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Structure Determination of Regioisomeric Fused Heterocycles by the Combined Use of 2D NMR Experiments and GIAO DFT ^{13}C Chemical Shifts

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Keywords: NMR spectroscopy / Structure elucidation / Density functional calculations / Oxazoloquinolinones / Oxazolocoumarins / Heterocycles

The combined use of 2D NMR correlation experiments and GIAO DFT ^{13}C NMR chemical shift calculations has allowed a reliable and simple structural determination of regioisomeric heterocyclic systems that originate from the reactions of quinolinone or coumarin derivatives with hydroxylamine. In general, the proposed method may find application in the regioisomeric structural determination of heterocyclic compounds.

Introduction

It is axiomatic that chemical, biological, and pharmacological activities depend on the stereochemical structure of a molecular system.[1] To this end isomeric features have a particularly strong impact on a variety of molecular properties.[2] Therefore the search for structure–property relationships is a fundamental step in the rational design of new compounds.[1,3] This assumption has promoted the search and development of new and more effective methods for the structural analysis of complex systems, particularly in solution.

In this context NMR spectroscopic methods are very attractive due to the high sensitivity of NMR chemical shifts to the nuclear magnetic environment and consequently to structural variations. Thus, information about the structure of new compounds can be obtained by comparison of their chemical shifts with "fingerprints" of simple model fragments. Moreover, modern 2D NMR correlation experiments have changed the quality of experimental NMR information in a revolutionary way and now structure assignment can be achieved through the detection of connectivities between nuclei.[4] However, in practice, there are some limitations because nuclear correlations (HMBC) are often lost for technical and/or structural reasons. This problem is particularly crucial in "proton-poor" fused heterocyclic compounds and could lead to uncertainty in the determination of molecular structures. Particularly serious problems arise from structurally closely related compounds, for example, for isomers or when a molecule undergoes only minimal modification of some its fragments, although this may have a great impact on its properties. A great number of examples relating to fused heterocyclic compounds have been reported in the literature in which the same 1D/2D NMR spectroscopic data have been interpreted within the framework of different structural hypotheses[5] and only rigorous and time-consuming synthetic methods supported by X-ray data allowed the right structure to be established.[6]

The evaluation of NMR chemical shifts for likely hypothetical structures and their comparison with experimental data might be helpful to distinguish between "right" and "wrong" structures. However, due to a lack of appropriate models and reliable empirical rules widely used for simple systems (the additive scheme),[7] this approach may be unsuccessful for fused heterocyclic compounds. Thus, prediction of an NMR spectrum based on fundamental physical models without relying on empirical correlations/databases may represent an efficient alternative.

Recently, particular emphasis has been devoted to the structure elucidation of organic compounds through gauge-including atomic orbital (GIAO) calculations of NMR chemical shifts and coupling constants by density functional theory (DFT) methods.[3e,3f,3h,8] This could represent a powerful strategy for the interpretation of experimental NMR spectroscopic data in relation to structure elucidation problems. An open question with respect to computed chemical shifts is whether a given method is sufficiently accurate to capture the magnetic effects associated with regiochemical differences. High accuracy is required for defini-

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tive correct assignment, particularly when not all the isomers are available for comparison. So, when a nearly complete set of such compounds is available, the computational method may be a useful benchmark for evaluation. In this work we wish to report on the application of this approach to the structure assignment of some regioisomerically fused heterocyclic systems.

The quinolinone and coumarin derivatives **3a**,**b**–**5a**,**b** depicted in Figure 1 were chosen as substrates to demonstrate the ability of the GIAO method using the B3LYP/6-31G(d) functional to distinguish between regioisomers using experimental and theoretical chemical shift data.

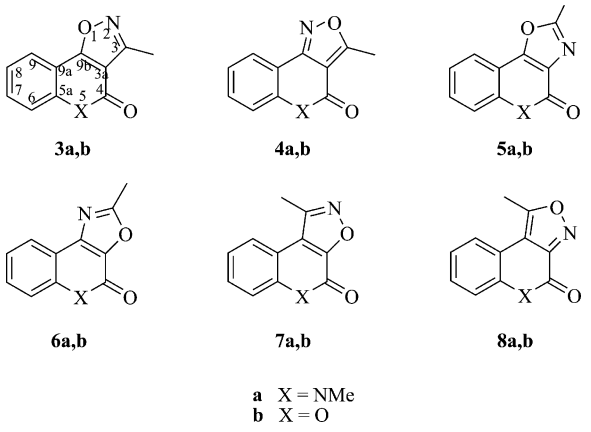
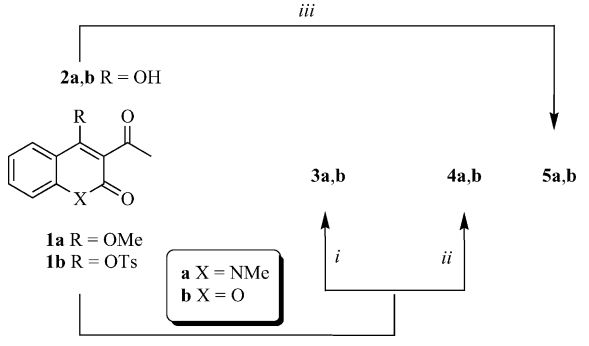


Figure 1. The chemical structures of **3a**,**b**–**8a**,**b**.

Results and Discussion

To evaluate the computational approach, compounds **3a**,**b**–**5a**,**b** were independently synthesized by reaction of a bis-nucleophile (hydroxylamine) with the appropriate 3-acetyl derivatives **1a**,**b** and **2a**,**b** under different reaction conditions, as described in Scheme 1.



Scheme 1. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, ethylene glycol; (ii) $NH_2OH{\cdot}HCl$, Et_3N, EtOH; (iii) $NH_2OH{\cdot}HCl$, AcOH.

The structures of the quinolinone derivatives **3a**–**5a** were determined by 2D NMR experiments. X-ray analysis of **3a** and **5a** was also carried out to provide a good reference for regioisomeric structures (Figure 2).

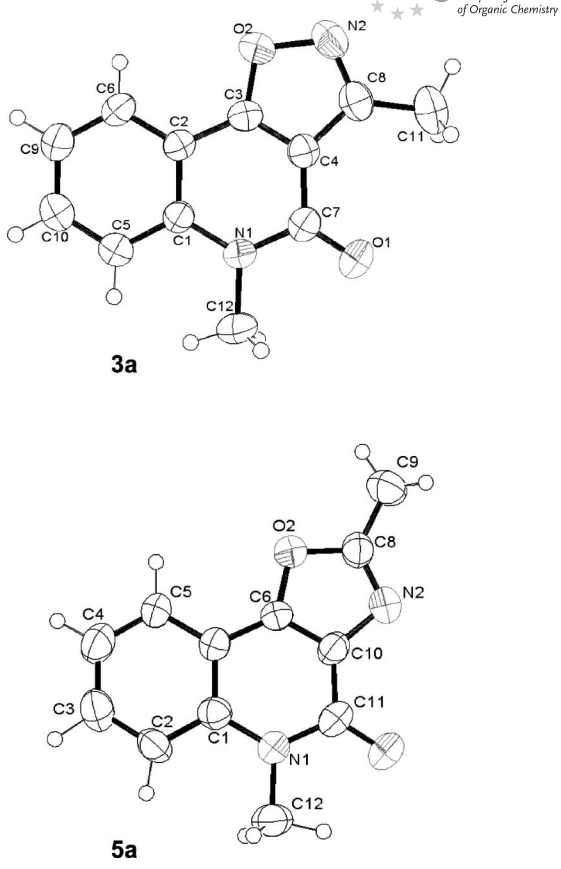


Figure 2. ORTEP drawings of compounds **3a** and **5a**.

In theory, three additional unknown regioisomers, namely **6a**,**b**–**8a**,**b**, must be taken into consideration. Thus, for each synthesized compound six possible regioisomers must be evaluated. ^{13}C NMR chemical shifts are very sensitive to chemical environments and can be used to recognize isomeric structures. Therefore, each experimental set of chemical shifts has been compared with the estimated values for the six theoretically possible isomers.

The GIAO B3LYP/6-31G(d)//HF/6-31G calculated and experimental ^{13}C and ^{15}N chemical shifts for **3a**–**8a** are summarized in Table 1. Brief inspection shows that the most significant variations in the chemical shifts are predicted (and observed) for the quaternary carbon atoms at the junction points (C-3a and C-9b), whereas the peripheral C-6, C-7, and C-8 are practically unaffected. On this basis they were not used in further analysis.[9] The GIAO-calculated chemical shift values for the optimized structures of compounds **3a**–**8a** were then compared with experimental ^{13}C NMR spectroscopic data for **3a**–**5a**.

In general, the least-squares linear-fitting parameters (R^2) of the correlation plots between computed (without scaling) and experimental chemical shift values can be employed to discriminate between the possible structures. For example, such a comparison is depicted in Figure 3 for all the possible regioisomers of compound **3a**, whereas the results of the linear regression analysis comparing the experimental shifts to the GIAO ones for all the synthesized quinolinones **3a**–**5a** are summarized in Table 2. Analysis of these

Table 1. Experimental ($CDCl_3$, 298 K) and calculated[a] ^{13}C and ^{15}N NMR chemical shifts for compounds **3a**–**8a**.

Atom	**3a**		**4a**		**5a**		**6a**	**7a**	**8a**
	Exp.	Calcd.	Exp.	Calcd.	Exp.	Calcd.	Calcd.	Calcd.	Calcd.
C-1	–	–	–	–		–	–	148.1	157.7
C-2	–	–	–	–	162.7	151.5	156.3	–	–
C-3	158.6	153.2	174.3	167.8	–	–	–	–	–
C-3a	108.75	106.6	107.1	104.1	128.8	128.0	135.4	149.4	144.5
C-4	158.6	150.1	158.7	150.8	157.3	147.5	143.6	143.2	146.6
C-5a	140.3	133.3	140.4	133.4	138.2	131.9	132.0	131.6	131.3
C-6	115.4	107.8	115.5	107.9	115.2	107.7	107.4	108.2	108.4
C-7	132.4	124.0	131.95	123.5	130.1	121.9	121.5	120.5	120.1
C-8	122.8	114.5	123.0	115.0	122.45	114.1	114.9	115.0	114.9
C-9	123.3	118.0	124.8	119.3	121.4	115.3	118.4	116.9	117.8
C-9a	110.65	105.5	112.2	107.5	111.3	105.7	110.2	110.5	110.4
C-9b	167.2	158.8	156.3	148.8	152.3	146.1	137.8	116.2	108.6
CH_3	10.8	11.8	12.85	11.1	14.2	12.3	12.8	12.8	12.7
N-CH_3	29.1	27.1	28.7	26.8	29.6	27.4	27.3	27.6	27.5
N(5)	–238.3	–227.7	–	–233.6	–236.6	–225.5	–225.8	–225.0	–229.6
N(*x*)	–4.0	9.9	–16.0	0.7	–135.0	–115.0	–123.5	7.2	14.7

[a] At the GIAO B3LYP/6-31G(d)//RHF/6-31G level of theory.

data unequivocally demonstrates that such large differences in the R^2 values for the "wrong" versus "right" structures may serve to validate the correct structure.

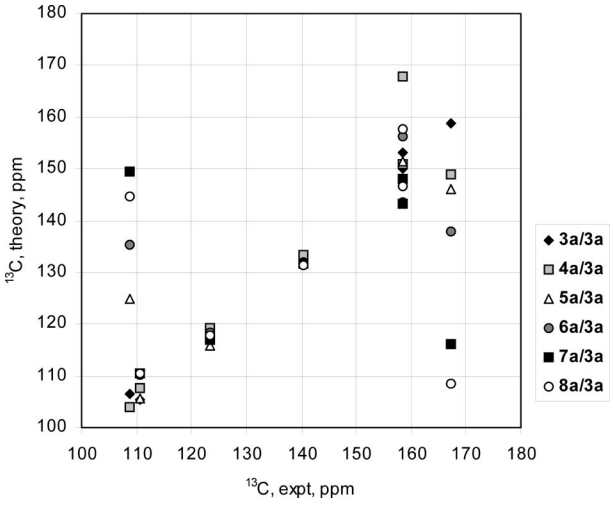


Figure 3. Correlation of theoretical chemical shifts versus experimental ones for different regioisomers of compound **3a**.

Table 2. Correlation coefficients of least-squares linear fits (R^2) of the theoretical [GIAO RB3LYP/6-31G(d)//RHF/6-31G] versus experimental ^{13}C NMR chemical shifts for compounds **3a**–**8a**.

Compound	R^2					
	3a	**4a**	**5a**	**6a**	**7a**	**8a**
3a	**0.997**	0.890	0.821	0.516	0.028	0.043
4a	0.919	**0.998**	0.814	0.629	0.090	0.158
5a	0.861	0.870	**0.991**	0.879	0.307	0.131

As for the ^{15}N NMR chemical shifts, the combined use of correlation experiments and GIAO calculations (theory overestimates ^{15}N chemical shifts by ca. 10–12 ppm)[10] can also be of diagnostic value although with some limitations. For example, in the compounds under examination there should be a protonated carbon atom as substituent in the five-membered heterocyclic system in order to invoke ^1H–^{15}N HMBC connectivity to distinguish between structures with the nitrogen atom vicinal to the carbon-bearing proton (Figure 4, structures **3a**,**b** and **5a**,**b**–**7a**,**b**), whereas the lack of ^1H–^{15}N HMBC connectivity is evident in compounds **4a**,**b** and **8a**,**b**.

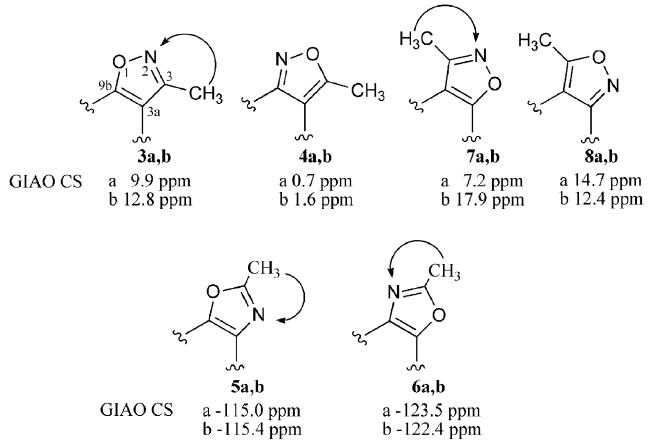


Figure 4. $^3J_{H-N}$ correlation in five-membered ring systems and calculated GIAO ^{15}N chemical shifts for **3a**,**b**–**8a**,**b**.

GIAO ^{15}N chemical shift calculations may be helpful to distinguish between 1,2- and 1,3-oxazole structures because the former show characteristic chemical shifts close to 0 ppm whereas the latter resonate at lower frequencies (ca. –120 ppm).[11] Thus, compounds **5a** and **6a** (as well as **3a** and **7a** or **4a** and **8a**) cannot be distinguished merely on the basis of ^{15}N NMR spectroscopic data and additional arguments (e.g., consideration of the chemical shifts and connectivities of the quaternary carbon atoms at the 3a- and 9b-positions) are needed. We can conclude that ^{15}N NMR spectroscopy is a less general method and can only be used in conjunction with other NMR spectroscopic data.

Additional evidence for the quality of this approach was obtained by examining isomeric structures of the coumarin

Table 3. Experimental ($CDCl_3$, 298 K) and calculated[a] ^{13}C and ^{15}N NMR chemical shifts for compounds **3b**–**8b**.

Atom	**3b**		**4b**		**5b**		**6b**	**7b**	**8b**
	Exp.	Calcd.	Exp.	Calcd.	Exp.	Calcd.	Calcd.	Calcd.	Calcd.
C-1	–	–	–	–	–	–	–	148.7	158.3
C-2	–	–	–	–	163.6	152.2	157.9	–	–
C-3	158.6	153.2	177.0	169.0	–	–	–	–	–
C-3a	104.7	103.3	103.6	101.8	124.8	121.7	132.0	146.5	142.5
C-4	156.6	147.0	156.6	147.8	155.5	144.4	140.8	140.2	143.4
C-5a	154.2	148.0	153.4	147.4	152.8	147.2	147.6	146.5	145.3
C-6	117.7	109.8	117.9	110.0	117.6	109.7	109.3	110.0	110.4
C-7	133.8	125.2	132.9	124.4	131.4	123.0	122.5	121.7	121.1
C-8	125.0	116.9	125.1	117.1	124.8	116.5	117.1	117.3	117.2
C-9	122.9	117.5	124.4	118.8	121.3	115.6	118.0	116.4	117.2
C-9a	110.7	106.3	111.2	107.4	111.5	106.6	110.8	110.9	109.9
C-9b	169.9	161.4	156.2	149.5	155.8	148.6	141.2	118.9	109.6
CH_3(5)	10.4	11.2	12.9	11.0	14.2	12.2	12.7	12.3	12.1
N(*x*)	–2.3	12.8	–13.2	1.6	–127.5	–115.4	–122.4	17.9	12.4

[a] At the GIAO B3LYP/6-31G(d)//RHF/6-31G level of theory.

analogues **3b**–**8b**. The proposed method allowed us to achieve a simple and safe structure determination by using a combination of 2D NMR methods and nonempirical chemical shift calculations.

Experimental and calculated chemical shifts for compounds **3b**–**5b** are given in Table 3. As for the quinolinone derivatives, additional hypothetical regioisomers (**6b**–**8b**) have also been considered. The results of the regression analysis are summarized in Table 4. For the oxazolocoumarins, the "right" combinations of theoretical versus experimental chemical shifts give high R^2 values (0.988–0.998), whereas for the "wrong" ones the observed values are notably lower and do not exceed 0.9. Thus, such an analysis has allowed us a straightforward determination of regioisomeric structures of compounds **3b**–**5b**.

Table 4. Correlation coefficients of least-squares linear fits (R^2) of the theoretical [GIAO RB3LYP/6-31G(d)//RHF/6-31G] versus experimental ^{13}C NMR chemical shifts for compounds **3b**–**8b**.

Compound	**3b**	**4b**	**5b**	**6b**	**7b**	**8b**
3b	0.996	0.879	0.848	0.589	0.061	0.056
4b	0.896	0.998	0.836	0.710	0.154	0.205
5b	0.891	0.901	0.988	0.884	0.324	0.307

Once again the ^{15}N NMR spectroscopic data showed the same trends as those previously discussed for compounds **3a**–**5a**.

Finally, we wish to point out that in general ^{1}H NMR chemical shifts also depend on the isomeric structure, although to a lesser extent because most of the protons are far from the variable fragment. Nevertheless, the trends shown by the experimental chemical shifts are partly reproduced by theory. However, these changes are very small and may also be due to medium effects that cannot properly be taken into account. Therefore, ^{1}H NMR spectroscopic data cannot really be used to validate the regioisomeric structures of these kinds of compounds.

Influence of the Level of Theory on the Performance of the Method

The correlation coefficients of least-squares linear fits (R^2) have been used as an index of agreement between theoretical and experimental chemical shifts. To distinguish between "wrong" and "right" structures there should be a reliably large gap in their values for the proposed structures. To start, we used a "basic" combination of chemical shift calculations and geometry optimization [B3LYP/6-31G(d)//HF/6-31G], which has proved to be reliable for other heteroaromatic systems.[10a] For the compounds under examination this level produces reasonably high R^2 values (0.99–1.00) for the "right" structures and sufficiently small values (<0.90) for the "wrong" structures. With the aim of verifying if this differentiation depends or not on the theoretical approach used in the calculations, we tested two additional methods of geometry optimization. It is in fact well known that agreement between theoretical and experimental NMR chemical shifts depends on the geometry used in the calculations.

To obtain a good geometry and hence reliable chemical shift values for heterocyclic compounds, some authors recommend using the DFT level for geometry optimization with diffuse functions included in the basis set. Thus, we performed calculations on compounds **3a**,**b**–**8a**,**b** using the B3LYP/6-31G(d)//B3LYP/6-31G(d) combination (see Table S1 and Table S2 of the Supplementary Information) but no improvement in the R^2 values for the "right" structures was found nor an increased difference in R^2 between "right" and "wrong" structures (see Table S3 and Table S4 of the Supplementary Information).

On the other hand, all NMR experiments were carried out in chloroform and therefore to take into account medium effects we also performed geometry optimizations with solvent effects included in the framework of the polarization continuum model (PCM). Calculations on this geometry afforded a slightly better correlation of the chemical shifts (see Table S1 and Table S2 of the Supplementary In-

formation) with respect to that obtained for the HF/6-31G geometry. For the "wrong" structure the R^2 values are almost the same as those determined by the B3LYP/6-31G(d)//HF/6-31G combination (see Table S5 and Table S6 of the Supplementary Information). Thus, accounting for solvent effects improves the diagnostic values of R^2, but in an insignificant way and taking into account the fact that such calculations remarkably increase the computational time and computer demands, inclusion of the solvent under geometry optimization does not give any advantage. Indeed, the B3LYP/6-31G(d)//HF/6-31G combination may be used with confidence.

Conclusions

In this work we have demonstrated that the combined use of 2D NMR correlation experiments with GIAO DFT ^{13}C NMR chemical shift calculations allows a reliable and simple determination of regioisomeric heterocyclic systems that originate from the reaction of quinolinone or coumarin derivatives with hydroxylamine. Application of the same approach to ^{15}N NMR spectroscopic data is less useful for these compounds although it can be used in conjunction with other NMR spectroscopic data.

In general, we believe that the proposed method may be used to solve the problem of regioisomeric structure determination of heteroaromatic compounds. In the mean time we realize that the presence of even low levels of saturation in the molecules can introduce geometric ambiguity and the potential for more than one low-energy structure.

Experimental Section

General Remarks: Melting points were measured with a Büchi 510 apparatus and are uncorrected. Compounds **1a**,[12a] **1b**,[12b] **2a**,[12c] **2b**,[12d] **3a**–**5a**,[12a] and **5b**,[12e] were prepared as reported in the literature. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck 230–400 mesh) were used for analytical TLC and for column chromatography, respectively. Solvents were removed under reduced pressure. All 1D and 2D NMR experiments were performed with a Varian Mercuryplus-400 spectrometer (399.95 MHz for ^1H, 100.57 MHz for ^{13}C, and 40.54 MHz for ^{15}N) with a 5 mm indirect detection probe equipped with a gradient coil at 298 K. Chemical shifts (δ in ppm) are referenced to the solvent $CDCl_3$ (δ = 7.26 ppm for ^1H and 77.0 ppm for ^{13}C NMR) and to external CD_3NO_2 (0.0 ppm) for ^{15}N NMR spectra (conversion factor to NH_3: +380.2 ppm).[7b,11] All coupling constants are given in Hz. Assignments were made by using ^1H, ^{13}C, DEPT, and NOESY 1D experiments and gHSQC, gHMBC, and COSY 2D experiments. All pulse sequences were used as provided by Varian and processing was performed by using standard Varian methods.

3-Methyl-4*H*-chromeno[3,4-*d*]isoxazol-4-one (3b): Hydroxylamine hydrochloride (47 mg, 0.68 mmol) was added in one portion to a stirred solution of 3-acetyl-2-oxo-2*H*-chromen-4-yl 4-methylbenzenesulfonate (**1b**) (200 mg, 0.56 mmol) in ethylene glycol (5 mL) and the reaction mixture was heated at reflux for 2 h. After cooling, water was added (50 mL) and the solid obtained was filtered and purified by column chromatography with ethyl acetate/petroleum ether 40–70 (1:3) as eluent (R_f = 0.56). Yield 44% (50 mg); m.p. 177–178 °C (ref.[12e] 175–176 °C, from ethanol). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.99 (dd, ^3J = 8.1, ^4J = 1.6 Hz, 1 H, 9-H), 7.68 (ddd, ^3J = 8.7, 7.5, ^4J = 1.6 Hz, 1 H, 7-H), 7.48 (dd, ^3J = 8.7, ^4J = 1.0 Hz, 1 H, 6-H), 7.42 (ddd, ^3J = 8.1, 7.5, ^4J = 1.0 Hz, 1 H, 8-H), 2.65 (s, 3 H, 3-CH_3) ppm.

3-Methyl-4*H*-chromeno[4,3-*c*]isoxazol-4-one (4b): A solution of hydroxylamine hydrochloride (47 mg, 0.68 mmol) and Et_3N (90 μL, 0.68 mmol) in ethanol (7 mL) was stirred for 10 min at room temperature. 3-Acetyl-2-oxo-2*H*-chromen-4-yl 4-methylbenzenesulfonate (**1b**) (200 mg, 0.56 mmol) was subsequently added and the solution was heated at reflux for 3 h. Removal of the solvent left a yellow solid, which was suspended in a saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL) in a separating funnel. The organic phase was dried with sodium sulfate and the solvent removed under reduced pressure. The solid was purified by column chromatography with ethyl acetate/petroleum ether 40–70 = (1:3) as eluent (R_f = 0.53). Yield 53% (60 mg); m.p. 170–172 °C (ref.[12b] 180–182 °C, from ethanol). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.09–8.06 (m, 1 H, 9-H), 7.60–7.56 (m, 1 H, 7-H), 7.37–7.33 (m, 1 H, 8-H), 7.36 (d, ^3J = 8.0 Hz, 1 H, 6-H), 2.89 (s, 3 H, 3-CH_3) ppm.

2-Methyl-4*H*-chromeno[3,4-*d*][1,3]oxazol-4-one (5b): M.p. 195–196 °C, from ethanol (ref.[12e] 196–197 °C, from ethanol). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.81 (dd, ^3J = 8.2, ^4J = 1.6 Hz, 1 H, 9-H), 7.58 (ddd, ^3J = 8.4, 7.2, ^4J = 1.6 Hz, 1 H, 7-H), 7.50–7.47 (m, 1 H, 6-H), 7.40–7.37 (m, 1 H, 8-H), 2.71 (s, 3 H, 2-CH_3) ppm.

Crystallographic Data: Data sets were collected with a Oxford Diffraction KM4 Xcalibur2 diffractometer. Graphite-monochromated Mo-K_α radiation (4 mA/–40 kV) and a KM4 CCD/SAPPHIRE detector were used for cell parameter determination and data collection. The integrated intensities, measured by using the ω-scan mode, were corrected for Lorentzian and polarization effects.[13] The structures were solved by direct methods using SIR97[14] and refined by full-matrix least-square fits on F^2 with SHELXL97.[15]

X-ray Crystal Structure Analysis for 3a: Formula $C_{12}H_{10}N_2O_2$, M = 212.22, colorless crystal, monoclinic, space group $P21/a$, a = 6.994(5), b = 11.232(5), c = 13.130(5) Å, α = 90.000(5), β = 101.750(5), γ = 90.000(5)°, V = 1009.8(9) Å^3, Z = 4, T = 293(2) K, μ = 0.098 mm^{-1}, $F(000)$ = 448. 4343 reflections were collected in the range 3.96° < θ < 25.70°. The final R index was 0.0553 for reflections having $I > 2\sigma(I)$.

X-ray Crystal Structure Analysis for 5a: Formula $C_{12}H_{10}N_2O_2$, M = 212.22, colorless crystal, monoclinic, space group $P21/a$, a = 8.344(3), b = 13.174(3), c = 9.337(2) Å, α = 90.000(2), β = 103.070(3), γ = 90.000(2)°, V = 999.8(5) Å^3, Z = 4, T = 293(2) K, μ = 0.099 mm^{-1}, $F(000)$ = 448. 8110 reflections were collected in the range 4.48° < θ < 23.26°. The final R index was 0.0695 for reflections having $I > 2\sigma(I)$.

CCDC-689483 and -689484 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computational Details: The ab initio quantum chemical calculations were performed by using Gaussian 98[16] on an IBM PC compatible computer. Full geometry optimizations to a minimum energy were executed at the ab initio HF/6-31G level unless otherwise noted. Chemical shifts were determined by the GIAO method within the DFT framework by using a hybrid exchange-correlation functional, B3LYP, at the 6-31G(d) level of theory. Geometry optimization with solvent effects was performed within the framework

of the polarization continuum model (PCM). All values are referenced to calculated shieldings for TMS.

Supporting Information (see also the footnote on the first page of this article): Calculated ^{13}C and ^{15}N NMR chemical shifts for the regioisomers **3a**,**b**–**8a**,**b** (Tables S1 and S2), correlation coefficients of least-squares linear fits (R^2) of the theoretical versus experimental ^{13}C NMR chemical shifts for the regioisomers **3a**–**8a** (Tables S3 and S5) and **3b**–**8b** (Tables S4 and S6).

Acknowledgments

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[1] a) A. Albert, *Selective Toxicity and Related Topics*, 4th ed., Methuen, London, **1968**; b) E. Juaristi, *Introduction to Stereochemistry and Conformational Analysis*, Wiley, New York, **1991**; c) E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**.

[2] a) M. C. Nunez, F. Rodriguez-Serrano, J. A. Marchal, O. Caba, A. Aranega, M. A. Gallo, A. Espinosa, J. M. Campos, *Tetrahedron* **2007**, *63*, 183–190; b) P. Chaudhuri, B. Ganguly, S. Bhattacharya, *J. Org. Chem.* **2007**, *72*, 1912–1923; c) M. E. A. Zaki, M. F. Proenca, *Tetrahedron* **2007**, *63*, 3745–3753; d) T. Cailly, F. Fabis, R. Legay, H. Oulyadi, S. Rault, *Tetrahedron* **2007**, *63*, 71–76; e) E. Manzo, M. Gavagnin, G. Bifulco, P. Cimino, S. Di Micco, M. L. Ciavatta, Y. W. Guoc, G. Cimino, *Tetrahedron* **2007**, *63*, 9970–9978.

[3] a) C. A. Nijhuis, B. J. Ravoo, J. Huskens, D. N. Reinhoudt, *Coord. Chem. Rev.* **2007**, *251*, 1761–1780; b) F. Rong, S. Chow, S. Yan, G. Larson, Z. Hong, J. Wu, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1663–1666; c) S. Chen, X. Xu, Y. Liu, W. Qiu, G. Yu, H. Wang, D. Zhu, *J. Phys. Chem. C* **2007**, *111*, 1029–1034; d) G. Bifulco, P. Dambruoso, L. Gomez-Paloma, R. Riccio, *Chem. Rev.* **2007**, *107*, 3744–3779; e) K. W. Wiitala, C. J. Cramer, T. R. Hoye, *Magn. Reson. Chem.* **2007**, *45*, 819–829; f) M. Barfield, *Magn. Reson. Chem.* **2007**, *45*, 634–646; g) E. A. Basso, G. F. Gauze, R. J. Abraham, *Magn. Reson. Chem.* **2007**, *45*, 749–757; h) C. Bassarello, G. Bifulco, P. Montoro, A. Skhirtladze, E. Kemertelidze, C. Pizza, S. Piacente, *Tetrahedron* **2007**, *63*, 148–154.

[4] a) S. Berger, *Prog. Nucl. Magn. Reson. Spectrosc.* **1997**, *30*, 137–156; b) T. Parella, *Magn. Reson. Chem.* **1998**, *36*, 467–495; c) M. Kline, S. Cheatham, *Magn. Reson. Chem.* **2003**, *41*, 307–314; d) M. Findeisen, S. Berger, *Magn. Reson. Chem.* **2003**, *41*, 431–434; e) R. A. E. Edden, J. Keeler, *J. Magn. Reson.* **2004**, *166*, 53–68.

[5] a) H. Morita, Y. Sato, K.-L. Chan, C.-Y. Choo, H. Itokawa, K. Takeya, J. Kobayashi, *J. Nat. Prod.* **2000**, *63*, 1707–1708; b) H. Morita, Y. Sato, K.-L. Chan, C.-Y. Choo, H. Itokawa, K. Takeya, J. Kobayashi, *J. Nat. Prod.* **2002**, *65*, 1748; c) Y. L. Yang, F. R. Chang, Y. C. Wu, *Tetrahedron Lett.* **2003**, *44*, 319–322; d) M. Chakrabarty, S. Sarkar, Y. Harigaya, *Synthesis* **2003**, 2292–2294; e) P. Matyus, B. U. W. Maes, Z. Riedl, G. Hajos, G. L. F. Lemiere, P. Tapolcsanyi, K. Monsieurs, O. Elias, R. A. Dommisse, G. Krajsovszky, *Synlett* **2004**, 1123–1139; f) K. Monsieurs, P. Tapolcsanyi, K. T. J. Loones, G. Neumajer, J. A. D. De Ridder, K. Goubitz, G. L. F. Lemiere, R. A. Dommisse, P. Matyus, B. U. W. Maes, *Tetrahedron* **2007**, *63*, 3870–3881; g) K. Suzuki, S. Yahara, K. Maehata, M. Uyeda, *J. Nat. Prod.* **2001**, *64*, 204–207; h) Atta-ur-Rahman, M. I. Choudhary, S. Hayat, A. M. Khan, A. Ahmed, *Chem. Pharm. Bull.* **2001**, *49*, 105–107; i) S. Venkateswarlu, G. K. Panchagnula, M. B. Guraiah, G. V. Subbaraju, *Tetrahedron* **2005**, *61*, 3013–3017; j) S. Venkateswarlu, G. K. Panchagnula, M. B. Guraiah, G. V. Subbaraju, *Tetrahedron* **2006**, *62*, 9855–9860; k) S. Venkateswarlu, G. K. Panchagnula, G. V. Subbaraju, *Tetrahedron* **2007**, *63*, 6909–6914.

[6] K. C. Nicolau, S. A. Snyder, *Angew. Chem. Int. Ed.* **2005**, *44*, 1012–1044.

[7] a) M. Shamma, D. M. Hindenlang, *Carbon-13 NMR Shift Assignment of Amines and Alkaloids*, Plenum Press, New York, **1979**; b) G. C. Levy, *Topics in Carbon-13 NMR Spectroscopy*, 2nd ed., Wiley-Interscience, New York, **1980**; c) E. Breitmaier, W. Voelter, *Carbon-13 NMR Spectroscopy*, VCH, Weinheim, **1987**.

[8] a) K. Wolinsky, J. F. Hinton, P. Pulay, *J. Am. Chem. Soc.* **1990**, *112*, 8251–8260; b) G. Barone, L. Gomez-Paloma, D. Duca, A. Silvestri, R. Riccio, G. Bifulco, *Chem. Eur. J.* **2002**, *8*, 3233–3239; c) G. Barone, D. Duca, A. Silvestri, L. Gomez-Paloma, R. Riccio, G. Bifulco, *Chem. Eur. J.* **2002**, *8*, 3240–3245; d) A. R. Katritzky, N. G. Akhmedov, J. Doskocz, P. P. Mohapatra, C. D. Hall, A. Güven, *Magn. Reson. Chem.* **2007**, *45*, 532–543; e) P. Cimino, L. Gomez-Paloma, D. Duca, R. Riccio, G. Bifulco, *Magn. Reson. Chem.* **2004**, *42*, S26–S33; f) I. Alkorta, J. Elguero, *Tetrahedron* **2006**, *62*, 8683–8686; g) F. Blanco, I. Alkorta, J. Elguero, *Magn. Reson. Chem.* **2007**, *45*, 797–800; h) A. Bagno, F. Rastrelli, G. Saielli, *J. Org. Chem.* **2007**, *72*, 7373–7381; i) A. B. Sebag, R. N. Hanson, D. A. Forsyth, C. Y. Lee, *Magn. Reson. Chem.* **2003**, *41*, 246–252; j) E. Kleinpeter, S. Klod, W.-D. Rudorf, *J. Org. Chem.* **2004**, *69*, 4317–4329; k) R. M. Claramunt, C. Lopez, M. D. Santa Maria, D. Sanz, J. Elguero, *Prog. Nucl. Magn. Reson. Spectrosc.* **2006**, *49*, 169–206; l) D. Sanz, R. M. Claramunt, A. Saini, V. Kumar, R. Aggarwal, S. P. Singh, I. Alkorta, J. Elguero, *Magn. Reson. Chem.* **2007**, *45*, 513–517; m) S. Rosselli, M. Bruno, A. Maggio, G. Bellone, C. Formisano, C. A. Mattia, S. Di Micco, G. Bifulco, *Eur. J. Org. Chem.* **2007**, *15*, 2504–2510; n) G. Bifulco, R. Riccio, C. Gaeta, P. Neri, *Chem. Eur. J.* **2007**, *13*, 7185–7194; o) A. R. Katritzky, N. G. Akhmedov, J. Doskocz, C. D. Hall, R. G. Akhmedova, S. Majumder, *Magn. Reson. Chem.* **2007**, *45*, 5–23.

[9] The chemical shifts of all the carbon atoms could be used in the regression analysis but this would give an "apparently good" impact on the overall correlation coefficients for the "right" and "wrong" structures.

[10] a) A. Balandina, A. Kalinin, V. Mamedov, B. Figadère, Sh. Latypov, *Magn. Reson. Chem.* **2005**, *43*, 816–828; b) V. Semenov, L. Galiullina, O. Lodochnikova, O. Kataeva, A. Gubaidullin, A. Chernova, Yu. Efremov, Sh. Latypov, V. Reznik, *Eur. J. Org. Chem.* **2007**, 4578–4593; c) A. Kozlov, V. Semenov, A. Mikhailov, A. Aganov, M. Smith, V. Reznik, Sh. Latypov, *J. Phys. Chem. B* **2008**, *112*, 3259–3267.

[11] M. Witanowsky, L. Stefaniak, G. A. Webb, *Annual Reports in NMR Spectroscopy* (Ed.: G. A. Webb), Academic Press, London, **1986**, vol. 18.

[12] a) S. Chimichi, M. Boccalini, A. Matteucci, *Tetrahedron* **2007**, *63*, 11656–11660; b) T. Steinfuhrer, A. Hantschmann, M. Pietsch, M. Weissenfels, *Liebigs Ann. Chem.* **1992**, 23–28; c) W. Stadlbauer, P. Roschger, *Liebigs Ann. Chem.* **1990**, 821–823; d) S. Sukdolak, S. Solujic, N. Manojlovic, N. Vukovic, *J. Heterocycl. Chem.* **2004**, *41*, 593–596; e) B. Chantegrel, A. I. Nadi, S. Gelin, *J. Org. Chem.* **1984**, *49*, 4419–4424.

[13] N. Walker, D. Stuart, *Acta Crystallogr., Sect. A* **1983**, *39*, 158–166.

[14] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacobazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115–119.

[15] G. M. Sheldrick, *SHELXL97: A Program for Crystal Structure Refinement*, University of Göttingen, Germany.

[16] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A., Montgomery Jr, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas,

J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian 98 (Revision A.6), Gaussian Inc., Pittsburgh, PA, **1998**.

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