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Chiral discrimination of ethyl and phenyl *N*-benzyloxycarbonylaminophosphonates by cyclodextrins

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Abstract—Enantiodifferentiation of N-protected ethyl and phenyl α-aminophosphonates with application of commercially available cyclodextrins as chiral solvating agent was studied by means of nuclear magnetic resonance spectroscopy. Four cyclodextrins (α-CD, β-CD, γ-CD and HP-γ-CD) were chosen due to the differences in the size of their inner cavities and substitution of the rim, which in turn might change the affinity of the compounds analyzed to these chiral selectors. The influence of solution pD and host concentration on the enantiodiscrimination efficiency was also studied. As a result, a methodology for the simple and rapid assessment of the enantiomeric composition of various *N*-benzyloxycarbonyl-α-aminophosphonates has been elaborated upon. 2D Rotating frame nuclear Overhauser and exchange spectrometry experiments and continuous variation methods were applied for establishing the molecular recognition mechanism and structure of the guest–host assemblies.

1. Introduction

One of the most striking features of recognition in biological systems relies on its chiral character. This originates from the formation of stereospecific non-covalent interactions between the individuals involved in the creation of an assembly structure. The unique spatial arrangement of such individual components is determined by the absolute configurations of their asymmetric atoms. Apparently, this also concerns synthetic compounds constructed to affect biological targets. Knowledge of the absolute configuration of all the stereogenic atoms, or at least the enantio-/diastereomeric composition is absolutely indispensable for discussing their activity rationally.

α-Aminophosphonates/phosphinates, which contain a phosphorus moiety instead of a carboxyl group, form a very attractive group of amino acid analogues, isosterically and isoelectronically mimicking the corresponding natural counterparts. Consequently, they are the targeted synthetic products, as they are widely applied as potential enzyme inhibitors, antibiotics, effectors of neurotransmission, agrochemicals, etc.[1] Additionally, appropriately functionalized, α-aminophosphonates represent substrates for their further modification, mainly as an introduction into peptide chains. The resulting phosphorus containing pseudopeptides contain a moiety mimicking the high-energy tetrahedral transition state of amide bond hydrolysis, which results in their ability to selectively inhibit proteases, particularly metallo-dependent ones.[1b,2]

In view of this, the necessity of developing both methods to obtain enantiomerically pure α-aminophosphonates, as well as elaboration of the appropriate techniques for the determination of their enantiomeric composition, seems clear. To achieve the first aim, a plethora of studies on asymmetric synthesis and chemical or enzymatic resolution of the enantiomers have been carried out and summarized elsewhere.[3] Conversely, the availability of general, reliable and rapid analytical methods to control the enantiopurity is still limited. High-performance liquid chromatography using chiral stationary phases and capillary electrophoresis with chiral additives to the background electrolyte have been most frequently applied to face this challenge.[4]

NMR spectroscopy (particularly ^{31}P NMR, which uses the characteristic feature of an organophosphorus molecule) might also represent a valuable tool for the determination of enantiomeric composition of organophosphonates. Indeed, with it being easy to perform, simple to interpret,

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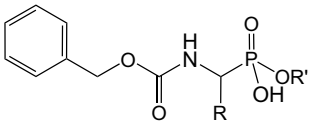
repetitive and relatively inexpensive, this technique has been successfully utilized to analyze α-aminophosphonates. However, in the majority of cases, additional N-derivatization of free aminophosphonates with chiral reagents to form covalent diastereoisomers has been required prior to analysis.[5] Reports on the direct determination of the enantiopurity of aminophosphonates by the addition of suitable shift reagents are scarce. Cyclodextrins (CDs) have been successfully applied for this purpose in the study of a series of non-protected aminophosphinic and aminophosphonic acids.[6] The same goal was achieved for several aminophosphonic acid analogues via formation of their diastereoisomeric complexes with Pd(II).[7] The complexes exhibit an MeL_2 stoichiometry with two chiral molecules chelating the homochiral centre. Integration of the appropriate ^{31}P NMR signals (the enantiomeric pair (*RR*)/(*SS*) and the *meso* form) allows the calculation of the ratio of the enantiomers. NMR stereodifferentiation for a series of N-protected aminophosphonic acids and their monoesters was also performed by application of 1-(1-naphthyl)ethylamine and ephedrine as chiral shift reagents.[8]

Recently, we reported the results of studies on the determination of stereoisomeric compositions of *N*-benzyloxycarbonylaminophosphonic and phosphinic acids by means of ^{31}P NMR via the use of α-cyclodextrin and hydroxypropyl-γ-cyclodextrin.[9] These studies showed that cyclodextrins appeared to be the most general and efficient agents for the enantiodiscrimination of various aminophosphonates. Encouraged by these promising results, including our recent NMR results on N-protected derivatives,[9] we decided to extend this approach for phenyl and ethyl *N*-benzyloxycarbonylaminophosphonates, key substrates in the synthesis of phosphonamidate and phosphonate pseudopeptides.[1b,10] Herein, we recommend CDs as useful chiral shift reagents for the relatively fast and easy analysis of the enantiomeric excess of N-protected aminophosphonic acid monoesters **1** and **2** (Fig. 1) by ^{31}P NMR. In order to shed some light on the complexation mode, additional NMR experiments including 2D rotating frame nuclear Overhauser and exchange spectrometry experiments (2D-ROESY) were performed. A continuous variation method was used to determine the stoichiometry of the complexes.

2. Results and discussion

Differentiation of the enantiomers in the NMR spectroscopy upon the application of chemical solvating agents (CSAs) only takes place when they are able to form labile diastereoisomeric complexes of different free enthalpies with each enantiomer. This effect is achieved when different association constants and/or different stereochemical arrangements characterize the solvates obtained.[11] As a consequence, enantioselectivity is strongly influenced by the structure and concentration of both selector and selectand, as well as the pD of solution. Therefore, the elaboration of an efficient and reliable methodology for the distinction of the enantiomers ought to be based on the optimization of these factors. In order to examine the influence of the type of CSA on enantiodifferentiation, four various CDs (α-CD, β-CD, γ-CD and HP-γ-CD) were chosen because of differences in size of their inner cavities and substitution of their rim, that in turn could modify the affinity of individual compounds to a chiral selector.



R = CH_3 (**a**), CH_3CH_2 (**b**), $(CH_3)_2CH$ (**c**), $(CH_3)_2CHCH_2$ (**d**), C_6H_5 (**e**), $C_6H_5CH_2$ (**f**).

R' = C_6H_5 (**1**), CH_2CH_3 (**2**).

Figure 1. The general structure of the analyzed *N*-benzyloxycarbonylaminophosphonates.

The investigated phenyl **1** and ethyl monoesters *N*-benzyloxycarbonylaminophosphonic acids **2** (Fig. 1), similar to their parent N-protected acids exhibit restricted rotation around the C–N bound of their carbamate group.[8,9,10d] As a consequence, they exist in solution in *cis*- and *trans*-forms, with the equilibrium shifted towards the formation of *trans*-isomers (more than 83% in case of monoesters analyzed, except for compound **1f**—76%). Our investigation was mainly focused on enantiodiscrimination of the predominant *trans*-stereoisomers.

The exchange between the free state of compounds **1** and **2** and the form complexed with cyclodextrin is fast on the NMR timescale. Thus, only one set of signals can be observed in the NMR spectrum for free and bound species, which means that ^{31}P NMR signal splitting results only from enantiomeric composition. A representative example of a differentiation between the racemic and (*S*)-enantiomer of **1e** in the presence of α-CD is shown in Figure 2.

The N-protected phenyl and ethyl aminophosphonates **1** and **2** studied reveal the same ionization state within the analyzed range of pD (5–12). Thus, similar to the previously described *N*-benzyloxycarbonylaminophosphinic acids,[9] pD did not influence the enantiodifferentiation of these compounds. Due to its significantly higher solubility in basic conditions, pD 12 was chosen for routine analyses.

As expected, the concentration of a cyclodextrin had a significant impact on the enantiodiscrimination efficiency. The representative dependences of $\Delta\delta$ (the chemical shift difference of ^{31}P NMR signals) of monoester **1a** enantiomers on an excess of selected CDs is presented in Figure 3. A continuous increase of $\Delta\delta$ was observed for α-CD in the analyzed range, while a plateau was reached for HP-γ-CD at a CD/guest ratio exceeding 7. Thus, similar to previous studies,[6,9] the aminophosphonate to cyclodextrin ratio of 1:10 seems to be the most rational choice, if considering the limited aqueous solubility of cyclodextrins and relatively high concentration of the guest required for the acquisition of the NMR experiments.

The enantiodiscrimination efficiencies obtained for the studied phenyl **1** and ethyl **2** monoesters under the elaborated optimal condition with α-, β-, γ- and HP-γ-CDs as

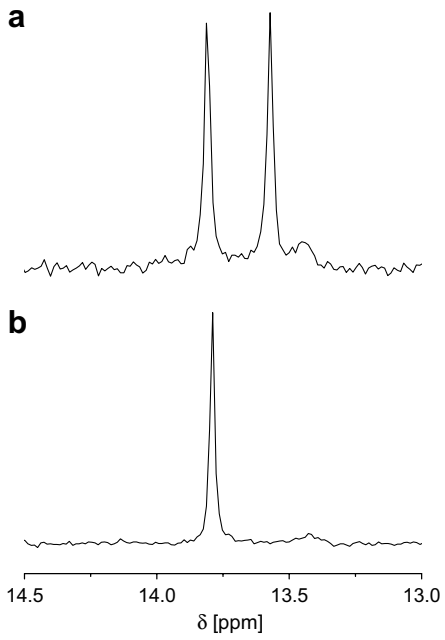


Figure 2. ^{31}P NMR spectra of racemic (a) and the (*S*)-enantiomer (b) of **1e** with α-CD (1:10 ratio) in D_2O solution (pD = 12.5).

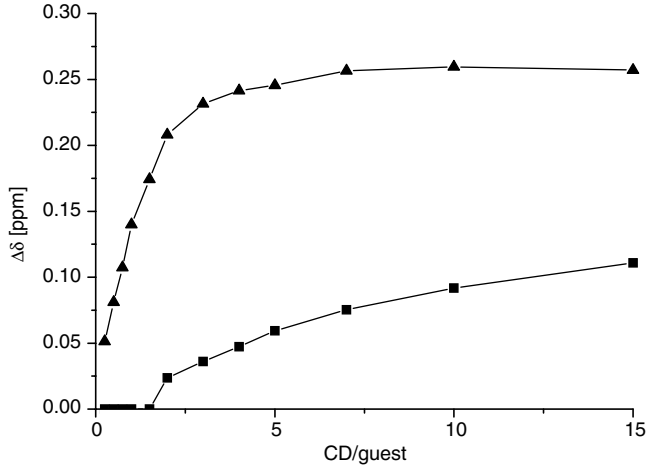


Figure 3. Dependence of chemical shift non-equivalence (Δδ) on cyclodextrin to guest (**1a**, 10 mM) ratio for α-CD (■) and HP-γ-CD (▲).

CSAs are shown in Table 1. A baseline separation of NMR signals allowing the determination of enantiomeric composition was achieved for non-equivalence equal to or higher that 0.1 ppm. Generally, Δδ appeared much more significant for phenyl ester derivatives in comparison to ethyl phosphonates. This observation is not surprising as compounds of general structure **1** possess an additional structural fragment able to interact with the CDs inner cavity. If considering the affinity of the hosts, α-CD and HP-γ-CD were the most universal for enantiomer analysis of almost all the examined compounds. Although the ^{31}P NMR chemical shift non-equivalences achieved for α-CD were moderate, this CSA was only convenient for the distinction of the complete set of ethyl analogues **2**. The second striking feature is its high affinity towards phenylglycine analogues **1e** and **2e** (above 0.2). It should be noted that application of HP-γ-CD was much more effective, as shown by the baseline signal resolution for all the phenyl esters **1a**–**e** studied. Conversely, it is difficult to derive any relationship between the enantiodifferentiation efficiency and analytes structure for γ-CD. The use of β-CD, however, gave partially satisfactory results, because its limited aqueous solubility experiments have to be performed at a considerably lower concentration (1 mM analyte vs 10 mM β-CD). This causes substantially longer time of acquisition for NMR spectra, which is not desirable if considering routine analysis.

Table 1. ^{31}P NMR chemical shift differences (Δδ) observed for racemic mixtures of analyzed *N*-benzyloxycarbonylaminophosphonic acid esters in the presence of studied cyclodextrins (10 mM:100 mM ratio for α-CD and HP-γ-CD and 1 mM:10 mM for β-CD)

Entry	R	R′	Δδ (ppm)			
			α-CD	β-CD	γ-CD	HP-γ-CD
1a	CH_3	C_6H_5	0.048	0.223	0.081	0.262
1b	CH_3CH_2	C_6H_5	0.036	0.203	0	0.229
1c	$(CH_3)_2CH$	C_6H_5	0.047	0.104	0.081	0.119
1d	$(CH_3)_2CHCH_2$	C_6H_5	0	0.163	0	0.273
1e	C_6H_5	C_6H_5	0.240	0.273	0.068	0.352
1f	$C_6H_5CH_2$	C_6H_5	0.045	0	0.221	0.122
2a	CH_3	CH_2CH_3	0.043	0	0	0.027
2d	$(CH_3)_2CHCH_2$	CH_2CH_3	0.059	0	0.022	0.049
2e	C_6H_5	CH_2CH_3	0.223	0.162	0.058	0

In order to obtain more detailed information on selector–selectand interactions, additional NMR studies were performed. Thus, the Job method was used to determine the stoichiometry of phenyl monoester **1e** and CD complexes while 2D-ROESY experiments were applied to examine the through-space interactions. Compound **1e** was chosen intentionally as it was preferentially enantiodiscriminated by all the hosts examined. Furthermore, it represented the only known monophenyl N-protected aminophosphonate, which was successfully resolved for the antipodes.[12] Previously, we reported the NMR analysis of the complexation of *N*-benzyloxycarbonylaminophosphonic and phosphinic acids by α-CD.[9] The phenyl monoester **1e** analyzed possesses an additional aromatic group and therefore it can interact differently with cyclodextrin molecule. As well as the possible complexation of the benzyloxycarbonyl fragment and *R* (side chain) groups, inclusion of the phenyl ester moiety may occur. Thus, several types of complexes with α-CD of stoichiometry varying from 1:1 up to 1:3 are probable. According to the Job theory, if the [host] + [guest] is constant, then the dependence of the ^{1}H complexation-induced shifts of appropriate atoms [guest or host] by molar fraction of the guest versus molar fraction of guest in solution should reach a maximum for the stoichiometric selector–selectand mixture.[13] Plots based on the induced ^{1}H NMR chemical shifts of the aromatic protons of the guest were constructed for both (*R*)-**1e** and (*S*)-**1e**, when complexed with α-CD. The maximum relative amount of α-CD is equal to 0.6, which indicates the presence of a mixture of complexes of different stoichiometry in solution. The same result was achieved for different total concentrations of guest and host (10 mM and 100 mM).

2D-ROESY spectra of the mixture of **1e** and α-CD (10 mM:10 mM) recorded for both individual enantiomers did not show significant differences of host–guest interactions similar to those obtained for the higher concentration (50 mM:50 mM). Contacts between the protons of the guest molecule **1e** and inner protons of α-CD represented by crosspeaks on representative 2D-ROESY spectra are shown in Figure 4. Similar to the complexation of *N*-benzyloxycarbonylaminophosphonic and phosphinic acids, close contacts between the benzyl group and/or phenyl side chain (*R*) of guest compound **1e** and H3 and H5 inner protons of cyclodextrin were observed. However, substantial overlapping of the aromatic signals does not allow us to ascribe ROESY crosspeaks unambiguously. Moreover, contacts between the phosphonate phenyl ester moiety and cyclodextrin were detected, thus, at least two of the three aromatic rings of the molecule analyzed interact with α-cyclodextrin. Taking into account that the bulkiness of studied substituents allows the possibility of inclusion of only one group into the cavity of α-CD, several types of complexes may exist in equilibrium at the same time in solution. Additionally, the presence of crosspeaks between CH_2 group and both H3 and H5 protons of α-CD suggests that inclusion of phenyl ring of the benzyloxycarbonyl group can occur from both sides of α-CD. However, a slightly stronger contact with H5 proton indicates that penetration from the narrower side of host molecule is more preferable. This considerably enlarges the number of possible complexation modes.

The mode of complexation between phenyl esters **1** and native, as well as HP-γ-CD was also studied. The literature data proved[14] that the cavities of these CDs were large enough to simultaneously accommodate two aromatic rings without the necessity of close contact. This feature can significantly change the method of complexation of the compounds studied in comparison to α-CD, which possess a smaller inner cavity. Job's plot based on the induced ^{1}H NMR chemical shifts of aromatic protons of (*S*)-**1e** with γ-CD (total concentration 100 mM) indicates that complexes of a 1:1 stoichiometry are preferentially formed. Unfortunately, the overlapping of signals of the aromatic protons of **1e** strongly complicates the analysis of 2D-ROESY spectrum thus making it impossible to distinguish intramolecular interaction between the two aromatic rings (protecting moiety benzyl group and phenyl side chain—*R*).

Interestingly, analysis of the *cis–trans*-isomeric ratio revealed a significant disproportion between the free and complexed forms for the individual molecule **1f**. Among the studied aminophosphonates, analogue **1f** is characterized by the highest contribution of *cis*-isomer up to 24%. This can be attributed to the stabilization of the *cis*-isomer by a preferential folded conformation driven by hydrophobic interactions. Furthermore percentage of this stereoisomer increases considerably upon complexation with γ-CD up to 38%. These values correspond to the determined Gibbs free energy changes (ΔG) for non-complexed and complexed system *cis–trans*-isomerization that are equal to 2.87 kJ/mol and 1.21 kJ/mol, respectively. Additionally, the differentiation of the enantiomers of *cis*-**1f** with these CDs was obtained with satisfactory efficiency ($\Delta\delta = 0.040$). Similar effects were observed for HP-γ-CD, where its presence leads to an increase of percentage of the *cis*-stereoisomer of **1f** up to 43% (ΔG 0.70 kJ/mol) and

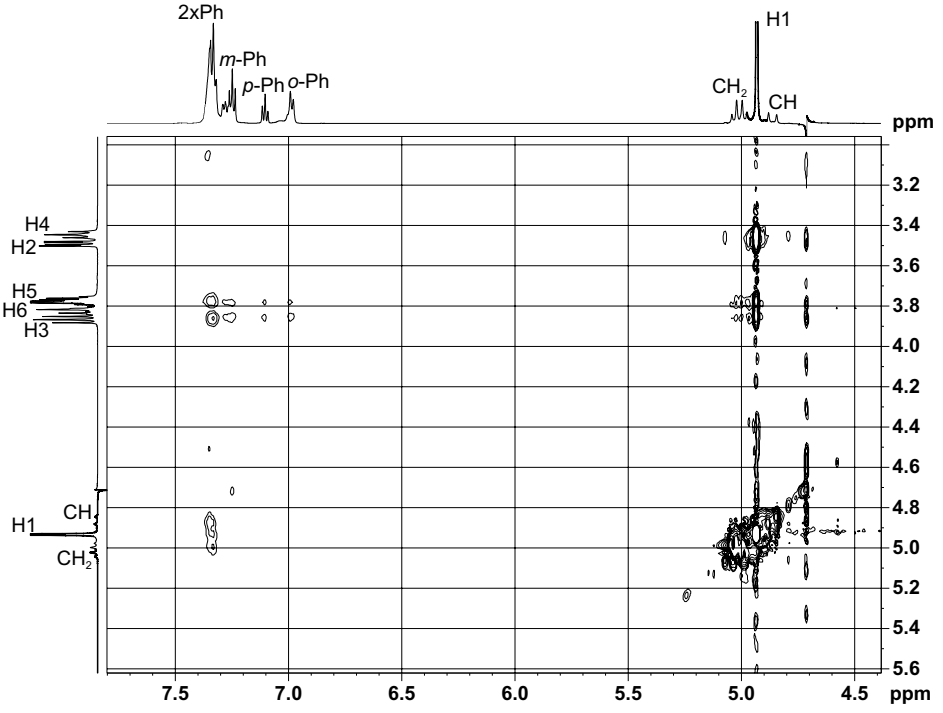


Figure 4. Representative regions of 2D-ROESY spectra of (*R*)-**1e** and α-CD 10 mM:10 mM mixture (pD = 13.0).

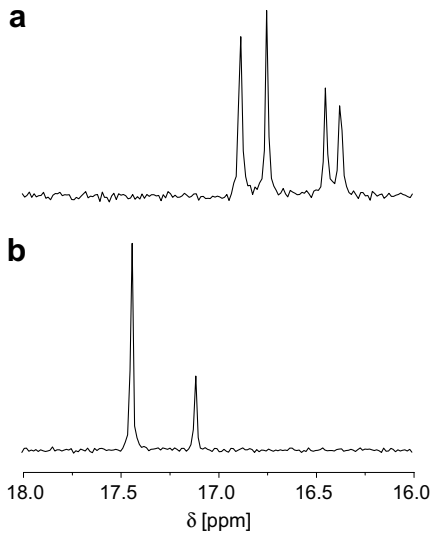


Figure 5. ^{31}P NMR spectra of **1f** complexed with HP-γ-CD (10 mM: 100 mM) (a) and in free form (b) in D_2O solution (pD = 12.5).

gives enantioselectivity $\Delta\delta = 0.075$ (Fig. 5). When α-CD was applied, no resolutions of the ^{31}P NMR signals of *cis*-**1f** were observed and the contribution of these isomers in free and complexed forms was the same (24%). The results obtained indicate that the complexation with both γ-CD and HP-γ-CD stabilized the *cis*-isomer of this analyte. Thus complexes with the two folded aromatic rings of **1f** inserted in one cavity of γ-CD or HP-γ-CD exist in solution.

3. Conclusions

The present paper completes our research program to use the nuclear magnetic resonance technique for the enantiodifferentiation of various aminophosphonates by means of cyclodextrins. The cyclic oligosaccharides proved versatile and universal chemical shift reagents for analyzing the enantiomeric composition of the compounds were studied. Conditions allowing simple and repetitive ^{31}P NMR experiments were subsequently established for all possible analogues. This included: free α-aminophosphonic/phosphinic acids,[6] their N-protected derivatives[9] and finally N- and P-termini disubstituted aminophosphonates described here.

At the same time more advanced NMR techniques were applied to investigate the complexation mode in some detail. However, the pattern of the guest/host interactions has become more and more complicated, along with an increase of complexity of the aminophosphonate used, namely with the number of hydrophobic fragments present in the molecule and able to be included into the cyclodextrin inner cavity. As a result, the formation of various dynamic supramolecular assemblies by differing the structure and the stoichiometry was evidenced. Moreover, the influence of *N*-benzyloxycarbonylaminophosphonate complexation by γ-CD and HP-γ-CD on *cis–trans*-carbamate isomerization has been shown for the first time.

4. Experimental

Deuterium oxide, NaOD and DCl solutions were purchased from Armar Chemicals, Döttingen, Switzerland. α-Cyclodextrin was obtained from Lancaster Synthesis, England, Germany. Other cyclodextrins (β-CD, γ-CD and HP-γ-CD with 0.6 degree of substitution) were obtained from Sigma–Aldrich, Poznań, Poland. All *N*-benzyloxycarbonylaminophosphonic acid monoesters were synthesized according to the standard methods.[15]

NMR experiments were performed on a Bruker Avance™ 600 MHz at 298 K. Measurements were made in D_2O solution, adjusted to the proper pD with diluted NaOD and DCl solutions. Tetramethylsilane for ^1H spectra or 85% phosphoric acid in H_2O for ^{31}P spectra were used as external standards. The final concentrations of 10 mM for N-protected α-aminophosphonates and 100 mM for α-cyclodextrin, γ-cyclodextrin or hydroxypropyl-γ-cyclodextrin and 1 mM of a guest compound and 10 mM for β-cyclodextrin were used. 2D-ROESY experiments were carried out at 200 ms mixing time. Samples for a continuous variation method were prepared by mixing a 100 mM (or 10 mM) solution of guest compound in enantiomerically pure form in D_2O with 100 mM (or 10 mM) solution of cyclodextrin in D_2O in appropriate ratio.

The results are presented as a difference of ^{31}P chemical shift ($\Delta\delta$) of two diastereomeric aminophosphonate/cyclodextrin complexes in case of NMR measurements.

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