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Use of Local Alignment Tensors for the Determination of Relative Configurations in Organic Compounds

Christina M. Thiele,*,† Arnold Maliniak,‡ and Baltzar Stevensson‡

Clemens Schöpf Institut für Organische Chemie und Biochemie, Technische Universität Darmstadt, Petersenstr. 22,
D-64287 Darmstadt, Germany, and Division of Physical Chemistry, Arrhenius Laboratory, Stockholm University,
S-10691 Stockholm, Sweden

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The determination of relative configurations in organic compounds by NMR spectroscopy always requires a simultaneous treatment of configuration and conformational interconversion, which is usually accomplished by using dihedral angles derived from ^3J couplings[1−3] distances from the nuclear Overhauser effect (NOE)[4,5] or projection angles from cross correlated relaxation.[6,7]

These conventional NMR parameters, however, do not always lead to unambiguous configurational assignments. It has recently been shown that residual dipolar couplings (RDCs) provide complementary information[8,9] about configurational assignments, even in the case of moderate flexibility of the molecule.[10]

The interpretation of RDC data in organic compounds usually relies on the fitting of RDCs to molecular structures, which differ in relative configurations and/or diastereotopic assignments. The configurational assignment is then based on the quality of the numerical fit. Conformational flexibility can be incorporated into this procedure by using an average structure[10a] or by superimposing different conformers in a physically sensible way with one common alignment tensor for all conformers. Yet another analysis method is to determine one alignment tensor for each conformer. Clearly, all of these approaches have their advantages and drawbacks.[11,12]

In the present communication a conceptually different approach will be presented, namely the determination of one alignment tensor per rigid subunit (local alignment tensor) and the assignment of relative configurations from the relative orientation of these local alignment tensors.[13] This is shown here as a *proof of principle* for the α-methylen-γ-butyrolactone **1**.

The molecule chosen for this study contains two adjacent stereogenic centers and exhibits moderate flexibility: two conformers for each possible diastereoisomer, *trans*-configured **1** and *cis*-configured **2**. As conventional NMR restraints failed due to conformational flexibility, we have previously determined the relative configuration of the stereogenic centers by fitting RDC data either to single rigid conformers including the transition structure between the two conformers, which is a fair representation of the average conformation, or to an ensemble of two conformers.[10a,12] Furthermore, the relative populations of these conformers were determined.[12] Here we show that from the orientation of the two local alignment tensors of the two stereogenic centers the relative configuration can be deduced. In particular, the local alignment tensors must coincide for the correctly assigned configuration; see Figure 1.

The determination of the local alignment tensor in any nonplanar chiral rigid subunit/stereogenic center requires at least five linearly independent RDCs.[14] This is however not the situation in our model system where a smaller number of RDCs was determined for both C2 and C3. In principle this problem can be solved by measuring $^{13}C-^{13}C$ dipolar couplings.[15] Due to the low solubility of the compound in the orienting medium used ($C_{12}E_5$/*n*-hexanol/D_2O)[16] we refrained from these measurements. We therefore need to transfer information between fragments, so that we can calculate the missing $^{13}C-^{13}C$ dipolar coupling data.

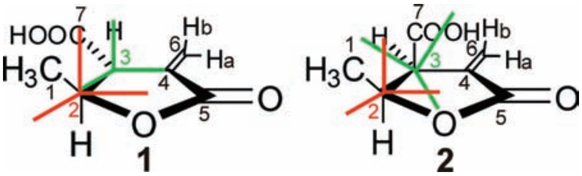

Figure 1. Two possible diastereoisomers of the α-methylen-γ-butyrolactone **1** (*trans*-configured) and **2** (*cis*-configured) with the two local alignment tensors indicated for the two stereogenic centers C2 (red) and C3 (green).

To obtain D_{C3-C4}, which is needed for the determination of the local alignment tensor on C3, we calculate the tensor of C4 from the eight previously determined RDCs[10a] (see Supporting Information, Table S1). The subunit C4 belongs to the exomethylene unit, and as it is a planar rigid fragment (comprised of C3, C4, C5, C6, H6a, and H6b) only three order parameters (RDCs) are required.[14] From the local alignment tensor in C4, the $^{13}C-^{13}C$ dipolar coupling linking C3 and C4 can be calculated to be $D_{C3-C4} = 0.65 \pm 0.06$ Hz, where the error limit is estimated from the Monte Carlo analysis using 10 000 steps.[13] Note that D_{C3-C4} is essentially identical for all possible conformers (and transition structures) of the two diastereoisomers (Table S2).

The local alignment tensor located at C3 can now be determined using the four $^1H-^{13}C$ RDCs together with D_{C3-C4}. There is, however, a complication frequently encountered in rigid molecular fragments: the corresponding measured RDCs are not strictly linearly independent (column 3 of Table S2). This problem can be solved using two different approximations: (*i*) In addition to conformationally independent couplings, RDCs that are weakly dependent on the conformation can be included. The resulting overdetermined system is solved using a least-squares (LSQ) fitting procedure. Thus this method is referred to as LSQ; or (*ii*) the remaining missing order parameter can be determined by minimizing the value of the general degree of order (GDO):[17,18] $\vartheta = (^2/_3\Sigma S^2_{\alpha\beta})^{1/2}$, where the summation runs over $\alpha,\beta \in \{x,y,z\}$, which define the local frame, and $S_{\alpha\beta}$ are the elements of the local alignment tensor. In weakly ordered systems the orientational entropy $\Delta S \approx -5\vartheta^2/2$; thus the minimum of ϑ corresponds to maximum of the orientational entropy.[19] This method is referred to as GDO, and the relation between the orientational entropy and the generalized degree of order is derived in the Supporting Information.

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† Technische Universität Darmstadt.
‡ Stockholm University.

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In analogy with the $^{13}C-^{13}C$ coupling between C3 and C4 we transport information from C3 to C2 by calculating D_{C2-C3}. We have used both methods stated above, which give very similar results (see Table S2): D_{C2-C3} is determined to be 1.84 ± 0.19 Hz (LSQ)/1.52 ± 0.16 Hz (GDO) for the *trans*-configured **1** and 1.78 ± 0.18 Hz (LSQ)/1.50 ± 0.17 Hz (GDO) for the *cis*-configured **2**, respectively. As expected, this coupling is essentially independent of the configuration and, in fact, also independent of the molecular conformation, Table S2.

With D_{C2-C3} at hand five RDCs in the C2 subunit are available for the analysis: D_{C1-H2}, D_{C2-H2}, D_{C3-H2}, D_{C2-C3}, and D_{C1-C2} derived from the $D_{C1-H1a,b,c}$ coupling in the methyl group assuming the three site jump model for the methyl group.[9c] From these RDCs the local alignment tensor for C2 can be determined for both diastereoisomers **1** and **2**. The eigenvectors of the local tensors of the two stereogenic centers calculated using the LSQ approximation are displayed in Figure 2. The corresponding plot for the GDO approximation can be found in the Supporting Information (Figure S1). In this representation the eigenvectors of the two local tensors are projected onto a unit sphere. Clearly, the alignment tensors for both stereogenic centers using both approximations coincide for the *trans*-configured **1** and are displaced for *cis*-configured **2**. The distribution of eigenvectors is rather broad, which is manifested in the spread of eigenvectors constructed using 1000 Monte Carlo steps, and thus is a graphical representation of the experimental error. It can, nevertheless, be concluded that the two stereogenic centers are oriented as in the case of **1**; therefore the relative configuration can safely be assigned as trans. This procedure is a powerful demonstration of the utility of employing local alignment tensors in organic structure determination and is not limited to such deceptively simple cases of relative configuration determination, but could also be used for any task in which relative orientations of fragments need to be assessed.

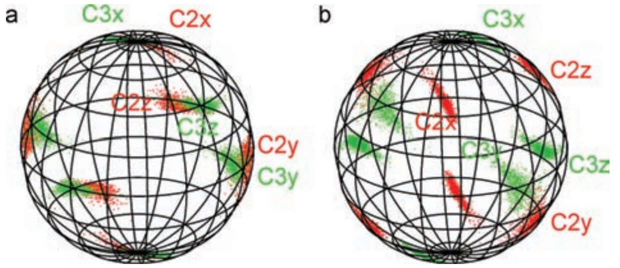

Figure 2. Eigenvectors as projections onto a unit sphere for the two stereogenic centers C2 (red) and C3 (green) in the *trans*-configured **1** (a) and in the *cis*-configured **2** (b) using the LSQ approximation. All four symmetry equivalent solutions are depicted. Monte Carlo analysis (1000 steps) was used to assess the spread of eigenvectors.

At this point two limitations of the applicability of this method in relative configuration determination need to be mentioned: first, there is a 4-fold degeneracy of orientations, which may lead to ambiguities. This can, however, be solved if two orienting media, exhibiting independent ordering, are used.[20] Work along these lines is currently in progress in our lab. Second, RDCs are insensitive to inversion, so that the relative configurations can only be solved if the two stereogenic centers can be related in some way. This could, as in the present case, be done by judging the bonding situation or by using ^3J couplings and NOEs. For more flexible compounds, in which stereogenic centers are far apart, a different strategy has to be developed, which is also one of our current research interests.

In summary we have shown that relative configurations in moderately flexible compounds can be determined using local alignment tensors. These tensors were derived from residual dipolar couplings employing transport of information from a subunit where an excessive number of RDCs was measured to the stereogenic center that lacks a sufficient number of RDCs. We have also demonstrated two methods for analysis of partly linearly dependent RDCs in a rigid molecular fragment.

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Supporting Information Available: The eigenvector plot for the GDO approximation, tables containing experimental and calculated RDCs, coordinates of the conformers, and the derivation of the expression for the orientational entropy in the low order approximation. This material is available free of charge via the Internet at http://pubs.acs.org

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