VIP Structure Elucidation

DOI: 10.1002/anie.201007305

Residual Dipolar Couplings as a Powerful Tool for Constitutional Analysis: The Unexpected Formation of Tricyclic Compounds**

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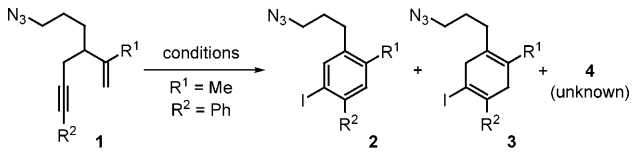
Anisotropic NMR parameters in partially aligned samples, such as residual dipolar couplings (RDCs), residual chemical shift anisotropy (RCSA), and residual quadrupolar couplings (RQCs), contain valuable structural information.[1] As has been shown on a multitude of examples, RDCs are a useful tool to determine the configuration[2] and the conformation[3] of small to medium-sized organic molecules. Herein, we now add a further facet by demonstrating the power of RDCs in the analysis of the constitution of an unknown small molecule.

The molecule we investigated in this case study is one of the products obtained by reacting the azide-containing 1,5-enyne **1** in the presence of electrophilic iodine sources (Scheme 1). Recently, it was reported that enyne **1** (R^1 = Me, R^2 = Ph) can be selectively transformed into either aryl **2** or cyclohexadiene **3**, depending on the exact conditions.[4] Additionally, in studies of the reactivity of enyne **1** with I_2 and K_3PO_4, it was surprisingly found that temperatures above 0 °C led to the generation of the unknown compound **4** in low yield.[5] These seminal studies, while clearly indicating that the iodonium-induced carbocyclization of enynes shows great promise, leave the unanswered question of what the structure of **4** is. Assuming that the electrophilic cyclization of enynes will become a growing field,[6] we felt that the structure elucidation of compound **4** would be indispensable for a better understanding of the mechanisms at work.



	2	3	4	yield [%]
a) NIS, 50 °C, CH_2Cl_2	76	0	0	Ref. [4]
b) I_2, K_3PO_4, 0 °C, CH_2Cl_2	0	99	0	Ref. [4]
c) I_2, K_3PO_4, 23 °C, CH_2Cl_2	16	0	38	
d) I_2, K_3PO_4, 50 °C, CH_2Cl_2	23	0	47	

Scheme 1. Reaction leading to the formation of unknown product **4**. NIS = *N*-iodosuccinimide.

Classical methods for the structure determination of small quantities of compounds, including mass spectrometry, IR spectroscopy, and conventional NMR experiments like one-dimensional (1D) ^1H and ^{13}C, and two-dimensional (2D) COSY, HSQC, and HMBC experiments could not be used to solve the constitution of compound **4**. The molecular formula $C_{16}H_{18}IN$ and eleven fragments could be identified: a phenyl group, a methyl group, five methylene groups (three forming an isolated chain), a tertiary nitrogen atom, an iodine atom, and four quaternary carbon atoms (see the Supporting Information). The $^1H,^{13}C$ HMBC spectrum revealed 63 and the $^1H,^{15}N$ HMBC spectrum 7 cross peaks, correlating almost every fragment with every other fragment, and thus only indicating a very compact structure. Even the acquisition of a 2D 1,1-ADEQUATE spectrum[7] could not solve the structure, although five additional $^{13}C,^{13}C$ correlations could be identified, reducing the number of fragments to six (see the Supporting Information).

Since classical NMR analysis failed, we decided to approach the problem in an unconventional way by adopting residual dipolar couplings. RDCs and other anisotropic NMR parameters contain unique angular information of internuclear vectors with respect to the static magnetic field which has been shown to be useful for the verification/falsification of a proposed configuration[2] or conformation.[3] We therefore assumed that as long as sufficient anisotropic parameters can be measured and a large enough set of structural models can be constructed, it should also be possible to identify the correct constitution of our reaction product **4**.

For the measurement of RDCs, we used a stretched polystyrene/$CDCl_3$ gel[8] as an alignment medium for the induction of anisotropy. CLIP-HSQC spectra[9] were acquired for an isotropic sample as well as for the anisotropic gel sample, and $^1D_{CH}$ RDCs were extracted as the difference between the corresponding couplings measured. In addition, $^2D_{HH}$ RDCs between the geminal protons of methylene groups were obtained from corresponding P.E.HSQC spectra.[10] Altogether 17 RDCs were gained for the structural analysis (see Supporting Information).

As the next step, we created a set of structures of compound **4** to be tested (Scheme 2), which fulfill the molecular formula $C_{16}H_{18}IN$, the basic fragments known

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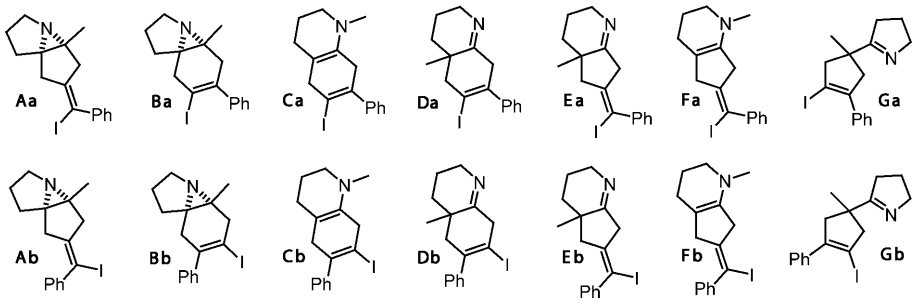
[**] S.F.K. thanks the Deutsche Forschungsgemeinschaft (DFG) and the Fonds der Chemischen Industrie (FCI) for support. B.L. thanks the FCI and the DFG (Heisenberg program LU 835/2,3,4,7 and Forschergruppe FOR 934).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201007305.



Scheme 2. Potential structures of **4**.

from 1D, COSY, and HSQC spectra (see above), and, in addition, make sense from the chemist's point of view. To not miss any unusual product, we also included several structural models that were unlikely, either based on the reaction mechanism or because of spectral data like individual HMBC signals and chemical shift values.

To test whether the experimental RDCs are consistent with the proposed structures, SVD fits using the program PALES[11] ("bestFit" option) were made. Therefore, pdb files of the 14 suggested input structures were created and energy-minimized using the program Sybyl. Within the fitting process, all prochiral assignments for the five methylene groups were permutated, leading to $2^5 = 32$ fits for each of the 14 structures. Furthermore, the assignment of the two isolated methylene groups was varied as their position could not be identified unambiguously on the basis of 1D, COSY, and HSQC spectra. The number of fits therefore increased to 64 for each suggested molecule, leading to a total number of $64 \times 14 = 896$ SVD fits.

To compare the quality of the fits, n/χ^2 values[2e] were calculated for each fit. In Figure 1a the resulting quality factors for the best permutation of each of the 14 structures are summarized (see the Supporting Information for all values and a description of the quality factor). Clearly, only the aziridine structure **Ba** has a n/χ^2 value significantly larger than 1, indicating a good agreement with experimental data. Also, the comparison of measured and back-calculated RDCs (Figure 1b) demonstrates that this structural model is consistent with the experimental data. As for all structures other than **Ba**, the quality factor for the SVD fit is poor and corresponding structures can be excluded, **Ba** can be considered to be the correct constitution of reaction product **4**.

To make sure that the constitution determined by RDCs is the correct one, efforts were made to independently verify the obtained result with alternative methods. Therefore almost 100 mg of the reaction product was synthesized and a 2D INADEQUATE spectrum[12] was acquired, verifying the carbon skeleton of the substance. Additional evidence could be obtained by labeling the starting material of the reaction with ^{15}N-azide and measuring ^{13}C,^{15}N couplings for the ^{15}N-labeled compound. Both additional experiments clearly support the structure determined by RDCs (see the Supporting Information).

Interestingly, the constitution **Ba** determined by RDCs was almost excluded from the set of structures, because the ^{13}C chemical shifts predicted by ChemDraw differed significantly from the experimental data. We also did not expect a priori to find two intensive $^5J_{CH}$ cross peaks in the ^{1}H,^{13}C HMBC spectrum, correlating two protons with the *ortho*-carbons of the (rotating) phenyl group (see the Supporting Information).

Besides the interesting case study for structure determination by NMR spectroscopy, the identified constitution also reveals a novel

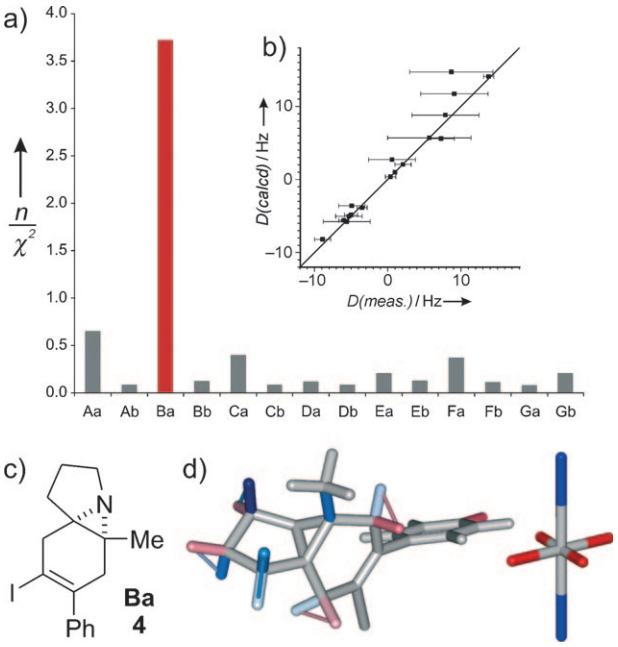
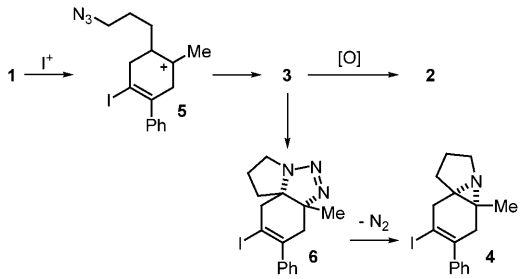


Figure 1. a) Comparison of quality factors n/χ^2 for the SVD fits done with PALES (for each structure only the permutation with the best n/χ^2 value is shown). b) Plot of back-calculated RDCs, *D*(calcd), against experimental RDCs, *D*(meas.), for the best permutation of assignment for structure **Ba**. c) Molecular formula of the determined reaction product. d) The structural model of **Ba** depicted with color-coded bonds (red: negative; blue: positive RDCs) and the axis of the corresponding alignment tensor next to it.

domino reaction leading to the unexpected formation of tricyclic compound **4**.[13] As hypothesized in Scheme 3, iodonium activation of the starting 1,5-enyne **1** gives cyclic cation **5**, which undergoes proton abstraction to give cyclohexadiene **3** under the reaction conditions. Most likely, aziridine **4** then results from intramolecular 1,3-dipolar cycloaddition followed by loss of nitrogen.[14] This view that aziridine formation proceeds via diene intermediate **3** and not through direct cyclization[15] of the cationic intermediate **5** is supported by the following observation: upon treatment with I_2 and K_3PO_4 in CH_2Cl_2 at room temperature, **3** smoothly transforms into a mixture of aziridine **4** and aromatic compound **2**. It is particularly significant that simple heating of cyclohexadiene **3** results in only traces of **4**, thus indicating that I_2 might be involved in the aziridine-forming step. Our



Scheme 3. Possible mechanism for the formation of aziridine **4**.

results on the synthesis of tricyclic aziridine **4** represent a remarkable example of how easily molecular complexity can be generated from simple acyclic precursors. Moreover, our results are in perfect agreement with the previous report[4] that in the electrophilic cyclization of 1,5-enyne **1** the ultimate products (**2** or **4**) are typically formed via key intermediate **3**.

In summary, we have shown that RDCs are a valuable tool to determine the constitution of unknown compounds, thus offering a novel approach to the structure elucidation of small molecules. Our method provided evidence for the unexpected formation of a previously unidentified tricyclic compound by which novel insights into the electrophilic cyclization of 1,5-enynes were revealed. Although additional investigations are warranted to define the scope of RDCs more precisely, this study constitutes an important step toward a prolific use of RDCs as a powerful alternative and complementary approach to commonly used spectroscopic methods for structure determination.

Received: November 20, 2010
Published online: February 18, 2011

Keywords: electrophiles · enynes · NMR spectroscopy · residual dipolar couplings · structure elucidation

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[5] Broadening the scope of this unexpected result was difficult since, even after attempted optimization compounds of type **4** were typically formed in only low yields (R^1 = Me, R^2 = 2-naphthyl, 23 %; R^1 = Me, R^2 = 4-MeO_2C-(C_6H_4), 23 %; R^1 = Me, R^2 = Me, 32 %; R^1 = Bu, R^2 = Ph, 30 %) along with arenes of type **2**.

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