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Assignment of the absolute configuration of 7-substituted 3-azabicyclo[3.3.1]nonan-2-ones by NMR-titration experiments

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Abstract—The configuration assignment of 7-substituted 3-azabicyclo[3.3.1]nonan-2-ones **2**–**5** was made possible using the known chiral lactam **1** as a reference compound. Lactam **1** formed exclusively heterochiral complexes with the compounds under investigation. The detection of these complexes was possible by ^{1}H NMR. The downfield shift of the NH proton in compounds **2**–**5** indicated complex formation whereas the NH-signal remained unchanged in homochiral systems. The phenomenon somewhat resembles an (inverse) molecular handshake. Only heterochiral compounds can interact whereas homochiral compounds do not fit together.

1. Introduction

The rapid development of stereoselective methods in all fields of organic synthesis has led to a great demand for analytical procedures to determine the enantiomeric excess and the absolute configuration of new chiral products. The classical instrumental methods used for the determination of the absolute configuration,[1,2] such as X-ray crystallography, specific rotation, circular dichroism (CD) or optical rotatory dispersion (ORD) often hold some inconveniences for the bench chemist. X-ray diffraction, for example, requires single crystals of sufficient quality and, in the absence of a chiral reference (e.g., a chiral auxiliary), special techniques (anomalous X-ray diffraction). The chiroptical methods require either a closely related reference substance or a good computational prediction of the CD spectra or of the specific rotation.[3] Responding to a growing interest in simpler methods, a variety of new assignment protocols have been developed, mostly based on NMR spectroscopy.[2,4] The advantages of NMR methods are mainly due to the ease of their application, their applicability to both liquid and solid samples and the fact that they are non-destructive as the analyte can be recovered in most cases after examination.

For the measurement of the enantiomeric excess (ee) it is sufficient to induce a non-equivalence of single peaks in the NMR spectra of the two enantiomers by introducing some kind of chiral information. This can be achieved by measuring the spectrum in a chiral solvent or by adding a chiral solvating agent (CSA).[5] Another possibility is the use of chiral lanthanide shift reagents.[6]

Various attempts have been made to correlate the change in chemical shift $\Delta\delta$, especially the sign of $\Delta\delta$, with the absolute configuration of the analyte. In many cases, however, the difference in chemical shift induced by the chiral environment is either too small or the sign of $\Delta\delta$ is ambiguous. The lack of a defined and strong complexation of the analyte by a chiral solvent or a chiral solvating agent obviates the formation of a detectable diastereomeric complex. For these reasons, in the majority of cases, the absolute configuration is determined by NMR spectroscopy using a derivatisation method, for example, the Mosher ester protocol.[7] The covalent attachment of both enantiomers of a chiral derivatising agent (CDA) converts the sample into two diastereomeric compounds, which exhibit different spectra. The observed $\Delta\delta$ values allow in most cases for a correct assignment of the configuration using empirical models. The main disadvantages of all derivatisation methods are the additional synthetic efforts and the fact that neither analyte nor chiral reference can be recovered after examination. Thus the development of new CSAs or chiral NMR solvents, which allow for a better correlation

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between configuration and spectroscopic results, is still under investigation. Kishi and co-workers have reported the use of a chiral bidentate NMR solvent, which allows the determination of the absolute configuration of secondary and tertiary alcohols using ^{13}C NMR spectroscopy.[8] Cyclodextrins, which have been repeatedly used as CSA for the determination of enantiomeric purity, have also been applied to the assignment of the absolute configuration of chiral trisubstituted allenes.[9]

In the 1980s Rebek first reported the recognition capabilities of 3-azabicyclo[3.3.1]nonanones derived from Kemp's triacid.[10] Based on this research, various complexation studies have been performed with host compounds containing one or two 3-azabicyclo-[3.3.1]nonanone moieties binding the substrate via hydrogen bonding. Other recognition studies use a Kemp's triacid based scaffold with one remaining acid functionality for the determination of the enantiomeric excess of several chiral amines binding the latter via a salt bridge.[11] Recently we reported the use of chiral lactam **1** as an efficient ^{1}H NMR shift reagent for the ee determination of chiral lactams, quinolones and oxazolidinones.[12] We now show that lactam **1** also allows the determination of the absolute stereochemistry of closely related compounds.

2. Results and discussion

The observation that the chemical shift of the N–H proton of racemic lactam **1** is shifted downfield by 1–2 ppm, with respect to the separate enantiomers, provides the basis for this new assignment method. As shown in Figure 1 opposite enantiomers of this compound class are ideally suited for dimerisation via two hydrogen bonds (heterochiral recognition) and thus show a change in chemical shift in the presence of one another. The enantiomerically pure compounds in contrast cannot dimerise via hydrogen bonding as the sterically demanding shields prevent a close approach of the two lactam-binding sites.[13] In a titration experiment the addition of

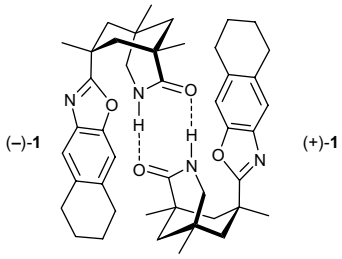

Figure 1. Heterochiral dimer of reference compound **1**. For a crystal structure of a closely related dimer see Ref. 14.

enantiomerically pure complexing agent **1** with known absolute configuration to a single enantiomer of another 3-azabicyclo[3.3.1]nonan-2-one with unknown configuration should therefore only induce a change in chemical shift if the unknown compound has the opposite configuration to compound **1**. The configuration of compounds (+)-**1** and (−)-**1** is known from anomalous X-ray diffraction methods.[14]

In the first set of experiments, we proved the validity of this method using the two enantiomers of a closely related 3-azabicyclo[3.3.1]nonan-2-one. Figure 2 shows a titration experiment using benzoxazole **2** with known[15] absolute configuration and **1** as reference. The two N–H protons of enantiomers (+)-**2** and (−)-**2** appear in the absence of **1** at 3.90 ppm. Upon addition of 0.5 equiv of (+)-**1**, the N–H signal of (−)-**2** was shifted to 4.91 ppm. Due to a twofold excess of (−)-**2** with respect to the concentration of (+)-**1** in the sample, the N–H signal of (+)-**1** is even shifted from about 4.0 ppm in the non-complexed state to 5.84 ppm.

The 1:1 complex after addition of another 0.5 equiv of (+)-**1** closely resembles the racemic mixture of both enantiomers of **2**. Only a single proton resonance with an integral of two protons was observed in this case with a chemical shift of about 5.6 ppm. The N–H resonance of a sample of racemic **2** having the same overall concentration as present in the titration experiment appears at

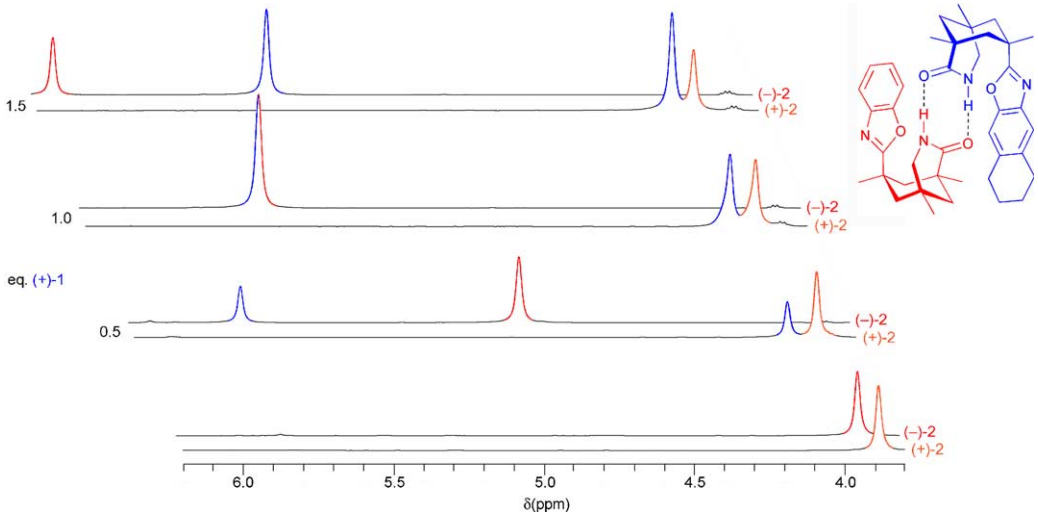

Figure 2. NMR-titration of (+)-**2** and (−)-**2** with the reference compound (+)-**1** in benzene-d_6.

5.65 ppm. A further change in chemical shift could be induced by adding another 0.5 equiv of compound **1** to the titration mixture. As expected, the signal belonging to (−)-**2** is again shifted downfield and the N–H resonance of **1**, now being the major component in the mixture, shows another shift upfield due to incomplete complexation.

In the titration of (+)-**2** with reference (+)-**1** the overall change in chemical shift after addition of 1.5 equiv of (+)-**1** is only around 0.13 ppm. This is in very good accordance with the change of chemical shift in a dilution experiment where only compound (+)-**1** is present in the solution: upon diluting a 0.15 M sample of compound **1** in toluene-d_8 to 0.06 mol/L, the chemical shift is also altered by about 0.1 ppm to higher field. The titration mixture (+)-**1** and (+)-**2** thus shows the same concentration dependence of the chemical shift as do the single enantiomers.

As expected only the heterochiral matched pair (−)-**2**/(+)-**1** shows distinct changes in chemical shift whereas in the homochiral mismatched case (+)-**2**/(+)-**1** the small changes in chemical shift can be easily explained by the dependence of the N–H resonance on the overall concentration present in the sample.

In a second set of experiments, we tested the menthyl esters **3** and **4** (Fig. 3) the configurations of which are also known.[14] As these 3-azabicyclo[3.3.1]nonan-2-ones are diastereoisomers, their amide resonance in the pure sample already differs by 2.5 ppm. Therefore, we examined their complexation behaviour using both enantiomers of reference compound **1**. Again only in the mixture of compounds having an opposite configuration at the lactam-binding site a distinct change in chemical shift was observed. Figure 4 shows the titration of **3** with (+)-**1** and (−)-**1**. The addition of 1.5 equiv of complexing agent (+)-**1** to a sample of **3** induced only a change in the chemical shift of about 0.06 ppm, while the other enantiomer of reference compound **1** (1.5 equiv (−)-**1**) caused a downfield shift of nearly 2 ppm. The opposite holds true for diastereomeric compound **4**. Here a distinct change in chemical shift was observed after the addition of compound (+)-**1** and only negligible changes were observed in the mixture with (−)-**1** (see Table 1, entries 5 and 6).

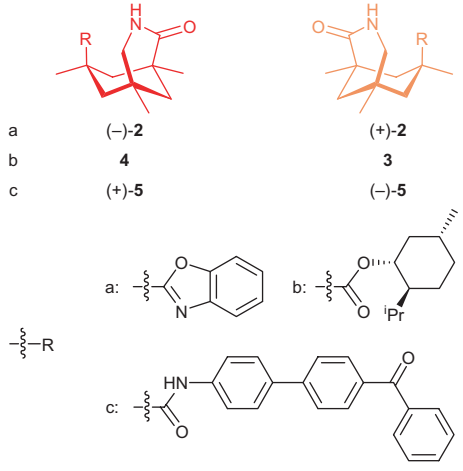

Figure 3. Examined compounds **2**–**5**.

Table 1. Titration experiments using **1** as reference compound

Entry	Analyte	Concn (solvent)	Ref.	$\Delta\delta$[a]
1	(+)-**2**	0.06 M (C_6D_6)	(+)-**1**	0.09
2	(−)-**2**	0.06 M (C_6D_6)	(+)-**1**	1.76
3	**3**	0.03 M (C_6D_6)	(+)-**1**	0.04
4	**3**	0.03 M (C_6D_6)	(−)-**1**	1.53
5	**4**	0.06 M (C_6D_6)	(+)-**1**	0.38
6	**4**	0.06 M (C_6D_6)	(−)-**1**	0.08
7	(+)-**5**	0.02 M (C_6D_6)	(+)-**1**	0.95
8	(−)-**5**	0.02 M (C_6D_6)	(+)-**1**	0.11
9	**3**	0.03 M ($CDCl_3$)	(−)-**1**	0.08

[a] After addition of 1.0 equiv of the reference compound.

Comparing the results obtained for these two experiments with the other experiments (see Table 1), the change in chemical shift for the matched case is quite small. This is due to an unusually large self association of compound **4**, which is already indicated by the enormous downfield shift of the N–H resonance of the pure compound [δ(N–H) ≅ 7.2 ppm].

The titration experiments with compounds **3** and **4** show that the availability of both enantiomers of the reference compound **1** allows the unambiguous assignment even if only one enantiomer of the analyte is available. A direct comparison of single experiments using only (+)-**1** and the diastereomeric compounds **3** and **4** can be misinterpreted whereas the performed experiments using both enantiomers of **1** leave no doubt about the configuration at the lactam-binding site.

In an ongoing photochemical research project we synthesised compound **5** (Fig. 3) having an amide connecting functional group between the bicyclic lactam and the shielding moiety. The two enantiomers could be separated by HPLC but the configuration of the individual enantiomers was difficult to assign. We consequently attempted to use our new shift method to make an assignment. Although this compound has two amide bonds, which can undergo a dimerisation via hydrogen bonding only one of the two enantiomeric 3-azabicyclo-[3.3.1]nonan-2-ones showed a clear change in chemical shift during a titration experiment as described above (see Table 1). We consequently assigned a (1*S*,5*R*,7*R*)-configuration as depicted on the left hand side of Figure 3 to compound (+)-**5** and a (1*R*,5*S*,7*S*)-configuration (depicted on the right) to its antipode.

As pointed out in earlier publications a strong complexation of substrates via hydrogen bonding is only achieved in apolar solvents.[13] Toluene-d_8 or benzene-d_6 turned out to be ideally suited for complexation studies using ^{1}H NMR spectroscopy. Other more common NMR solvents such as $CDCl_3$ are too polar and induce, for example, in the titration of **3** with (−)-**1** a change in chemical shift of only 0.08 ppm (Table 1, entry 9) compared to a change of 1.53 ppm under identical conditions using benzene-d_6 as solvent (Table 1, entry 4).

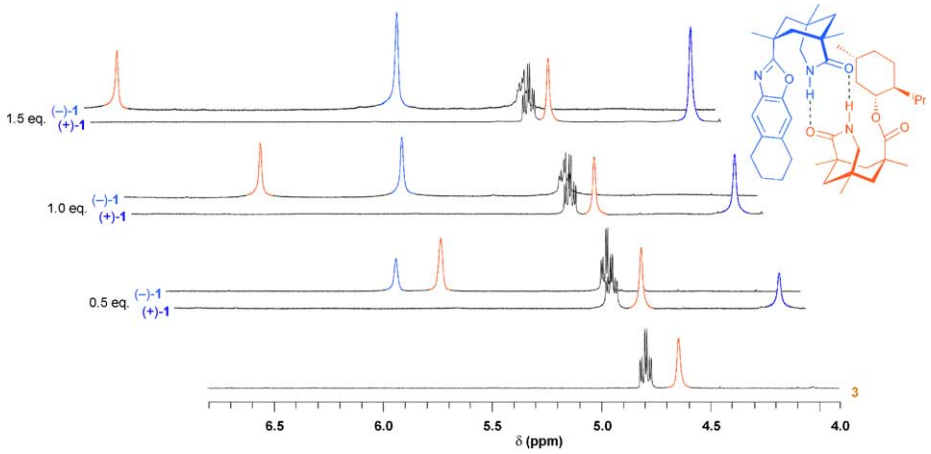

Figure 4. NMR-titration of **3** with both enantiomers of reference compound **1** in benzene-d_6.

The analysis of compound (±)-**5** shows the difficulties in determining the absolute configuration by the sign of the optical rotation. While compounds **1** and **2** show the same sign of optical rotation having the same absolute configuration at the lactam binding site, the opposite holds true for compound **5**. This is certainly due to the altered chromophore present in this compound.

3. Conclusion

The determination of the absolute configuration at the lactam-binding site of chiral 7-substituted 3-azabicyclo[3.3.1]nonan-2-ones derived from Kemp's triacid is possible performing a simple NMR-titration experiment using chiral lactam **1** as the reference compound. The chemical identity of the substituent in the 7-position plays only a minor role. The applicability has been shown for compounds having esters, amides or benzoxazoles as connecting functional group between the 3-azabicyclo[3.3.1]nonan-2-one scaffold and the shielding substituent. Even in the presence of other stereogenic centres in the analyte, the assignment remains unambiguous. Using this methodology we were able to assign the configuration of the new compound **5** as depicted in Figure 3.

4. Experimental

4.1. General procedure for NMR shift experiments

First, a ^{1}H NMR spectrum of the analyte solution (0.02–0.06 M in C_6D_6) was collected at 300 K using a BRUKER AV-500 spectrometer. Subsequently, enantiomerically pure reference compound **1** was dissolved in the analyte solution in portions of 0.5 equiv, respectively. Chemical shifts are reported relative to tetramethylsilane as the internal reference.

4.2. Synthesis of the literature-known chiral lactams

Compounds **1**, **3** and **4** were synthesised as previously reported;[14] racemic **2** was prepared as described by Curran and co-workers.[15] The enantiomers were separated by chiral semipreparative HPLC (Daicel Chiralpak-AD 250 × 20.0, *n*-hexane–*i*-PrOH 90:10). For the synthesis of compound **5** racemic 1,5,7-trimethyl-2-oxo-3-azabicyclo[3.3.1]nonane-7-carboxylic acid was prepared as previously reported,[16] 4-(4-aminophenyl)-benzophenone was synthesised as described.[17] For further general remarks, see Ref. 18.

4.3. 1,5,7-Trimethyl-2-oxo-3-azabicyclo[3.3.1]nonane-7-carboxylic acid (4″-benzoylbiphenyl-4′-yl)-amide (*rac*-5)

Diisopropylcarbodiimde (84 μL, 0.59 mmol) and 4-(4-aminophenyl)-benzophenone (148 mg, 0.54 mmol) were added to a stirred solution of racemic 1,5,7-trimethyl-2-oxo-3-azabicyclo[3.3.1]nonane-7-carboxylic acid in dichloromethane (1.2 mL). After stirring for three days at room temperature, the solvent was evaporated and the crude product purified by flash chromatography (toluene–EtOAc 1:1) to yield **5** (239 mg, 92%) as a white foam. The enantiomers were separated using semipreparative chiral HPLC (Daicel Chiralpak-AD 250 × 20.0, *n*-hexane–*i*-PrOH 60:40). $R_f = 0.23$ (toluene–EtOAc 1:1); mp = 258 °C; (+)-**5**: $[\alpha]_D^{20} = +58.1 \pm 0.4$ (*c* 0.1, $CHCl_3$); (−)-**5**: $[\alpha]_D^{20} = -59.3 \pm 0.4$ (*c* 0.1, $CHCl_3$); IR (KBr): $\tilde{\nu}$ 3354 cm^{-1} (m, N–H), 2957 (m, arom. C–H), 2926 (m, C–H), 1682 (vs, C═O), 1646 (s, C═O), 1594 (s, C═O), 1525 (vs, CON–H), 1315 (s, C–N), 1300 (s, C–N), 1283 (s), 700 (m). NMR data are given for enantiomerically pure (+)-**5**: ^{1}H NMR (500 MHz, toluene-d_8): δ (ppm) 0.74 (d, ^3J = 14.5 Hz, 1H, C*H*H), 0.80 (s, 3H, CH_3), 0.89 (d, ^3J = 12.7 Hz, 1H, C*H*H), 0.98 (d, ^3J = 14.5 Hz, 1H, CH*H*), 1.29 (s, 6H, CH_3), 1.40 (d, ^3J = 12.7 Hz, 1H, CH*H*), 2.33 (d, ^3J = 14.9 Hz, 1H, C*H*H), 2.60 (d, ^3J = 11.5 Hz, 1H, NHC*H*H), 2.97 (d, ^3J = 14.9 Hz, 1H, CH*H*), 3.13 (d, ^3J = 11.5 Hz, 1H, NHCH*H*), 5.73 (s, 1H, CON*H*CH$_2$), 7.27–7.34 (m, 2H, arom. H), 7.35–7.41 (m, 1H, arom. H), 7.60–7.67 (m, 2H, arom. H), 7.67–7.74 (m, 2H, arom. H), 7.90–7.95 (m, 2H, arom. H), 7.95–8.01 (m, 2H, arom. H), 8.07 (s, 1H, CONHAr), 8.09–8.16 (m, 2H, arom. H). ^{13}C NMR (90.6 MHz, $CDCl_3$, 300 K): δ (ppm) 25.0 (q, CH_3), 29.0 (q, CH_3), 30.6 (s, C), 32.6 (q, CH_3), 38.8 (s, C), 43.8 (s, C), 45.2 (t, CH_2), 46.1 (t, CH_2), 46.2 (t,

CH_2), 52.9 (t, $NHCH_2$), 122.0 (d, $C_{ar}H$), 126.8 (d, $C_{ar}H$), 127.8 (d, $C_{ar}H$), 128.4 (d, $C_{ar}H$), 130.1 (d, $C_{ar}H$), 130.9 (d, $C_{ar}H$), 132.5 (d, $C_{ar}H$), 135.9 (s, C_{ar}), 136.1 (s, C_{ar}), 137.9 (s, C_{ar}), 138.3 (s, C_{ar}), 144.9 (s, C_{ar}), 174.0 (s, CONH), 175.9 (s, CONH), 196.5 (s, CO); MS (EI, 70 eV): *m/z* (%) 480 (17) [M^+], 273 (100) [$M^+-C_{11}H_{18}NO_2$], 208 (13) [$C_{11}H_{18}NO_2^+$], 180 (25) [$C_{11}H_{18}NO^+$], 135 (7), 105 (5) [$C_7H_5O^+$], 44 (8); HRMS: $C_{31}H_{32}N_2O_3$: calcd 480.24130, *m/z* found 480.24098.

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