. This modification of the methodology, although effective in the case of *cis* isomers, gave less general results since a visible resolution was obtained mainly for alkyl derivatives. Nevertheless, the assumption concerning the three-dimensional structure of aminophosphonates seems to be correct as $\Delta\delta$ of the minor components were generally enhanced in comparison to the major ones (for example $\Delta\delta$ for the major signal of compound **1d** was 0.045 whereas for the minor one, it increased up to 0.220).

The interactions of selected compounds **1d**, **2a** and **2e**, bearing R substituents of different sizes, with α-cyclodextrin were investigated in more detail. 2D rotating frame ^{1}H–^{1}H nuclear Overhauser effect (2D ROESY) was mainly used because it is well known from the literature that this technique gives reliable results in these kinds of studies.[9] The 2D-ROESY spectrum of compound **2a** clearly indicated contacts between the protons from the inner cavity of cyclodextrin (H3, H5) with protons of the phenyl ring of the carbamate moiety. This shows that the only possible mode of complexation is the inclusion of the phenyl ring of the benzyloxycarbonyl group into cyclodextrin with formation of a 1:1 complex. The structure of the complex in a water box minimised with NMR restrains is shown in Figure 2. The major forces stabilising the complex are hydrophobic interactions between the apolar inner cavity of α-cyclodextrin and the phenyl ring. A negatively charged, polar fragment of the molecule is exposed to the solvent and forms a hydrogen bonding network with water molecules and the hydroxyl groups of cyclodextrin. In order to establish stability and flexibility of this complex

Table 1. ^{31}P NMR chemical shift nonequivalence ($\Delta\delta$) found for enantiomers of *N*-benzyloxycarbonyl-aminophosphonic and aminophosphinic acids complexed with cyclodextrins. (NS-not separated)

No	R	R′	$\Delta\delta$ [ppm] for α-CD	$\Delta\delta$ [ppm] for HP-γ-CD
1a	CH_3	OH	0.215	0.037
1b	C_2H_5	OH	0.122	0.038
1c	$CH(CH_3)_2$	OH	0.283	NS
1d	$CH_2CH(CH_3)_2$	OH	0.331	0.045
1e	Ph	OH	0.287	NS
1f	CH_2Ph	OH	0.047	0.034
2a	CH_3	H	0.247	0.050
2b	$CH(CH_3)_2$	H	0.052	0.029
2c	$CH_2CH(CH_3)_2$	H	0.196	0.068
2d	Ph	H	0.199	NS
2e	CH_2Ph	H	0.050	NS
2f	CH_2CH_2Ph	H	0.066	0.154

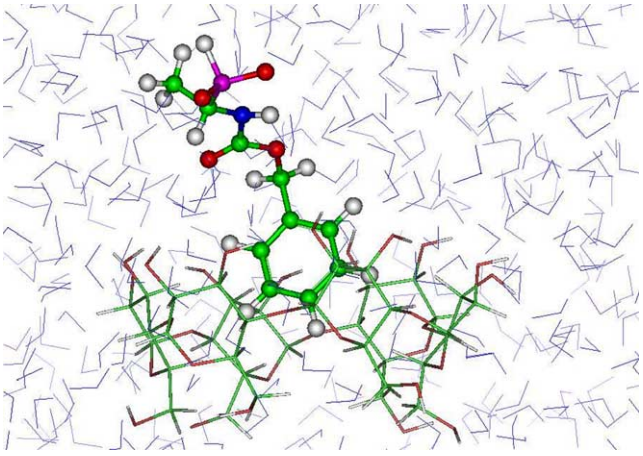

Figure 2. Minimised structure of the inclusion complex of *trans*-**2a** with α-cyclodextrin in aqueous solution.

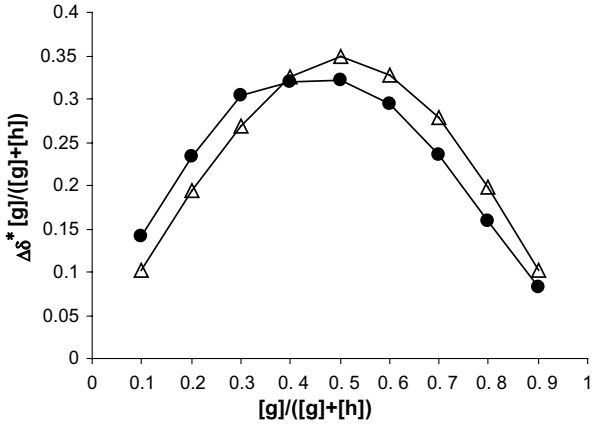

Figure 4. Job's diagram for enantiomerically pure (***R***)-**1d**/αCD (△) and (***R***)-**2e**/αCD (●) complexes based on the complexation chemical shift in ^{31}P NMR spectra.

molecular dynamics without any restrains during 60 ps with 1 fs step at 300 K was performed as the following step. The structure showed significant flexibility but did not substantially change. This may confirm the correctness of the proposed model.

A more complicated pattern was observed in the 2D-ROESY spectra of compounds **1d** and **2e**. Not only crosspeaks between the phenyl ring of *N*-protecting group and H3 and H5 protons of cyclodextrin were observed but resonances between the side-chain R substituent and cyclodextrin were also visible. This can be seen from representative parts of the ROESY spectrum of the 1:1 mixture of **1d** with α-cyclodextrin in Figure 3. To determine the stoichiometry of the complexes of **1d** and **2e** compounds with α-cyclodextrin in aqueous solution, Job's diagrams[10] based on the induced chemical shifts in ^{31}P NMR and ^{1}H NMR were plotted. The obtained results were contradictory. The continuous variation plot constructed according to the ^{31}P resonance signals of phosphonic group showed a maximum at the guest/(host + guest) ratio 0.5 indicating that there was one molecule of **1d** complexed with one molecule of α-cyclodextrin (Fig. 4); the value obtained for **2e** was 0.4 suggesting the existence of 2:1 complex. The analogous plots constructed for **1d** based on the ^{1}H resonance signals were ambiguous because the maxima observed in the Job plots were in range of 0.5–0.6 and thus are difficult to interpret. The plot having a maximum at 0.5 suggested the existence of a 1:1 complex, whereas the others are not easy to analyse (considering that two different and spatially separated groups in one molecule underwent diagnosis) and suggest that there is not only one uniform complex present in the aqueous solution (Fig. 5). Similarly, the results obtained for compound **2e** also indicated various modes of complexation with α-cyclodextrin. Hence the results of the 2D ROESY experiments and the continuous variation method do not appear to be fully effective for unambiguously determining the stoichiometry of examined complexes.

Three types of inclusions are possible here: two kinds with stoichiometry 1:1 and 1:2 (*N*-benzyloxycarbonylaminophosphonate to cyclodextrin). In the first case, the aromatic ring of the benzyloxycarbonyl moiety or a side chain of aminophosphonate molecule can be encapsulated into the cyclodextrin inner cavity. In the second case, the compound is sandwiched between two α-cyclodextrin molecules. In order to determine the accuracy of all the proposed structures they were minimised

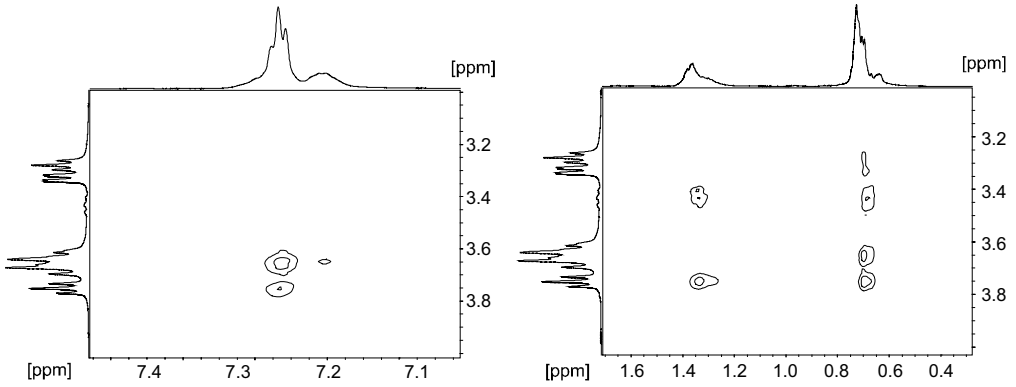

Figure 3. Selected regions of the 2D-ROESY spectrum of a 1:1 mixture of **1d** with α-cyclodextrin (crosspeaks between carbamate phenyl group of **1d** and H3 and H5 protons of α-cyclodextrin—left side, the resonances between the protons of alkyl fragment of **1d** and H3 and H5 protons of α-cyclodextrin and $C_{\alpha}H$ proton of **1d**—right side).

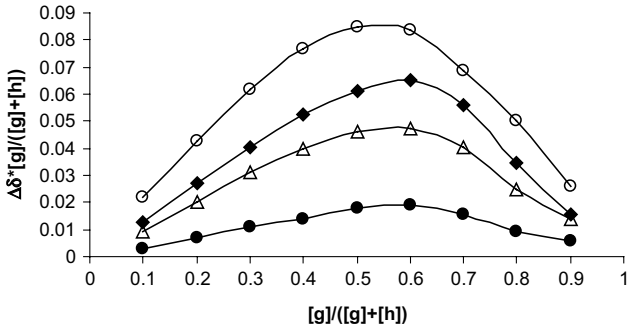

Figure 5. Job's diagrams for enantiomerically pure (***R***)-**1d**/αCD complex based on the complexation chemical shift in ^{31}H NMR spectra corresponding to: (●)—overlapped aromatic *o*- and *m*-protons of benzyloxycarbonyl group, (◆)—CH_2 group of leucine side chain, (△, ○)—CH_3 groups of leucine side chain.

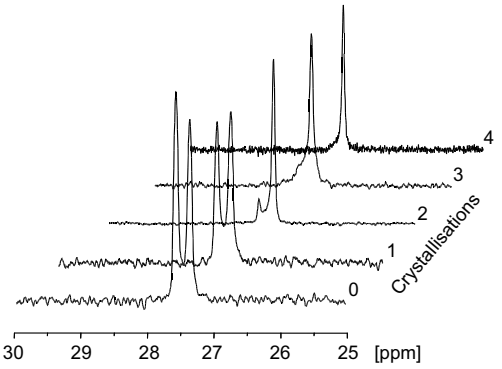

Figure 7. The set of ^{31}P NMR spectra of (−)-α-methylbenzylamine salt of **2a** with α-cyclodextrin following its fractional crystallisation.

by molecular mechanics using a cff97 force field with NMR restrains. The results obtained for compounds **1d** are illustrated in Figure 6. Molecular dynamics calculations without any restraints were performed for three different types of complexes and it was envisaged that they were stable in aqueous solution; however substantial flexibility was observed. Thus, the presented models only indicate representative minimised structures. Taking into consideration the results of modelling and the absence of multiple ^{31}P NMR signals originating from three types of complexes it could be concluded that might exist in a dynamic equilibrium while in solution.

The practical usefulness of the developed method for determining the enantiomeric excess of *N*-protected aminophosphonates was additionally demonstrated by the application of this method to follow the fractional crystallisation of **2a** upon resolution with (−)-α-methylbenzylamine. ^{31}P NMR spectra of **2a** with α-cyclodextrin which are presented in Figure 7 depict the enantiomeric excesses reached after each crystallisation step and were used to determine number of steps

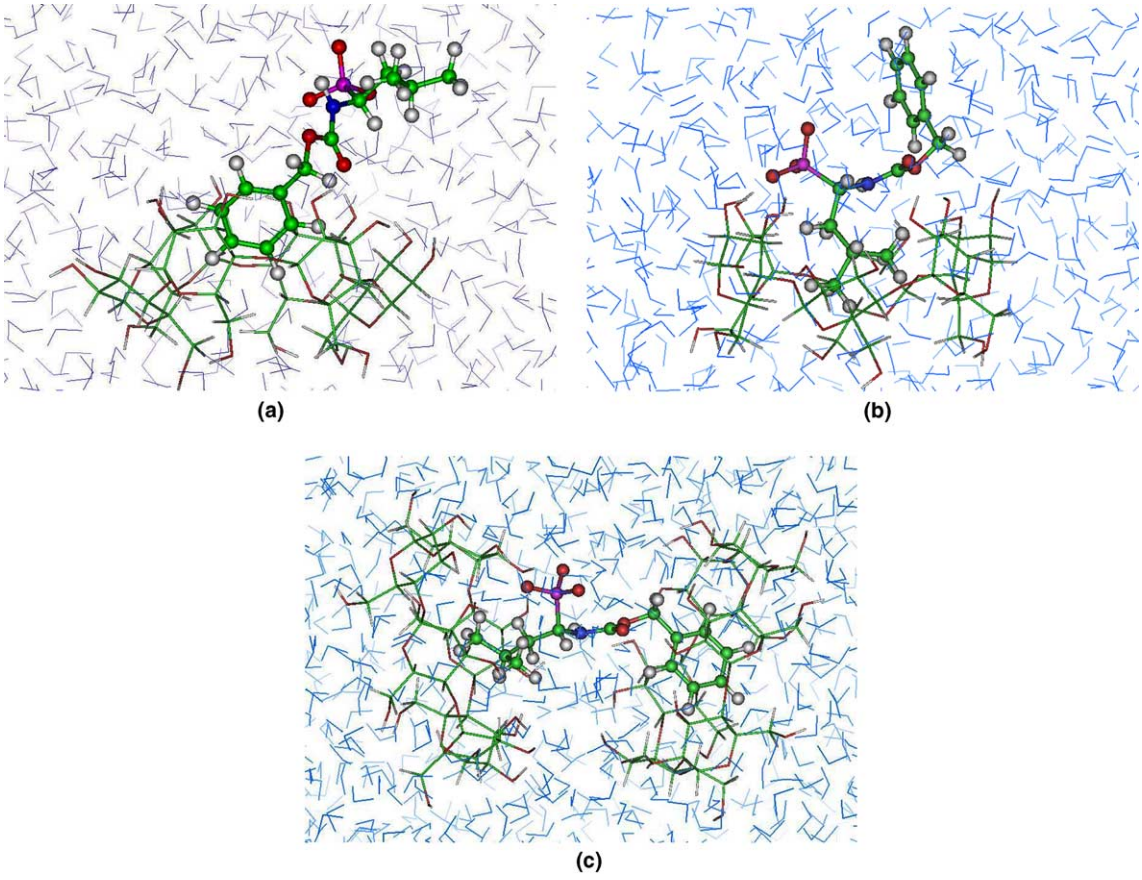

Figure 6. Minimised structures of three various types of **1d** with α-cyclodextrin complexes.

required in order to obtain the pure enantiomer. An unquestionable advantage of this method is the possibility of using **2a** in the form of its α-methylbenzylamine salt to determine the enantiomeric excess of the examined compound.

3. Conclusions

^{31}P NMR, using cyclodextrin as the chiral discriminators is a rapid and straightforward method for the determination of the enantiomeric excess of *N*-benzyloxycarbonylaminophosphonic and aminophosphinic acids. Such a strategy appeared to be successful for all of the studied compounds and seemed to be advantageous to the analysis of nonprotected aminophosphonates. The range of its application is broader also covering structures nonanalysable in their free, unprotected forms. The other reason is that the protection of the aminophosphonates is a simple and efficient reaction with the *N*-blocked derivatives being much more versatile substrates for the synthesis of biologically active compounds.

In comparison to other enantiodiscriminating techniques, such as high-performance liquid chromatography or capillary electrophoresis, the methodology presented seems to be much more rapid and easier to perform. Moreover, it uses commercially available, inexpensive reagents as opposed to other previously reported applications of NMR spectroscopy.

Detailed studies of three selected compounds, their structural analogy and consistent results of 1D NMR led us to conclude that *trans* conformers of the investigated compounds always form with α-cyclodextrin with at least one type of 1:1 complex with the phenyl ring of the protecting group being encapsulated. However, in the case of compounds possessing bulky R substituents the existence of other types of complexation has also been proven.

4. Experimental

D_2O and NaOD solutions were purchased from dr Glaser, AG Basel, α-cyclodextrin and hydroxypropyl-γ-cyclodextrin from Aldrich. All *N*-benzyloxycarbonyl-amino-phosphonic and phosphinic acids were synthesised according to standard procedures.[11] NMR experiments were performed on Bruker Avance DRX 300, Bruker AMX 500 and Bruker AMX 600 instruments at 298 K. Measurements were made in D_2O/NaOD solutions (pH ~ 13), except for compounds **1e** and **1f** (pH ~ 5). 10 mM solutions of guest compound and 100 mM of cyclodextrin in D_2O were used. TMS for ^{1}H spectra or 85% phosphoric acid in H_2O for ^{31}P spectra were used as external standards. ROESY experiments were recorded using 100 mM solution of guest compound and 100 mM of α-cyclodextrin. The experiments were carried out at 150 ms mixing time. Samples for continuous variation method were prepared by mixing 100 mM solution of guest compound in D_2O with 100 mM solution of α-cyclodextrin in D_2O in appropriate ratio.

Calculations were done with Accelryss Insight 2000[12] molecular modelling package on a Silicon Graphics Onyx workstation. All minimisations and molecular dynamics simulations were done with program Discover[13] using a cff97[14] molecular force field. The conjugate gradient algorithm was applied for minimisation. Default values were assumed for all parameters. The initial structures of guest molecules and cyclodextrin were built in a Builder module from standard fragments and minimised initially in vacuo. The complex was placed in box of water of dimension: 30 Å*30 Å*30 Å. The whole system was minimised with restraints from ROESY spectra up to RMS derivative equal to or less than 0.1 kcal/mol. All restraints were defined as a generic distance with upper limit 4.0 Å. Restraints between *o*- and *p*-protons of phenyl ring (of the benzyloxycarbonyl group or a side chain) and H3 and H5 protons of cyclodextrin respectively (total four restraints), were applied for calculations of complexes in which a phenyl ring was included inside cyclodextrin cavity. In the case of an *iso*-butyl substituent being encapsulated, restraints between protons of CH_2 and CH_3 groups and H3 and H5 protons of cyclodextrin respectively were applied (total four restraints). Molecular dynamics was performed on a minimised system for 60 ps with 1 fs time steps at 300 K (with 1000 steps of equilibration) without any restraints. The coordinates were saved every 0.1 ps.

Acknowledgements

The calculations were carried out using hardware and software resources (including the Accelrys programs) of the Supercomputing and Networking Centre in Wrocław. We wish to thank The Foundation for Polish Science for the Subin Program. This work was supported by Polish Committee of Science.

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