Chinese Chemical Letters Vol. 15, No. 6, pp 675-678, 2004
http://www.imm.ac.cn/journal/ccl.html

Using the Chiral Organophosphorus Derivatizing Agents for Determination of the Enantiomeric Composition of Chiral Carboxylic Acids by ^{31}PNMR Spectroscopy

Chao CHE[1], Zhong Ning ZHANG[1]*, Gui Lan HUANG[2],
Xin Xing WANG[1], Zhao Hai QIN[3]

[1] State Key Laboratory of Integrated Management of Insects and Rodents, Institute of zoology, Chinese Acadamy of Sciences, Beijing 100080
Graduate School of the Chinese Academy of Sciences, Beijing 100039
[2]The Sixth Research Center, Institute of Chemical Defence, Beijing 102205
[3]Department of Applied Chemistry, China Agricultural University, Beijing 100094

Abstract: The use of chiral organophosphorus derivatizing agents prepared *in situ* from chiral tartrate or chiral diamine for the ^{31}PNMR determination of the enantiomeric composition of chiral carboxylic acids is described. The method is accurate, reliable and convenient.

keywords: Chiral tartrate, chiral diamine, enantiomeric composition determination, ^{31}PNMR, carboxylic acids.

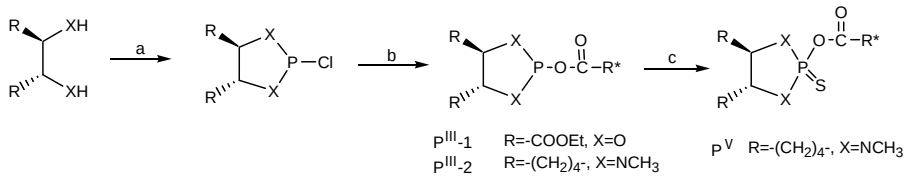
The enantiomeric compositions of chiral compounds can be determined by a variety of methods[1], among which the conversion of enantiomers into diastereomers with a chiral derivatizing agent and analysis by NMR techniques take an important place[2]. ^{31}P is a particularly attractive nucleus to use for chiral analysis due to the large chemical shift dispersion and the simplicity of spectra[3]. Over the past two decades, various chiral phosphorus derivatizing agents (CPDA) have been developed, and furthermore, most of them have been applied to the determination of the enantiomeric composition of chiral alcohols[4], amines[4c~f, 5], thios[4d, 4f, 6] and aminoacids[5b, 7]. However, there were relatively few examples reported with CPDA for analysis of chiral carboxylic acids[8]. To our knowledge, in addition, the utilization of CPDA prepared *in situ* from tartrate for enantiomeric composition determination of chiral carboxylic acids has not been defined. Herein, we reported the results of the use of diethyl D-(-)-tartrate together with chiral diamine for enantiomeric compositon determination of chiral carboxylic acids by ^{31}PNMR spectroscopy.

As shown in **Scheme 1**, chiral diethyl tartrate or diamine, containing C_2 axis of symmetry was reacted with PCl_3 in the presence of base, such as dimethylaniline or N-methylimidazole, leading to the very reactive derivatizing agent. This reagent is sensitive to moisture, and therefore we prepared it *in situ* directly in $CDCl_3$ solution in

* E-mail: zhangzn@panda.ioz.ac.cn

NMR tube. This reaction proceeded instantaneously. Once the chiral carboxylic acids were added, the diastereomeric derivatives formed instantaneously. A first ^{31}PNMR spectrum of this trivalent phosphorus derivatives (P^{III}) could be recorded for analysis of enantiomeric composition. Further reaction with excess elemental sulfur afforded new pentavalent phosphorus derivatives (P^{V}) and allowed a second ^{31}PNMR determination. It should be mentioned that sulfuration of P^{III}-1 derivatives prepared from diethyl tartrate was unsuccessful, whereas sulfuration of P^{III}-2 derivatives prepared from chiral diamine led to the desired P^{V} derivatives.

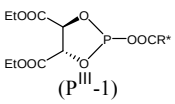
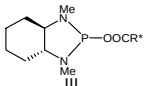
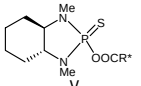
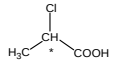
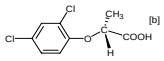
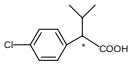
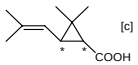
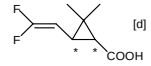
Scheme 1



Reagent: a) $CDCl_3$, PCl_3, DMA; b) *RCOOH; c) S_8

The typical results of the chemical shifts and shift differences of diastereomeric derivatives performed on the chiral carboxylic acids with CPDA were summarized in the **Table 1**.

Table 1 ^{31}PNMR chemical shifts and shift differences of diastereomeric derivatives performed on the chiral carboxylic acids with CPDA ($CDCl_3$).

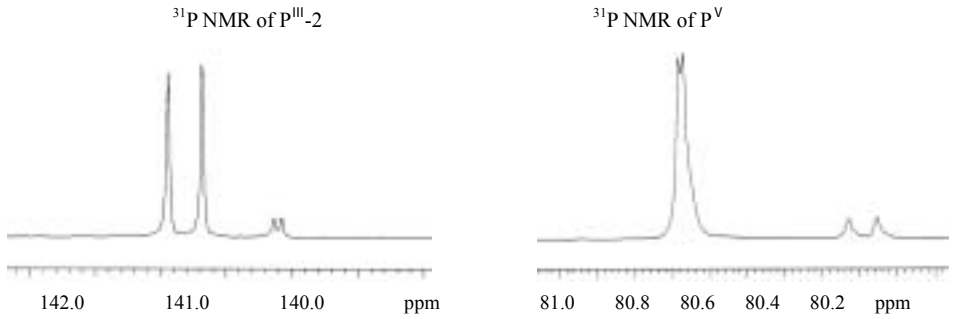
Entry	Substrate[a]	 (P^{III}-1)	 (P^{III}-2)	 (P^{V})
1		134.977 134.736 Δδ=0.241	147.388 - 	83.364 82.324 Δδ=1.040
2		135.527 134.901 Δδ=0.626	147.064 146.853 Δδ=0.211	82.324 82.037 Δδ=0.287
3		135.037 134.660 Δδ=0.377	143.701 - 	81.705 81.638 Δδ=0.067
4		134.298 134.200 134.132 133.921	140.941 140.677 140.127 140.074	80.786 80.770 80.326 80.250
5		134.389 134.140 Δδ=0.249	143.429 - 	81.057 80.876 Δδ=0.181

Notes: - no separation at all; a. Integration of the diastereomer signals for racemic acids corresponds to 50:50 (±2%); b. 27.3 ee % (found), 27.9 ee % known by mixing R-enantiomer with racemate; c. *trans* : *cis* = 10 : 1; d. *trans*-isomer

Diethyl tartrate or diamines were tested in order to determine the most appropriate CPDA. In all cases of carboxylic acids, a good separation of ^{31}PNMR signals, which were sufficient to be able to determine enantiomeric excess by integration, occurred with P^{III}-1 derivatives. There was no chemical shift difference in the 2-chloro-propionic acid (entry 1) on the P^{III}-2 derivatives, however, the two enantiomeric signals were clearly distinguished by ^{31}PNMR on the P^{V} derivatives. The same phenomenon occurred with entry 3 and entry 5. 2-(2,4-Dichlorophenoxy)-propionic acid showed baseline separation, both on the P^{III}-2 and P^{V} derivatives (entry 2). Therefore, addition of sulfur in the NMR tube could be a powerful tool to determine the enantiomeric composition of chiral carboxylic acids in contrast to the alcohols and amines[4e].

The method not only allowed the determination of enantiomeric purity but also the diastereomeric composition of a mixture. This possibility was shown in the entry 4. By ^{31}PNMR, four signals, two for one enantiomer pair, two for the other, were distinguished on P^{III}-1 derivatives. Interestingly, the enantiomers of *trans*-acid were well separated on the P^{III}-2 derivatives; whereas, the enantiomers of *cis*-acid were separated on the P^{V} derivatives (**Figure 1)**. For this reason, recording ^{31}P NMR spectra of P^{III} derivatives and P^{V} derivatives could be accurate for enantiomeric excess determination of chiral carboxylic acids.

Figure 1 ^{31}P NMR spectra of P^{III}-2 and P^{V} diastereomeric derivatives of chrysanthemic acid (*trans* : *cis*=10: 1) with CPDA



2-(2,4-Dichlorophenoxy)-propionic acid (entry 2) is known to be easily racemized in basic media. But in the mild base (dimethylaniline) condition, P^{III} and P^{V} derivatives were stable, without any detectable racemization; however, racemization was observed when triethylamine was used as base.

For an enantiomeric excess determination method involving diastereomer formation to be useful, it is necessary to demonstrate that the reaction is kinetically unselective. In our study, an enantiomeric excess determination was performed on partially enriched 2-(2,4-dichlorophenoxy)-propionic acid (entry 2), the observed values for enantiomeric excess based on the ^{31}P NMR integration of diastereomers showed good correlation with actual values measured by weight. Furthermore, in all cases of racemic acids the enantiomeric excess was found to be less than 2%.

In conclusion, the chiral phosphorus derivatizing agents prepared *in situ* from chiral diethyl tartrate or chiral diamine gave excellent results in enantiomeric composition

determination of a series of carboxylic acid using ^{31}PNMR spectroscopy. Extension of this methodology to wider range of compounds, such as alcohols, amines, aldehydes and ketones, is in progress.

Acknowledgments

The authors wish to thank Chinese Academy of Sciences (CAS) Innovation Program for financial support.

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Received 26 May, 2003