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An Enantiomerically Pure 1,5,7-Trimethyl-3-azabicyclo[3.3.1]nonan-2-one as ^{1}H NMR Shift Reagent for the *ee* Determination of Chiral Lactams, Quinolones, and Oxazolidinones

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Abstract: The chiral lactam **1** (or its enantiomer *ent*-**1**) was shown to be an effective ^{1}H NMR shift reagent for the *ee* determination of chiral lactams, quinolones, and oxazolidinones. It was successfully employed in many cases in which a detection of enantiomers by chromatographic methods failed. The method was extended to a broader range of simple substrates bearing a lactam moiety to evaluate its scope. The NH signals of the substrate enantiomers showed the strongest separation and were used for ^{1}H NMR integration. In most cases, compound **1** (1.5 equiv; 0.06 M solution) induced a baseline separation of the NH signals and it can consequently be regarded as a generally applicable shift reagent for chiral products with a lactam moiety.

In the past decade, the synthesis of enantiomerically pure compounds turned out to be more and more important in all fields of organic chemistry. Parallel, there was an increasing demand for reliable methods to determine the optical purity of chiral products. Ideally, the enantiomeric excesses (*ee*) are proved by different independent methods. In most cases, chromatography (GC and HPLC with a chiral stationary phase) and spectroscopy (NMR, circular dichroism) are applied.

NMR methods offer a lot of advantages:[1] They are nondestructive analytical methods, are easy to handle, and are well suited to study dynamic processes. Optically pure discriminating agents can be divided into chiral derivatizing agents (CDA), reacting with the analyte, and chiral solvating agents (CSA) that bind in situ to the substrate.[1a] In the latter case, temporary formation of complexes with an enantiomerically pure reagent causes differential shifts of the two enantiomers. A clear advantage of CSAs over CDAs such as Mosher's acid[2] is the fact that the chiral compound can be fully recovered after NMR analysis. In addition, the *ee* of the CSA affects only the shift difference $\Delta\delta$ relative to the maximum whereas the *ee* of the CDA affects the *ee* measurement, i.e., insufficient enantiomeric purity of the CDA leads to wrong *ee* data.[3] For the temporary formation of diastereomeric complexes, chiral lanthanide shift reagents have been frequently used. Complex formation via other noncovalent interactions, mostly H-bonds, is a valuable alternative. A variety of substrates, such as amines, amides, lactams, and carboxylic acids, are suitable substrates in this respect. Crown ethers[4] and cyclodextrins[5] are examples of nonmetallic CSAs which receive increasing attention. Amides are especially suited to be used as shift reagents in this context as they possess a coordination motif that forms definite complexes of a distinct orientation with the substrate. There are only a few examples in the literature on the use of amides or lactams as NMR shift reagents.[6] The U-shape structural motif present in Kemp's acid derivatives has been applied in NMR recognition studies[6b,c] of the binding behavior of chiral amines. If the reversible process observed is fast on the NMR time scale, the spectrum will be that of a single species showing averages of the chemical shifts and coupling constants of the individual species, the positions of the signals being weighted according to the population of the different states in the equilibrium.

In the course of recent work directed toward enantioselective photoreactions in solution, the chiral lactams **1** and *ent*-**1**[7] (Scheme 1) proved to be most effective chiral complexing agents.[8] Prochiral lactams are bound via two hydrogen bonds to its lactam binding site. In the complex, one of the enantiotopic faces of the substrate is shielded from any chemical attack by the bulky tetrahydronaphthalene group.

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(3) We thank a reviewer for pointing this out to us. In addition, the reviewer remarked that in the case of CSA **1** a nonlinear relationship between the *ee* of the CSA and the observed $\Delta\delta$ is to be expected. The expectation is based on the different association constants for **1**·**1** and **1**·*ent*-**1**.

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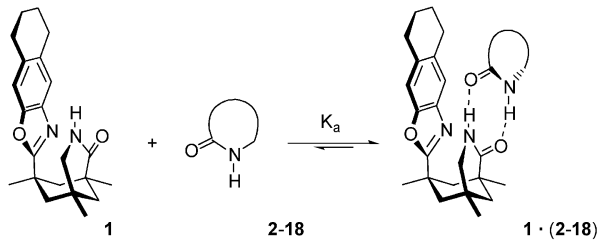
SCHEME 1. Association Equilibrium of Chiral Complexing Agent 1 with Compounds 2−18



1 **2-18** **1 · (2-18)**

While studying the *ee* of some reaction products by common methods we realized that the complexing agent itself can act as a NMR shift reagent. Indeed, we were delighted to see that it was an effective probe for the enantiomeric purity of many chiral lactams we had not been able to separate by chromatographic means. We consider this application of the chiral lactam complexing agents of broader interest and wish to report their potential as a general shift reagent for chiral compounds containing a lactam moiety. In all cases, the NH signal of the substrate showed the strongest separation. Two effects can be held responsible for this observation. The participation in the H-bonds with concomitant magnetic deshielding induces a shift to lower field of the NH signal. With the exchange in the association equilibrium being fast on the NMR time scale the observed chemical shifts are determined by the weighted average of the chemical shift of the free and the complexed molecules. Different equilibria (K_a, Scheme 1) will therefore lead to unequal average chemical shifts. In the complex with the chiral template the corresponding protons of the enantiomers become diastereotopic to one another. The chemical shifts of the complexed enantiomers are therefore inherently different. Since any substituents of the lactam ring pointing toward the tetrahydronaphthalene shield causes unfavorable interactions the association constant of the enantiomers of such compounds will be markedly different. The enantiomer with the bulky groups pointing away from the shield will exhibit a higher association constant and therefore the chemical shift of the complexed compound will contribute more strongly to the averaged signal. This causes a stronger downfield shift of the NH proton.

The dependence of the induced shift from the amount of template added was exemplified for the Diels−Alder product **7** that is without derivatization, not GC viable, and could not be separated by chiral HPLC. Figure 1 shows the separation of the NH signals of **7**/*ent*-**7** as a consequence of the addition of increasing amounts of **1** to a solution of **7** in acetone-d_6 at 298 K (0.01 M). Using more than 1.0 equiv of **1** the NH peaks of the enantiomers are baseline separated. With more than 4 equiv (0.04 M) the separation went into saturation at $\Delta\delta_{RS}(\mathrm{NH}) \cong 0.4$ ppm.

The difference in the association constants of the two enantiomers with the chemical shift reagent **1** is evidently the dominating factor, which is responsible for the chemical shift differentiation. As can be seen in Figure 1, both NH signals are shifted to lower fields—to different extents. The different interactions of the two enantiomers with the complexing agent translate to a different share of complexed molecules and therefore to different downfield shifts of the weighted averaged signals. It is surprising that the association in the polar solvent acetone is sufficient to ensure baseline-separated signals. The inherent inequality of the NH signals of **7**/*ent*-**7** in the diastereomeric complexes presumably plays a secondary role. Since both effects depend on the association, an experimental distinction is difficult.

In a first set of experiments we evaluated the accuracy of the enantiomeric excess determined by complexing agent **1**/*ent*-**1** as the chiral shift reagent. To this end, the *ee* values of the substituted quinolones and lactams **2**−**9** which were derived from chromatographical methods (GC and HPLC) with a chiral stationary phase were compared with the values obtained from NMR measurements with template **1** as the chiral shift reagent (Scheme 2). In all instances, an excess of 1.5 equiv (0.06 M) of template **1** induced a distinct discrimination of the chemical shift of the NH signal of both enantiomers (0.04 M solution). The induced differences of the chemical shifts $\Delta\delta$ varied between 0.21 and 0.63 ppm. Quinolones **2**−**6** and dihydropyridone **8** were examined in $CDCl_3$. The alcohol **7** was not soluble in $CDCl_3$. Even in acetone-d_6, however, **1** induced baseline-separated NH signals of both enantiomers with $\Delta\delta = 0.21$ ppm. The NH signal of lactam **9** was not fully separated in $CDCl_3$. To enhance binding and concomitantly the shift difference upon different association constants we employed benzene-d_6 as the solvent. Then, although broad, the peaks were indeed baseline separated. Even mixtures can be analyzed in the presence of template **1**. The single NH signal of a diastereomeric mixture of the cis and trans isomers **5** and **6** split into four separated signals, which allowed for the determination of the diastereomeric ratio and the enantiomeric excess of both diastereoisomers in one NMR experiment without separation of the compounds. In some instances, not only the NH signal was separated. The H-8 signal of the cyclobuta[c]quinolones **2**−**4** ($\Delta\delta =$ 0.05 ppm) and the H-6 signal of lactam **8** ($\Delta\delta = 0.08$ ppm) were also baseline separated. In all cases, the ^{1}H NMR spectroscopic *ee* values were in good accordance with the chromatographically determined values.

The error margin of the NMR spectroscopic determination of the optical purity can be estimated to be about ±1% *ee* in the range of up to 90% *ee*. This is comparable to chiral GC or HPLC that provide an accuracy of ±0.5% *ee* after averaging over repeated injections. With their higher sensitivity the chromatographic methods may be advantageous for higher enantiomeric excesses if applicable. The NMR method only guarantees accurate *ee* determination up to the level of 92−94% *ee* (ratio of enantiomers 96/4 to 97/3), possibly somewhat higher. Still, for the examined samples of high enantiomeric purity a good accordance of the *ee* values obtained by NMR and by chromatographic methods was observed.

As previously stated the NMR shift method was in several cases the only method that allowed at all for an *ee* determination. Examples include again [2+2]-,[8e] [4+2]-,[8h] and [4+4]-cycloaddition[8c] products, the structures of which have been reported. In addition, we keep applying the shift method to other lactams which are prepared enantioselectively but have not yet been published.

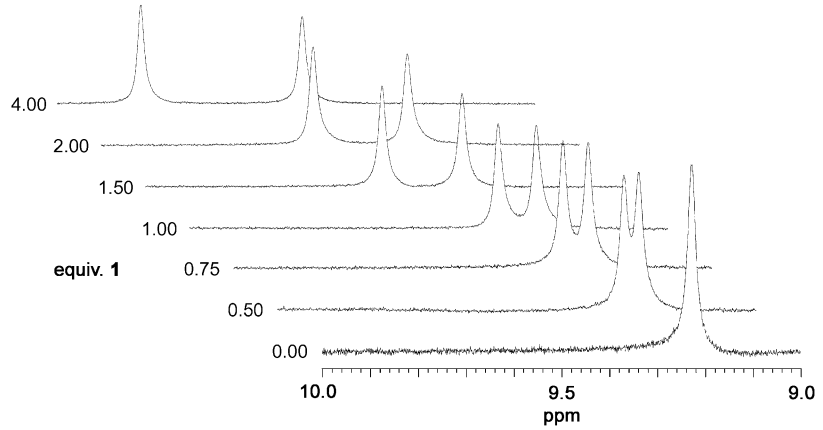
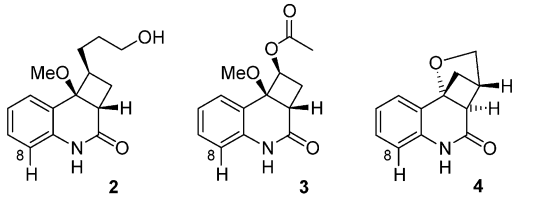
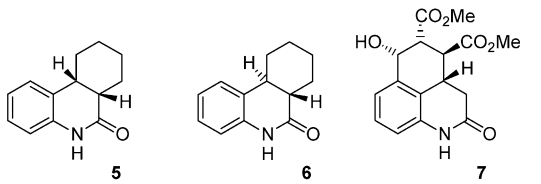


FIGURE 1. ^{1}H NMR spectrum of *rac*-**7** in acetone-d_6 (0.01 M) at 298 K in the presence of 0−4 equiv of **1** as the chiral shift reagent.

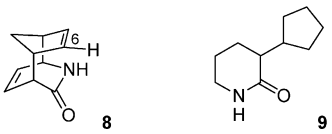
SCHEME 2. Comparison of the *ee* Values Determined by 1/*ent*-1 as the Chiral NMR Shift Reagent with the Values Obtained by Chromatographical Methods



	2	**3**	**4**
HPLC	26, 52, 74, 78, 81% *ee*	24, 61, 91% *ee*	4, 28, 74, 87, 93% *ee*
NMR (**1**/*ent*-**1**)	30, 50, 76, 81, 84% *ee*	21, 64, 92% *ee*	4, 31, 75, 85, 94% *ee*



	5	**6**	**7**
GC	0, 25% *ee*	0, 64% *ee*	0, 96% *ee*[a]
NMR (**1**/*ent*-**1**)	0, 24% *ee*	0, 64% *ee*	0, >90% *ee*

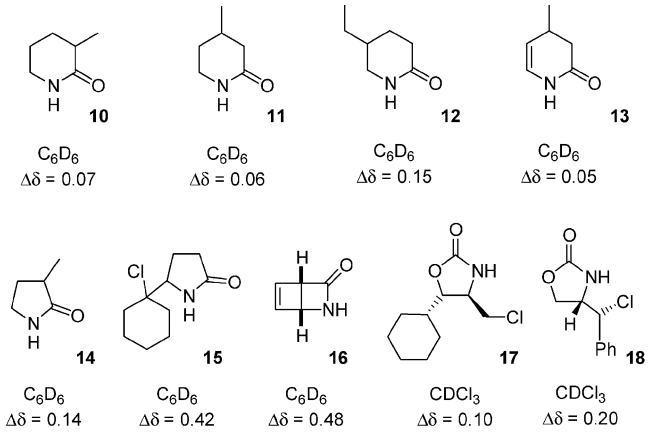


	8	**9**
HPLC	48, 76, 84% *ee*	0, 47% *ee*
NMR (**1**/*ent*-**1**)	45, 75, 80% *ee*	3, 48% *ee*

[a] Determined after derivatization.

The above-mentioned products are characterized by comparatively complex polycyclic structures. The association constants of the enantiomers with the chiral complexing agent should be markedly different. To demonstrate the general applicability of template **1**/*ent*-**1** as a chiral shift reagent for compounds containing a lactam moiety, structurally simple representatives of these substance classes were examined. Their enantiomers should have more similar association constants with the template. If template **1** allows for a differentiation of these substrates a general applicability can be claimed. Racemic tetrahydropyridones **10**−**12**, which are substituted with small alkyl substituents in the 3-, 4-, or 5-position, and 4-methyl-3,4-dihydropyridone (**13**) were chosen as simple representatives of six-membered ring-lactams. $CDCl_3$ proved to be too polar a solvent for these experiments. In benzene-d_6 (0.04 M solution) the signals were separated with the chemical shift differences $\Delta\delta$ given in Scheme 3, but the NH signals are broader. They were fully baseline separated in the case of compounds **10** and **12**. For lactams **11** and **13** the baseline separation was not fully complete.

SCHEME 3. Simple Chiral Lactams and the Difference of the Chemical Shift ($\Delta\delta$) of the NH Signals (in ppm) Induced by Template 1 (1.5 equiv; 0.06 M) in the Given Solvent at 298 K



The NH signals of the representatives of the five- and four-membered rings, racemic lactams **14** to **16**, also were not separated in $CDCl_3$. A baseline separation was obtained in benzene-d_6 with complexing agent **1** (1.5 equiv, 0.06 M). The signals of the bridgehead hydrogen atoms were differentiated as well. Racemic oxazolidinones **17** and **18** were tested as examples for other lactam-containing heterocycles. The NH signals of these compounds were already baseline separated in $CDCl_3$.

In summary, complexing agent **1** has been established as an appropriate ^{1}H NMR shift reagent for most chiral heterocycles of synthetic interest with a lactam linkage. The only weakness was observed for structurally simple

six-membered-ring lactams such as **11** and **13** for which the separated signals were not fully baseline separated. Evidently, the substituent in the 4-position does not have a sufficient effect on the association constants of the enantiomers with compound **1**. However, even in these cases the signals were well differentiated. For all other basic structures baseline separation was achieved. Concerning the more complicated lactams **2**−**8** and the oxazolidinones **17** and **18**, an accurate determination of the *ee* value was readily achieved even in the more polar solvents $CDCl_3$ and acetone-d_6.

Experimental Section.

General. ^{1}H NMR spectra were recorded at 300 K. Chemical shifts are reported relative to tetramethylsilane as internal reference. The chiral host compound **1**[7] and substrates **2**−**8**[8] and **16**−**18**[9,10] were synthesized as previously reported. The substrates **10**−**14** were prepared as described.[11−14]

General Procedure for NMR Shift Experiments. First, a spectrum of the substrate solution (0.04 M; for the corresponding solvent, see Scheme 3) was collected. Subsequently, 1.5−4 equiv of the chiral host **1** were added to the sample and a spectrum of the resulting complex was recorded.

Representative NMR Spectra. 1: ^{1}H NMR (500 MHz, acetone-d_6) δ 1.05 (s, 3 H), 1.10 (s, 3 H), 1.28 (s, 3 H), 1.35−1.41 (m, 2 H), 1.45 (dd, J = 14.0 Hz, J = 1.4 Hz, 1 H), 1.71 (br d, J = 12.6 Hz, 1 H), 1.78−1.82 (m, 4 H), 2.80 (d, J = 7.9 Hz, 1 H), 2.79−2.90 (m, 5 H), 2.92 (d, J = 11.5 Hz, 1 H), 3.25 (d, J = 11.4 Hz, 1 H), 5.55 (br s, 1 H), 7.12 (s, 1 H), 7.19 (s, 1 H).

7: ^{1}H NMR (500 MHz, acetone-d_6) δ 2.37 (virt. t, $J \cong$ 14.5 Hz, 1 H), 2.51 (dd, J = 16.1 Hz, J = 4.4 Hz, 1 H), 3.00−3.13 (m, 2 H), 3.19 (dd, J = 11.7 Hz, J = 3.5 Hz, 1 H), 3.70 (s, 3 H), 3.75 (s, 3 H), 4.70 (d, J = 6.6 Hz, 1 H), 5.08−5.12 (m, 1 H), 6.92 (d, J = 7.9 Hz, 1 H), 7.06 (d, J = 7.6 Hz, 1 H), 7.21 (virt. t, $J \cong$ 7.8 Hz, 1 H), 9.27 (br s, 1 H).

***rac*-7·1** (ratio 1/4): ^{1}H NMR (360 MHz, acetone-d_6) δ [**1**: 1.05 (s, 4 × 3 H), 1.10 (s, 4 × 3 H), 1.28 (s, 4 × 3 H), 1.35−1.41 (m, 4 × 2 H), 1.45 (d, J = 13.9 Hz, 4 × 1 H), 1.71 (br d, J = 12.9 Hz, 4 × 1 H), 1.76−1.81 (m, 4 × 4 H)], [**7**: 2.25 (virt. t, $J \cong$ 15.0 Hz, 0.5 H), 2.35 (virt. t, $J \cong$ 15.2 Hz, 0.5 H), 2.41−2.50 (m, 1 H)], [**1**: 2.76−2.93 (m, 4 × 7 H)], [**7**: 2.99−3.12 (m, 2 H), 3.16−3.21 (m, 1 H)], [**1**: 3.25 (d, J = 11.4 Hz, 4 × 1 H)], [**7**: 3.70 (s, 3 H), 3.74 (s, 1.5 H), 3.75 (s, 1.5 H), 4.67 (d, J = 6.2 Hz, 0.5 H), 4.70 (d, J = 6.2 Hz, 0.5 H), 5.07−5.12 (m, 1 H)], [**1**: 5.59 (br s, 4 × 1 H)], [**7**: 6.92 (d, J = 7.7 Hz, 1 H), 7.04−7.07 (m, 1 H)], [**1**: 7.12 (s, 4 × 1 H), 7.19 (s, 4 × 1 H)], [**7**: 7.19−7.25 (m, 1 H), 9.34 (br s, 0.5 H), 9.53 (br s, 0.5 H)].

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