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5-Amino-4-aryl-2,2-dimethyl-1,3-dioxans: application as chiral NMR shift reagents and derivatizing agents for acidic compounds

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Abstract

The use of (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxan (ADPD) and (4*R*,5*R*)-5-amino-(4′-biphenyl)-2,2-dimethyl-1,3-dioxan (ABDD) as chiral solvating agents (CSA) for the ee determination of compounds bearing an acidic proton by means of ^{1}H NMR spectroscopy is demonstrated. In addition, based on the well known rigid conformation of these amines, ADPD and ABDD are suitable as chiral derivatizing agents (CDAs) in order to determine absolute configurations.

1. Introduction

Apart from other analytical methods, such as HPLC[1] and GC[2] on chiral stationary phases, NMR spectroscopy is one of the most important methods for determining the enantiomeric purity of chiral molecules. Powerful tools for ee determination are chiral lanthanide shift reagents[3] and chiral solvating agents (CSAs) such as Pirkle alcohol.[4] A different approach to determine the enantiomeric excess of a molecule is the use of chiral derivatizing agents (CDAs) with a well known absolute configuration to form diasteromers via covalent bonds. The most prominent members of these CDAs are *O*-methylmandelic acid, introduced by Mislow and Raban and α-methoxy-α-trifluoromethylphenylacetic acid[5] (MTPA, Mosher's acid). By forming amides or esters via the corresponding acid chlorides, often a determination of the absolute configuration of amines[6] and alcohols[7] is possible and this has been extended recently by Kakisawa et al. to more complex natural products.[8]

In the course of the development of the synthesis of the primary amine ABDD[9] (Fig. 1), the corresponding Mosher amides of the (*R*,*R*)- and (*S*,*S*)-enantiomers were synthesized in order to determine the absolute configuration of the amine by means of ^{1}H NMR spectroscopy.

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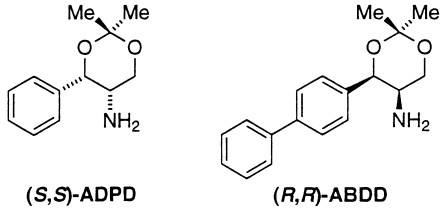


Figure 1.

It emerged that the signals of the phenyl ring belonging to the Mosher-part of both diastereomeric amides were strongly shifted, whereas the chemical shift of the protons of the biphenyl-unit was almost the same.[10] Thus, the ability of ABDD as a chiral shift reagent for molecules bearing an acidic proton was investigated. The results were compared to commercially available ADPD in every case. The possibility of determining the absolute configuration of acids based on amides of the amine ABDD is also shown.

2. Results and discussion

In general, it was found that an equimolar ratio of amine to acids A–E resulted in the greatest nonequivalence in chemical shift (Table 1). In the case of acid C, an opposite effect for the bold-faced proton and the methyl group was observed. ABDD gave larger chemical shift differences compared with ADPD due to the enlarged aromatic system. Surprisingly, the amide proton in secondary sulfonamide E, available by electrophilic amination of hydrazones,[11] was also found to be acidic enough to form diastereomeric complexes with the amines ADPD and ABDD.[12] Thus it is possible to determine the enantiomeric excess of chiral sulfonyl-protected α-aminoketones in this manner. It should be mentioned that it was not possible to induce a remarkable chemical shift difference with a sample of racemic phenethylalcohol under the same conditions.

Fig. 2 shows a part of the ^{1}H NMR spectrum of racemic acid D in the presence of an equimolar amount of ABDD.

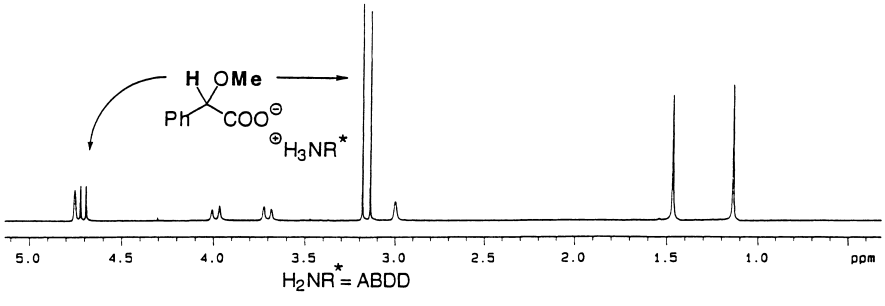
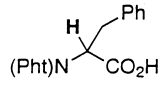
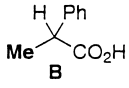
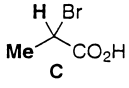
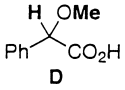
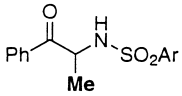


Figure 2.

Racemic acid B was converted to the (*R*,*R*)-ABDD amide derivative via its acid chloride using standard methods.[13] The diastereomers were separated by column chromatography on silica (pentane:ethyl acetate, 3:1). The determination of the absolute configuration of the original acid was achieved by means of NOE experiments in order to determine the conformation of the amides and by observing significant differences in the chemical shift of the ring-protons H^4–H^6 (Fig. 3).

The strong NOE in both diastereomers between the protons H^1 and H^2 indicate a *syn*-periplanar conformation as shown in Fig. 3 and thus a *syn*-orientation of the carbonyl group and the 1,3-dioxan residue on the nitrogen.[14] The significant shift to higher field of the ring-protons H^4–H^5 in diastereomer

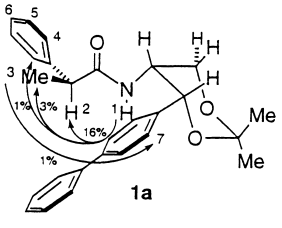
Table 1
Magnitude of the nonequivalence (Δδ, Hz) induced by the addition of ADPD or ABDD to the acidic compounds A–**E**[a]

Ratio (acid : CSA)	(1 :1)		(1 : 2)	
CSA	ADPD	ABDD	ADPD	ABDD
 **A** (Pht=Phthaloyl)	0.0	18.8	2.8[b]	13.5[b]
 **B**	1.7	2.5	1.7	2.7
 **C**	3.2(H) 0.6(Me)	6.9(H) 1.1(Me)	0.4(H) 2.1(Me)	3.6(H) 3.8(Me)
 **D**	9.3(Me) c	13.1(Me) 8.5(H)	9.1(Me) 3.6(H)	11.8(Me) c
 **E** Ar=2,4,6-Triisopropylbenzene	2.5	2.8	2.0	2.4

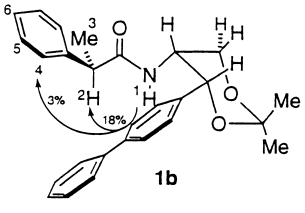
a) Exp. conditions: 20.0 mg acid **A-E** + CSA in 0.70 ml C_6D_6; 300 MHz Varian Gemini unit; b) Ratio = 1:3; c) Determination not possible.

1b indicates that these protons are under the influence of the ring current effect of the biphenyl system. The biphenyl-unit is connected to the rigid 1,3-dioxan ring (chair conformation) as an equatorial substituent. Diastereomer 1a shows a weak NOE between a ring proton H^7 and the protons H^3 of the methyl group. Thus, diastereomer 1a has the (*S*)-configuration, and the other diastereomer has the (*R*)-configuration.

In conclusion, the properties of the amines ADPD and ABDD as chiral shift agents for acidic compounds are demonstrated (ee determination). These two amines are also suitable as chiral derivatizing



Proton	δ (ppm)
H-4	7.12
H-5	7.28
H-6	7.28



Proton	δ (ppm)
H-4	6.95
H-5	7.16
H-6	7.16

Figure 3.

agents in order to determine the absolute configuration of acids after conversion into the amides as it is exemplified for ABDD.

3. Experimental

Racemic *N*-phthaloyl phenylglycine[15] A and racemic mandelic acid methyl ether[16] D were prepared according to the literature. The racemic carboxylic acids B and C are commercially available (Aldrich). Racemic α-aminoketone E was prepared by R. Joseph.[11]

NMR shift experiments were performed on a Varian Gemini 300 NMR spectrometer at room temperature. An amount of 20.0 mg acid and the given equiv. of a base were placed in an NMR tube and dissolved in 0.70 ml of C_6D_6.

NMR NOE experiments were performed on a Varian unity 500 NMR spectrometer using the 1D-NOE difference method with a 1 second mixing time between the selective irradiation of a single peak and the acquisition.

Acknowledgements

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