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Bijvoet in Solution Reveals Unexpected Stereoselectivity in a Michael Addition

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Abstract: The absolute configuration of small crystallizable molecules can be determined with anomalous X-ray diffraction as shown by Bijvoet in 1951. For the majority of compounds that can neither be crystallized nor easily be converted into crystallizable derivatives, stereocontrolled organic synthesis is still required to establish their absolute configuration. In this contribution, a new fundamental methodology for resolving the absolute configuration will be presented that does not require crystallization. With residual dipolar coupling enhanced NMR spectroscopy, ensembles of a limited number of structures are created reflecting the correct conformations and relative configuration. Subsequently, from these ensembles, optical rotation dispersion (ORD) spectra are predicted by DFT calculations and compared to experimental results. The combination of these two steps reveals the absolute configuration of a flexible molecule in solution, which is a big challenge to chiroptical methods and DFT in the absence of NMR spectroscopy. Here the absolute stereochemistry of the product of a new Michael addition, synthesized via a niobium(V) chiral enolate, will be elucidated by using the new methodology.

Keywords: configuration determination · Michael addition · niobium · NMR spectroscopy · optical rotation dispersion

Introduction

Although the determination of the relative configuration of stereocenters was first established by Fischer in 1891 through organic synthesis,[1] the question of absolute configuration was not solved until the work of Bijvoet et al. in 1951 with anomalous X-ray diffraction.[2] For the majority of compounds that can neither be crystallized nor easily be converted into crystallizable derivatives, organic synthesis is still required to establish their stereochemistry.[3,4] Over the past two decades, the situation has been improved with the development of chiroptical techniques, such as optical rotation dispersion (ORD)[5] and vibrational circular dichroism (VCD),[6] that allow the configuration of all stereogenic elements to be determined in solution. As this requires all conformations to be known, these techniques are limited to relatively rigid compounds. For molecules with greater than four rotatable bonds, the magnitude of the resulting conformational space is immense rendering the required calculations computationally infeasible.[7–10] In this contribution, a new fundamental methodology overcoming the flexibility issue to resolve the absolute configuration will be presented. Rather than sampling the entirety of the conformational space, ensembles of ten structures derived by NMR spectroscopy, which reproduce the experimental NMR spectro-

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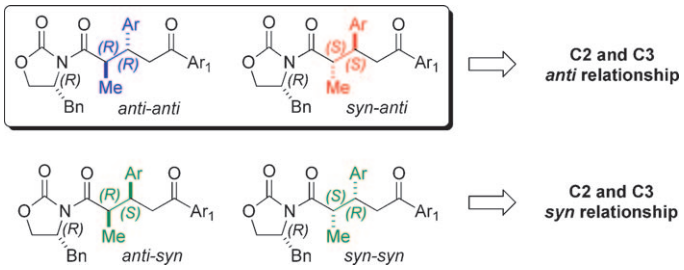
scopic data will be used to predict chiroptical properties of the molecule in solution. The technique involves two steps: residual dipolar coupling (RDC)-enhanced NMR spectroscopy to enable the determination of the conformational ensemble and the relative configuration;[11,12] and subsequent prediction of ORD spectra by DFT calculations to differentiate between enantiomers. Combined, the two steps reveal the absolute configuration of a flexible molecule in solution. We will show that the ORD values for the different conformations in the ensemble vary tremendously and, therefore, the determination of a faithful ensemble representing the situation in solution is mandatory for calculating correct ORD values with DFT. Here the absolute stereochemistry of the product of a new Michael addition, synthesized via a niobium(V) chiral enolate, will be elucidated using the new methodology. The conjugated addition to α,β-unsaturated compounds (Michael reaction) is one of the most important reactions in C–C bond formation.[13] A few examples that use metallic enolates prepared from chiral and achiral oxazolidinones in conjugated addition reactions have been described to prepare versatile intermediates in the synthesis of compounds with interesting pharmacological activities.[14–19] By using the new methodology we determine the relative configuration of the reaction product, reveal with this an unexpected stereoselectivity and provide an insight into mechanistic organic chemistry. In addition, we unequivocally determine the absolute configuration of this Michael addition product.

Results

Studies for the niobium-based stereoselective Michael addition: The application of niobium(V) compounds as Lewis acids has recently been demonstrated in a variety of organic reactions.[20,21] Based on our previously established methodology for preparing niobium enolates of oxazolidinones,[22] we decided to study the conjugated addition of these enolates to α,β-unsaturated systems, especially chalcones. The niobium(V)-catalyzed reaction is shown in Scheme 1.

This conjugate addition reaction involves the addition of a niobium enolate of the chiral auxiliary *N*-propionyl oxazolidinone (*R*)-**1** to a chalcone **2**. This can lead to the four diastereomers shown in Scheme 2.

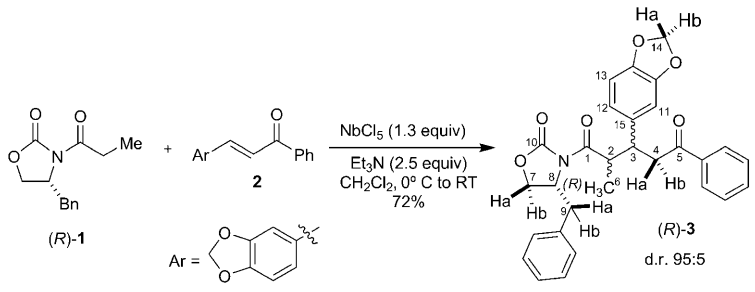


Scheme 2. Possible diastereomers from the Michael addition of the niobium(V) enolate of oxazolidinone (*R*)-**1** to chalcone **2**. Top left: (*R*,*R*,*R*)-**3**, top right: (*R*,*S*,*S*)-**3**, bottom left: (*R*,*R*,*S*)-**3**, bottom right: (*R*,*S*,*R*)-**3**.

The Michael product (*R*)-**3** (Scheme 1) was isolated with a yield of 72%. The identity of this adduct was confirmed by NMR spectroscopy and a high 95:5 ratio of two diastereomers was determined by integration of the methyl signals in the ^{1}H NMR spectrum of the crude product. We are not aware of any other example of an addition of a chiral oxazolidinone enolate to chalcones. Furthermore, when $TiCl_4$ was used as the Lewis acid under similar conditions no reaction was observed between these educts demonstrating the importance of $NbCl_5$ in this process.

Determination of the relative configuration of (*R*)-3: The Michael adduct (*R*)-**3** contains three stereocenters. The one located in the oxazolidinone ring (C8) is known to have an *R* configuration. To elucidate the relative configuration of the two unknown stereocenters C2 and C3 in the major product, *J*-coupling analysis was used to establish the *anti* relative configuration in agreement with the chemical approach (see the Supporting Information). Therefore, the possible diastereomers are reduced from four to just (*R*,*R*,*R*)-**3** and (*R*,*S*,*S*)-**3**, in which the stereocenters correspond to C8, C2, and C3, respectively (Scheme 1). However, the relative configuration of C2 and C3 to the known stereocenter C8 in (*R*)-**3** (Scheme 1) could not be defined by using conventional NMR spectroscopic tools. To solve this problem we developed a new analysis using residual dipolar couplings (RDCs) in addition to the conventional rotating-frame Overhauser enhancement (ROE) distance restraints.

Since the two neighboring unknown stereocenters and the known stereocenter in the oxazolidinone ring are separated by one fully and two partially rotatable bonds, long-range structure restraints were required to find the correct configuration. Such restraints were provided by quantitative ROEs, as well as by RDCs. A total number of 40 ROEs were derived from a ROESY experiment with 400 ms mixing time. A total of 36 local and remote ROEs (see the Supporting Information) were then used as the restraints in the following structure evaluation.



Scheme 1. Stereoselective conjugated addition of the niobium enolate of (*R*)-**1** to chalcone (*R*)-**3**; d.r. = diastereomeric ratio.

Due to the flexibility of this molecule, conformational averaging constitutes a methodological challenge. In this study, to sample the conformational space we calculated a molecular dynamics trajectory for each diastereomer in vacuo. Then 10,000 ensembles, each of 10 conformations, were generated for the diastereomers (*R*,*R*,*R*)-**3** and (*R*,*S*,*S*)-**3**. These 10 structures were randomly picked from the 1,000 snapshots of the molecular dynamics (MD) trajectory. The ROEs and RDCs were then used to rank the ensembles of both diastereomers according to the violation of the ROEs and the quality of the fit to the RDCs (*Q* factor). The violation (*U*) for the ROE in Å^2 is defined by Equation (1):

$$U = \begin{cases} \sum_j \left(\overline{r_j^{calcd}} - r_{\min}\right)^2, & \text{if } \overline{r_j^{calcd}} < r_{\min} \\ 0, & \text{if } r_{\min} \le \overline{r_j^{calcd}} \le r_{\max}, \\ \sum_j \left(\overline{r_j^{calcd}} - r_{\max}\right)^2, & \text{if } \overline{r_j^{calcd}} > r_{\max} \end{cases} \quad (1)$$

in which *j* is the index over all RDCs. $\overline{r_j^{calcd}}$ is the back-calculated ROE distance, averaged to the minus 6th power over all members of the ensemble as shown in Equation (2):

$$\overline{r_j^{calcd}} = \left[\frac{1}{N}\sum_i^N \left(r_{j,i}^{calcd}\right)^{-6}\right]^{-\frac{1}{6}} \quad (2)$$

in which *i* represents the members of the ensemble and *N* is the total number of the structures in one ensemble. The *Q* factor for the RDC is defined by Equation (3):

$$Q = \sqrt{\frac{\sum_j \left(D_j^{obs} - \overline{D_j^{calcd}}\right)^2}{\sum_j \left(D_j^{obs}\right)^2}} \quad (3)$$

in which *j* is the index over all RDCs and the back-calculated RDC ($\overline{D_j^{calcd}}$) is linearly averaged over all members of the ensemble. The fitting for each ensemble was performed independently for the two sets of RDC data (from a polyacrylamide (PH) gel[23] and a poly(acrylonitrile) (PAN) gel[24]) by calculating the alignment tensor using the Nelder–Mead simplex optimization method.[25] The ten structures in an ensemble were assumed to have equal populations. In this study, we use the assumption that all the structures in an ensemble have the same alignment tensor.[12,26] This assumption is justified, since the overall shape of the conformations in the ensembles is very similar (Figure 1 and Figure 2).

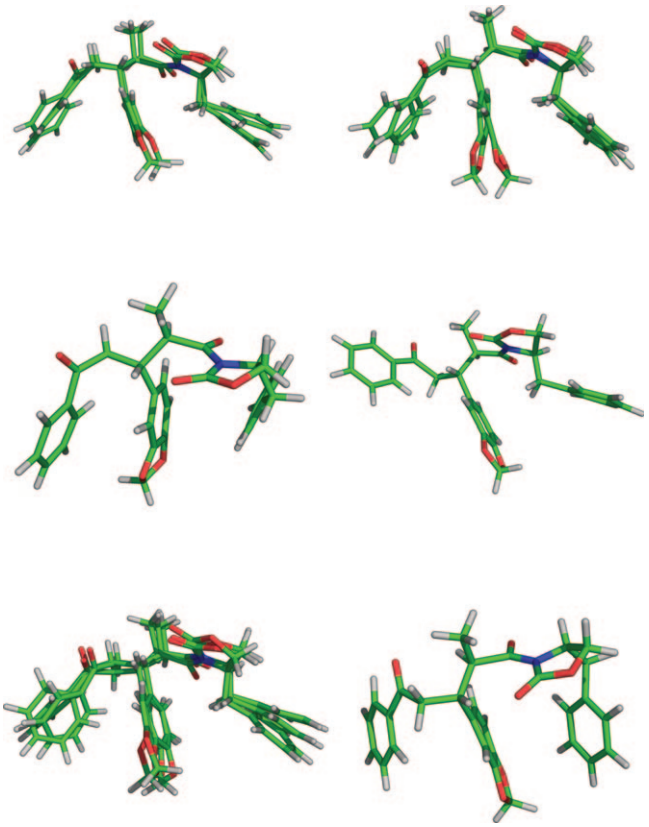


Figure 1. The ten structures of the best ensemble of (*R*,*R*,*R*)-**3**. For all conformations, the C^1–N bond is antiperiplanar.

To use the single alignment tensor approximation, the relative orientation of conformers in the ensemble is determined by superimposing each to the mean structure. For each ensemble the ROE violation was averaged to the minus 6th power over all members of the ensemble. The dots in Figure 3 represent the ROE violation in Å^2, the *Q* factor for the PH-gel data and the *Q* factor for the PAN-gel data for each ensemble. From Figure 3 it is obvious that the blue (*R*,*R*,*R*)-**3** and the red (*R*,*S*,*S*)-**3** datasets are well resolved. The ensembles of (*R*,*R*,*R*)-**3** fulfill the ROEs and RDCs significantly better than those of (*R*,*S*,*S*)-**3**. For all conformations and for both diastereomers, the C^1–N bond is antiperiplanar.

Another, less robust, method is to compare the best ensemble of (*R*,*R*,*R*)-**3** to that of (*R*,*S*,*S*)-**3**. Here "best" is defined as a combined *Q* factor by using quadratic averaging. The *Q* factor for the ROE is defined in Equation (4):

$$Q_{ROE} = \sqrt{\frac{U}{\sum_j \left(r_j^{obs}\right)^2}} \quad (4)$$

in which *j* is the index over all ROE distances and *U* is defined in Equation (1). The combined *Q* factor is defined in Equation (5):

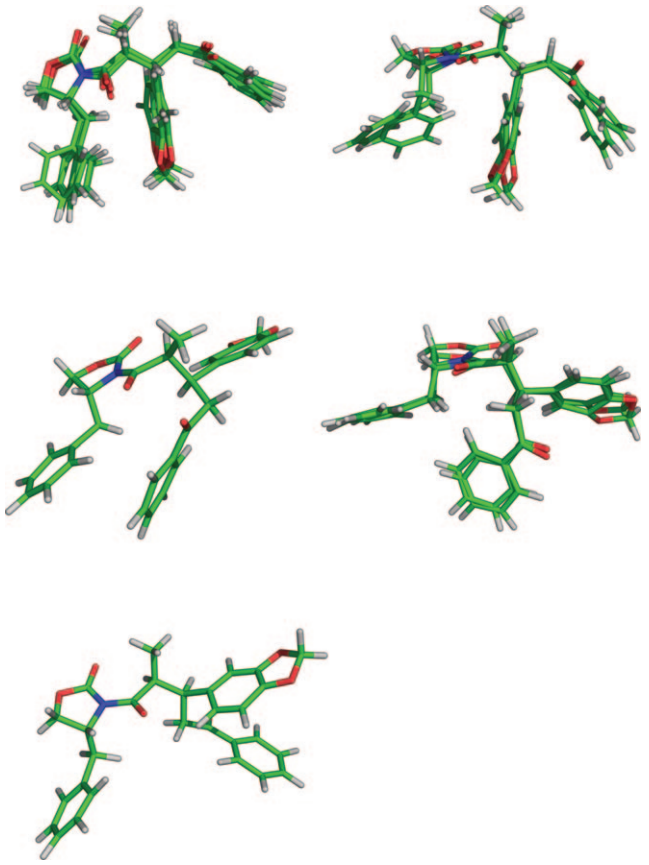


Figure 2. The ten structures of the best ensemble of (*R*,*S*,*S*)-**3**. For all conformations, the C^1–N bond is antiperiplanar.

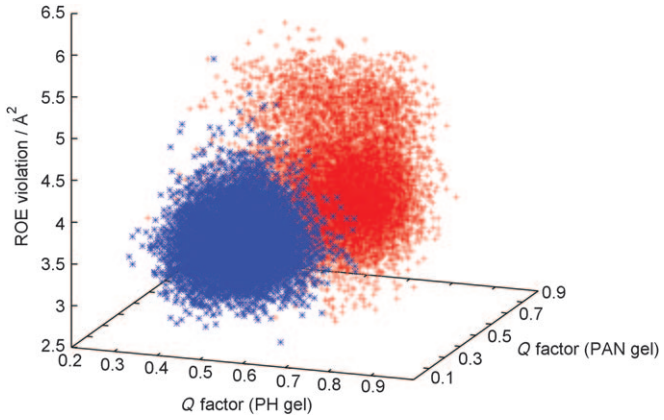


Figure 3. Distinguishing diastereomers by using RDCs and ROEs. The axes of the plot are the ROE violation in Å^2, the *Q* factor of the PH gel RDC data and the *Q* factor of the PAN gel RDC data. The 10,000 ensembles of 2 diastereomers are symbolized in different colors: (*R*,*R*,*R*)-**3** (blue) and (*R*,*S*,*S*)-**3** (red). 2D projections are presented in the Supporting Information. For both diastereomers, the C^1–N bond is antiperiplanar.

$$Q_{total} = \sqrt{Q_{PAN}^2 + Q_{PH}^2 + Q_{ROE}^2} \qquad (5)$$

For (*R*,*R*,*R*)-**3**, the best ensemble has *Q* factors of 0.16 and 0.32 for PAN and PH gels, respectively, whereas (*R*,*S*,*S*)-**3** has *Q* factors of 0.34 and 0.50, respectively. The ROE violation of these two best ensembles is smaller than 3.5 Å^2, corresponding to a Q_{ROE} factor of 0.10 [Eq. (4)]. Also the principal components of the alignment tensors A_{xx}, A_{yy}, and A_{zz} are smaller for the best ensemble of (*R*,*R*,*R*)-**3** than the (*R*,*S*,*S*)-**3** ensemble (Table 1). The largest RDC

Table 1. The diagonalized alignment tensors and the *Q* factors of the best ensembles of (*R*,*R*,*R*)-**3** and (*R*,*S*,*S*)-**3**.

Configuration	Medium	D_{xx} [Hz]	D_{yy} [Hz]	D_{zz} [Hz]	*Q* factor
(*R*,*R*,*R*)-**3**	PAN gel	−37.64	1.07	37.57	0.165
	PH gel	−6.69	−0.72	8.41	0.319
(*R*,*S*,*S*)-**3**	PAN gel	−52.05	2.71	50.35	0.336
	PH gel	−7.50	−2.75	11.24	0.499

value of (*R*)-**3**-*anti* in the PAN gel is 26.92 Hz, whereas that of the PH gel is 7.12 Hz. In both alignment media, the D_{zz} values of (*R*,*R*,*R*)-**3** rather than (*R*,*S*,*S*)-**3** are closer to the maximum experimental dipolar couplings. A similar observation has been made during the analysis of previous configurational studies,[12] in which fitting the experimental dipolar couplings with the wrong diastereomers yielded larger alignment tensors than fitting them with the correct diastereomer.

Without the presence of an organometal, the C^1–N amide bond is in slow exchange on the ^{1}H NMR spectroscopy time scale at room temperature due to its double-bond character. Since we see only one set of peaks, only one of the two possible configurations is populated. Above, we assumed that the configuration is C^1–N antiperiplanar. Here, we now show that this is not only in agreement with the literature, but is corroborated by the RDCs. We therefore repeated the above described analysis with the C^1–N bond in the synperiplanar configuration and compared this with the results assuming the antiperiplanar configuration. From Figure 4 it is obvious that the (*R*,*R*,*R*)-**3** (C^1–N antiperiplanar) configura-

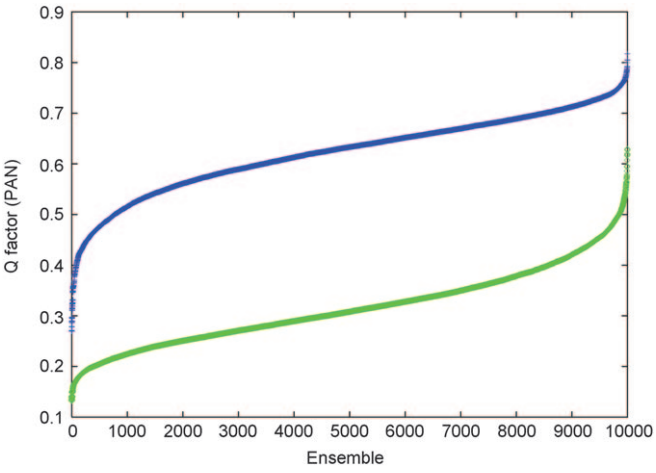


Figure 4. Comparison of the Q_{PAN} factors between the C^1–N^{33} antiperiplanar (green) and C^1–N synperiplanar (blue) configuration of the diastereomer (*R*,*R*,*R*)-**3**.

tion fulfils the RDC data measured in the PAN gel much better than the (*R*,*R*,*R*)-**3** (C^1–N synperiplanar) configuration. This result is in agreement with the literature,[27,28] which shows that the C^1–N antiperiplanar configuration is lower in energy than the C^1–N synperiplanar configuration. This analysis shows again the power of RDC, which could be used to determine the relative orientation of different moieties in one molecule. In contrast to the RDC, the NOE is not very sensitive due to the flexibility of the molecule and the minus 6th power dependence.

Determination of the absolute configuration: Extending the methodology to determine the absolute configuration without the knowledge that the stereochemistry of C8 is *R*, we measured ORD values at 4 different wavelengths and compared them with those calculated with DFT from the best ensemble of structures as determined by NMR spectroscopy. The MD snapshots were minimized before the DFT optimization. Table 2 and Figure 5 comprise the experimental and calculated ORD data measured at different wavelengths. The calculated ORD values for the different conformation in one ensemble are highly divergent and even change sign as demonstrated by Figure 6.

Table 2. Experimental and calculated ORD values at different wavelengths.

λ [nm] (source)	T [°C]	$[\alpha]^{exptl}$	$[\alpha]^{DFT}$ (*R*,*R*,*R*)-**3**	(*R*,*S*,*S*)-**3**	(*S*,*S*,*S*)-**3**	(*S*,*R*,*R*)-**3**
589 (Na)	20.3	−35	−59	82	59	−82
578 (Hg)	20.6	−37	−61	87	62	−87
546 (Hg)	20.6	−42	−70	104	70	−104
436 (Hg)	20.6	−76	−110	252	110	−252

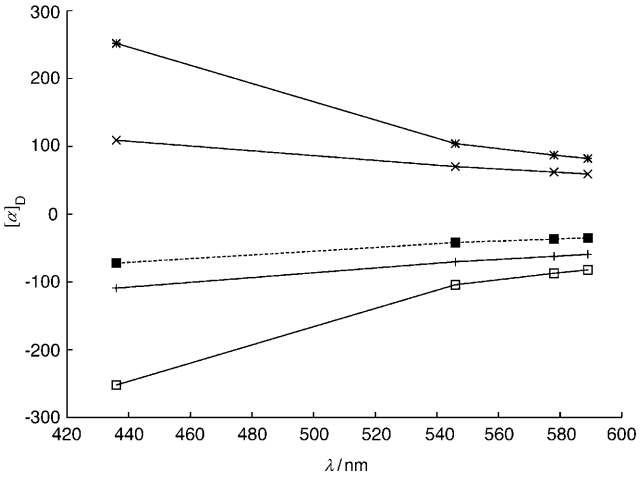


Figure 5. Comparison of experimental ORD values with those calculated by DFT for the four possible diastereomers of **3**. Experimental ORD curve (dashed line, ■) and the calculated curves (solid lines) for the two possible pairs of enantiomers with an *anti* relationship between C2 and C3; + = (*R*,*R*,*R*)-**3**, × = (*S*,*S*,*S*)-**3**, * = (*R*,*S*,*S*)-**3**, □ = (*S*,*R*,*R*)-**3**.

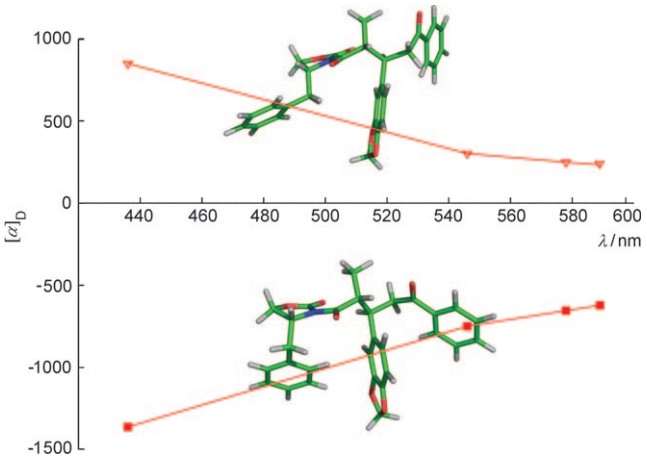


Figure 6. Plot of the calculated ORD values for two different conformations, selected from the best ensemble of (*R*,*R*,*R*)-**3**.

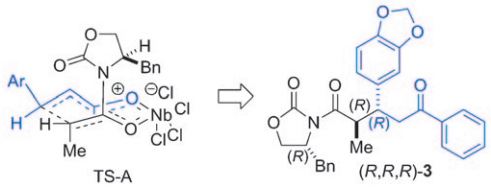
Discussion

Determination of the absolute configuration of flexible molecules is currently a very difficult problem to resolve. As mentioned in the introduction, chiroptical methods require the knowledge of the conformational ensemble to be accurate, which is very difficult to achieve in the absence of experimentally determined ensembles. Therefore, if the conformationally heterogeneous compound cannot be crystallized, chemical synthesis is the last resort. Herein, we present a new methodology using RDC-enhanced NMR spectroscopy to first determine the ensemble of conformations, which reveals the relative configuration by the NMR spectroscopy data and gives a faithful description of the solution ensemble. The chiroptical properties of the ensemble is then predicted by DFT and compared to experimental data to establish the absolute configuration.

Our results show that for a highly flexible molecule, such as compound (*R*,*R*,*R*)-**3** that was synthesized by a novel Nb(V)-catalyzed Michael addition, the relative configuration can be determined by carefully measuring *J*-couplings, NOE or ROE derived distances, and RDCs. Two different alignment media were used to obtain the anisotropic RDC data set. The distance and anisotropic data are then used to select the best ensemble of 10 structures, whereby each member is obtained randomly from free molecular dynamics simulations, from a large pool of 10,000 different ensembles. The fit of the RDCs used a single alignment tensor for all different conformations in the ensemble: this assumption is justified as illustrated in Figure 1 and Figure 2 from the similar shape of all conformations. As opposed to previous approaches,[12,26] no weighting of the RDCs and ROEs is required, which establishes a more robust way of analyzing the data. This procedure clearly shows that the ensembles with (*R*,*R*,*R*)-**3** configuration are in far better agreement with the experimental data than the (*R*,*S*,*S*)-**3** ensembles.

The stereochemical outcome ((*R*,*R*,*R*)-**3**) of the previously unused niobium(V)-catalyzed version of the Michael addi-

tion is quite surprising. Expected transition states of this reaction based on the literature[14–19] would lead to the (*R*,*S*,*S*)-**3** isomer (see the Supporting Information). Since the (*R*,*R*,*R*)-**3** isomer is formed instead, we suggest four new transition states with antiperiplanar and synclinal attack on the *Si* and *Re* faces of the chalcone (see the Supporting Information). In all cases, niobium is complexed to the carbonyl group of the chalcone, which promotes its activation and forms 8-membered cyclic transition states in that the *endo* carbonyl group of the oxazolidinone is opposite to the enolate to minimize electronic effects, such as the dipole moment (Scheme 3). The lack of activity of $TiCl_4$ in this reaction may be due to its inability to simultaneously complex to both carbonyl groups of the oxazolidinone and the chalcone. Whether these transition states are indeed formed in this reaction remains to be seen. They are, nevertheless, chemically plausible and lead to the observed products.



Scheme 3. Chair-like transition state (TS) for (*R*,*R*,*R*)-**3**.

Finally, we addressed the question of the absolute configuration of the Michael addition product formed in the reaction presented in Scheme 1. Although C8 is known to be in the *R* configuration, since the configuration of the chiral auxiliary was known a priori, here we present the hypothetical that all stereocenters are unknown and attempt to answer the absolute configuration question. This can be considered to be a test for the accuracy of the conformational ensemble. In addition, it would establish the combination of the ensembles determined by NMR spectroscopy and chiroptical measurement as a versatile method for the determination of the absolute configuration of flexible molecules.

Firstly, the *J* coupling shows that C2 and C3 must be either *R*,*R* or *S*,*S*. Secondly, the combined ROE- and RDC-based analysis provided the diastereomer (*R*,*R*,*R*)-**3** over (*R*,*S*,*S*)-**3**, but hypothetically, compound (*R*,*R*,*R*)-**3** cannot be distinguished from its (*S*,*S*,*S*)-**3** enantiomer. To answer this question, chiroptical measurements were employed. The chiroptical properties of the ensembles selected from the NMR spectroscopic analysis were calculated by DFT and compared to measured ORD values.

The ORD values are shown in Figure 5 and summarized in Table 2. Taking large errors in the calculated values into account, the measured negative values are compatible with both (*R*,*R*,*R*)-**3** and (*S*,*R*,*R*)-**3** configurations. Since the relative configuration of (*S*,*R*,*R*)-**3** is incompatible with the NMR spectroscopic analysis, and could therefore be eliminated, the absolute configuration is unambiguously determined to be (*R*,*R*,*R*)-**3**. This answer to the hypothetical question required no information about the configuration of the auxiliary. Thus, the finding of the configuration of the auxiliary used in the reaction, namely *R*, shows that the approach is useful for flexible molecules in solution. It should be noted from Figure 6 that the calculated ORD values of each member of the ensemble are highly divergent. Approximately half of the conformations in the ensemble yield single conformation ORD values that would suggest the (*S*,*S*,*S*)-**3** configuration. Only when we use the correct ensemble of conformations and average over the individual ORD values do we get the correct answer. Hence an accurate ensemble approximating the full conformational space of the molecule is essential for the calculation of the chiroptical properties. Clearly, ensembles without NMR spectroscopy distance and RDC restraints would not be sufficient.

Thus, combining diastereomer differentiation by using isotropic and anisotropic NMR spectroscopy data with enantiomer differentiation by experimental validation of the DFT-calculated chiroptical properties of ensembles derived from NMR spectroscopy, the hypothetical absolute stereochemistry question is unequivocally and indisputably answered, and is (*R*,*R*,*R*)-**3**. This determination of absolute configuration in solution establishes "Bijvoet in solution". We coined this term, since anomalous X-ray diffraction, the key to the determination of absolute configuration from crystals, is a chiroptical effect for X-ray radiation. This effect together with the known conformation and relative configuration established from conventional X-ray diffraction from crystals allows the determination of the absolute configuration. With Bijvoet in solution, we establish the conformational ensemble in solution and the relative configuration by NMR spectroscopy. We then use chiroptical methods to establish the absolute configuration.

Conclusion

We have introduced a robust way of combining RDC-enhanced NMR spectroscopy for the determination of the relative configuration of flexible molecules with ORD measurements in conjunction with predicted ORD values from the ensemble derived by NMR spectroscopy. Since the ORD values vary tremendously when the molecule adopts different conformations, the determination of a faithful ensemble representing the situation in solution is mandatory (of course the ensemble could also be obtained by other methods, not necessarily exactly in the way we propose). This allowed us to determine the correct relative and absolute configuration of the synthetic product (*R*,*R*,*R*)-**3** in solution. Compound **3** was obtained in a new niobium(V)-based Michael-type C–C bond-forming reaction, which requires a β-substituted Michael acceptor. The reaction was highly stereoselective and gave an unexpected stereochemical result that could be rationalized by a plausible transition state.

Experimental Section

General procedure: Oxazolidinone (*R*)-**1** (0.23 g, 1.0 mmol) diluted in dry dichloromethane (1 mL) was added to a suspension of $NbCl_5$ (0.35 g, 1.3 mmol) in dry dichloromethane (1.0 mL) at 0 °C. The reaction was vigorously stirred for 5 min. Then triethylamine (0.35 mL, 2.5 mmol) was added dropwise, resulting in a dark brown solution. After stirring for 5 min at 0 °C, a solution of chalcone **2** (1.1 mmol) in dry dichloromethane (1.0 mL) was added and the reaction was monitored by TLC. The reaction was stirred for 3 h at 0 °C and 72 h at room temperature and then saturated ammonium chloride solution (NH_4Cl, 10 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3×15 mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuum. Flash chromatography (hexanes/EtOAc = 60:40) afforded pure Michael product (*R*)-**3** in 72 % yield as a yellow oil.

MD simulations: To sample the conformational space of this flexible molecule, we calculated the molecular dynamics trajectory of each diastereomer with the DISCOVER software (Biosym Technologies, San Diego, CA, USA) using the consistent valence force field (CVFF),[29,30] a standard force field for small molecules. The MD-simulation was carried out at 298 K for 1 ns. A single structure was logged every 1 ps so that a trajectory with 1,000 structures was obtained.

RDC and ROE analysis: Superimposing each conformer to the mean structure was performed in the program MOLMOL2.1.[31] The full ROE and RDC analysis was implemented in the program relax.[32,33]

ORD analysis: The ten structures of the best ensemble of (*R*,*R*,*R*)-**3** and (*R*,*S*,*S*)-**3** were used as starting structures for DFT geometry optimization using Gaussian03 Revision C.02.[34] The optimizations were performed at the B3LYP/6–31G(d) level of theory. The optical rotation dispersion calculations at the four wavelengths 436, 546, 578, and 589 nm were performed with the optimized structures as input coordinates with the same basis set as the optimizations using the integral equation formalism variant polarizable continuum model (IEFPCM) solvent continuum model as implemented in Gaussian03 with DMSO as the solvent.

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