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Determination of the Absolute Stereostructure of a Helical Biaryl Lactone by Multiple Scattering X-Ray Experiments[1]

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Abstract: The elucidation of the absolute configuration of a lactone-bridged biaryl was performed by multiple scattering X-ray experiments. This helical, but configuratively unstable compound shows spontaneous deracemization by crystallization. For the rapid stereochemical correlation with the examined crystal, an analytical device was developed, by chromatography on a chiral HPLC phase.

INTRODUCTION

Benzonaphthopyranones of type **1**[2] constitute valuable substrates for stereoselective biaryl syntheses:[3] out of a mixture of - depending on the size of R - more or less rapidly helimerizing atropisomers *M*-**1** ⇌ *P*-**1** they can be ring-opened in some cases with very high stereocontrol,[4] using chiral nucleophiles. The mechanistic investigation of this novel principle presently concentrates on the determination of structure and dynamics of the starting materials **1**. For this purpose we have synthesized a hole series of further related bridged biaryls, among them the isopropyl/methyl-substituted lactone **2**.[5]

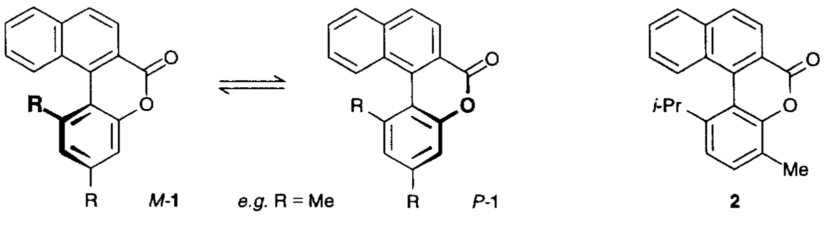


Fig. 1. Benzo[b]naphtho[1,2–d]pyranones as versatile starting material for the stereoselective synthesis of axially chiral biaryls.

Interestingly, crystalline material as obtained from a solution of the racemic substance in dichloromethane / petroleum ether, was found to consist of stereochemically homogeneous crystals of both enantiomeric series, as could be revealed from an ordinary X-ray structure analysis.[6] In organic solution, this enantiomerically pure substance isomerizes at room temperature. Since **2** does not dispose of heavy atoms, we chose the new method of multiple scattering X-ray structure analysis for the determination of the absolute configuration at the axis within the single crystals. For a related, yet configuratively stable seven-membered ring lactone, we had previously established the absolute stereostructure, paralleled by theoretical and experimental CD investigations.[7]

RESULTS AND DISCUSSION

The Determination of the Absolute Configuration

The determination of the absolute structure by X-ray diffraction experiments by means of Bijvoet pairs and the anomalous dispersions effect is possible only in the presence of heavy atoms. For light-atom structures, the absolute configuration can be determined by interference effects of X-ray wavefields excited in special positions of the crystal sample.

According to *Hümmer et al.*[8] it is possible to get information on invariant triplet phases by three-beam scattering X-ray experiments using a six-circle diffractometer.

Three structure factors F($-\underline{h}$), F($\underline{h}'$) and F($\underline{h}''$) are called a triplet if the vectors of the reciprocal lattice $-\underline{h}$, $\underline{h}'$ and $\underline{h}''$ add up to zero:

$$-\underline{h}+\underline{h}'+\underline{h}''=0, \qquad \text{therefore} \qquad h''=\underline{h}-\underline{h}'. \tag{1}$$

The sum of the structure factor phases $\phi(-\underline{h})+\phi(\underline{h}')+\phi(\underline{h}'') = \Phi(\underline{h},\underline{h}')$ is structure-invariant and does not change by shifts of the origin. Φ is called triplet phase. Enantiomorphic structures differ by the sign of the triplet phase Φ. By considering phases $\Phi \approx \pm 90°$, enantiomorphic structures can be distinguished unambiguously by the following experiment.

A six-circle diffractometer[9] is used with an additional mechanical Ψ-axis and high angular resolution (0.001 degrees). First a scattering vector of the reciprocal lattice $\underline{h} = (h,k,l)$ is moved to the Ψ-axis. Then $\underline{\mathrm{h}}$ and thus the Ψ-axis is moved to the diffraction position, *i.e.* the points (0,0,0) and (h,k,l) of the reciprocal lattice lie on the surface of the Ewald sphere (cf. Fig. 2, see below). The intensity of $\underline{h}$ is observed (in direction of $\underline{s}_{\underline{h}}$) while a Ψ-rotation around $\underline{h}$ is performed. If a secondary vector $\underline{h}'$ is moved with its end point (h',k',l') through the Ewald-sphere, the Bragg condition for this vector is also satisfied and an additional wavefield is excited in the crystal. This wavefield influences the wavefield related to the primary vector $\underline{h}$ *via* the difference vector $\underline{h}'' = \underline{h} - \underline{h}'$.

The secondary beam diffracted in $\underline{s}_{h'}$ direction acts as a primary beam for the difference vector $\underline{h}'' = \underline{h}-\underline{h}'$. The direction $\underline{s}_{h''}$ of the secondary beam related to $\underline{h}''$ is equivalent to $\underline{s}_{\underline{h}}$. Both wavefields interfere with each other since these are elastic scattering processes. The result of the interference is that the intensity in direction of $\underline{s}_{\underline{h}}$ is changed systematically during the rotation around Ψ. These changes are related to the structure invariant $\Phi = \phi(-\underline{h}) + \phi(\underline{h}') + \phi(\underline{h}'')$ unambiguously.[10,11] For $\Phi = +90°$ the intensity is decreased, for $\Phi = -90°$ the intensity of $\underline{\mathrm{h}}$ is increased during the passing of (h',k',l') through the surface of the Ewald sphere provided that the involved structure factor moduli do not differ too much from the ratio 1:2:2. Since no special properties such as anomalous dispersion are necessary, this procedure is especially suitable for structures containing only light atoms. Since the variation of the intensity is also influenced by other physical effects not related to phases of structure factors (Aufhellung and Umweganregung resulting from energy conservation[12]) centrosymmetric triplet phases $\Phi^+(-\underline{h}, \underline{h}', \underline{h}'')$ and $\Phi^-(\underline{h}, -\underline{h}', -\underline{h}'')$ must be investigated. The requirement for a successful three-beam experiment is a small mosaicity of the crystal sample (full width at half maximum of a reflection may not exceed 0.05 degrees). This method has been successfully applied to several light-atom structures.[7,13-15]

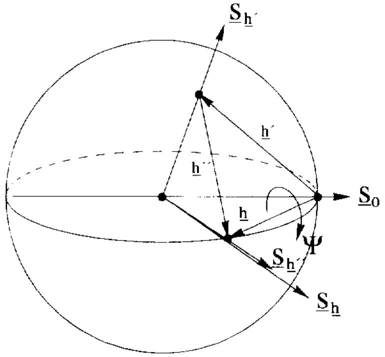


Fig. 2. Representation of a three beam experiment in the reciprocal space. During a Ψ-rotation of the crystal around $\underline{h}$, the end point of $\underline{h}'$ and the starting point of $\underline{h}'' = \underline{h} - \underline{h}'$ pass the Ewald sphere. This movement leads to an interference effect in direction of $\underline{s}_h$ and $\underline{s}_{h''}$.

The determination of the absolute structure was preceded by a redetermination of the structure using the same specimen. The refinement led to $R = 0.039$ and $R_w = 0.035$. The result is in very good agreement with the data previously obtained.[6] Table 1 shows the structure factors and their phases used for the determination and the changes of the recorded intensities on an arbitrary scale. The investigation clearly established a *P*-configuration for the molecules (Fig. 3).

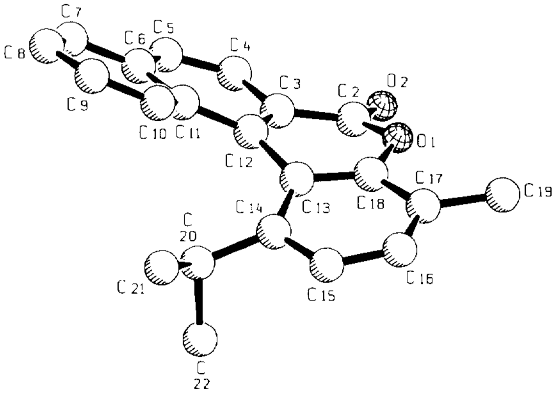
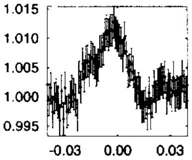
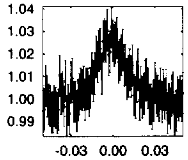
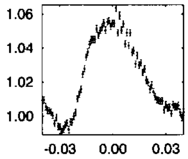
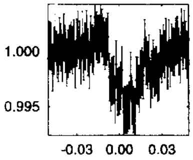
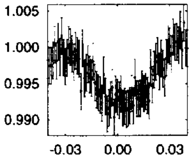
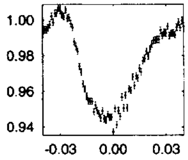
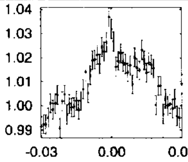
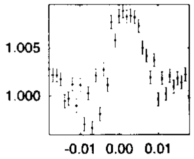
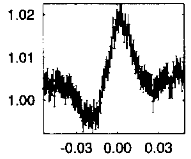
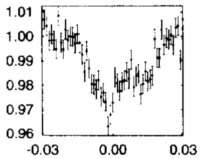
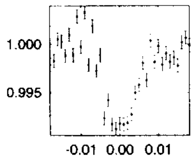
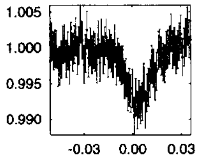


Fig. 3. The absolute stereostructure of *(P)*-**2** in the crystal, as determinated by multiscattering X-ray measurements.

Table 1. Data used for the determination of the absolute structure. The basic line is indicated by 1.0. The results are in very good agreement with the triplet phases calculated on the basis of the refined atomic coordinates. It should be emphasized that the full-widths at half-maximum of the changes do not exceed 0.03°. The triplets Φ_3, Φ_4 and Φ_5 were corrected for Umweganregung and Aufhellung. The experiments were performed with a six-circle diffractometer at a rotating anode generator (radiation: $Cu - K_{\alpha 1}$).

Structure factors used with moduli F_{obs} (measured) and phases ϕ_{cal} (calculated)								
hkl	F_{obs}	ϕ_{cal}	hkl	F_{obs}	ϕ_{cal}	hkl	F_{obs}	ϕ_{cal}
004	40.5	180°	400	215.3	0°	215	43.3	245°
122	60.8	14°	214	42.3	340°	511	125.5	212°
622	69.3	318°	101	100.2	90°	113	70.8	20°
112	53.9	309°	111	174.3	112°	021	134.2	180°
301	114.4	270°	323	83.4	199°			

Triplets used						
Triplet	**h**	ϕ_i	**h**	ϕ_i	**h**	ϕ_i
-h -k -l	004	180°	$\bar{2}\bar{1}5$	65°	$\bar{1}\bar{2}\bar{2}$	346°
h′ k′ l′	$\bar{6}\bar{2}\bar{2}$	42°	$12\bar{2}$	166°	101	90°
h″ k″ l″	$62\bar{2}$	42°	$1\bar{1}\bar{3}$	20°	021	180°
$\Phi = \sum_i \phi_i$	$\Phi_1^+ = -96°$		$\Phi_2^+ = -109°$		$\Phi_3^+ = -104°$	
						
-h -k -l	$00\bar{4}$	180°	$21\bar{5}$	295°	122	14°
h′ k′ l′	622	318°	$\bar{1}\bar{2}2$	194°	$\bar{1}0\bar{1}$	270°
h″ k″ l″	$\bar{6}\bar{2}2$	318°	$\bar{1}13$	340°	$0\bar{2}\bar{1}$	180°
$\Phi = \sum_i \phi_i$	$\Phi_1^+ = 96°$		$\Phi_2^+ = 109°$		$\Phi_3^+ = 104°$	
						
Triplet	**h**	ϕ_i	**h**	ϕ_i	**h**	ϕ_i
-h -k -l	$\bar{2}\bar{1}\bar{4}$	20°	$\bar{5}\bar{1}\bar{1}$	148°	$\bar{2}\bar{1}5$	65°
h′ k′ l′	$\bar{1}13$	340°	111	112°	$\bar{1}\bar{1}\bar{2}$	51°
h″ k″ l″	301	270°	400	0°	$32\bar{3}$	161°
$\Phi = \sum_i \phi_i$	$\Phi_4^+ = -90°$		$\Phi_5^+ = -100°$		$\Phi_6^+ = -83°$	
						
-h -k -l	214	340°	511	212°	$21\bar{5}$	295°
h′ k′ l′	$1\bar{1}\bar{3}$	20°	$\bar{1}\bar{1}\bar{1}$	248°	112	309°
h″ k″ l″	$\bar{3}0\bar{1}$	90°	$\bar{4}00$	0°	$\bar{3}\bar{2}3$	199°
$\Phi = \sum_i \phi_i$	$\Phi_4^+ = 90°$		$\Phi_5^+ = 100°$		$\Phi_6^+ = 83°$	
						

Correlation of the Atropisomers with their Retention Times on a Chiral Phase

The analysis shows that for the chosen crystal, lactone **2** has the *P*-helical form. For a further rapid stereochemical correlation of different lactone samples, we additionally developed a chromatographic enantiomer analysis on a chiral HPLC phase. Optimum results were obtained by chromatography on a Chiracel OF (Daicel Chem. Ind.) phase [length, 25 cm; temp., -10°C; eluent, 2-propanol/n-hexane (25 : 75); UV-detection at 280 nm]. By comparison of racemic material with the investigated crystal and with further single crystals, we could correlate the retention times to the absolute configuration of the respective isomers (*M*-**2**: R_t = 26.7 min, *P*-**2**: R_t = 35.8 min). By investigating a larger number of crystals, we were able to show that both the *M*- and the *P*-isomers crystallize from racemic solution in enantiomerically pure form.

Conclusions

The determination of the absolute configuration of **2** by multiple scattering X-ray experiments presented in this paper perfectly complements the chemical and chiroptical methods usually applied.[16,17] The specific additional value of this methodology becomes apparent in the stereoanalysis of configuratively unstable chiral substances, since the isomerization is inhibited in the crystal, so that no particular low temperature precautions have to been taken. Investigations on the experimental and computational determination of the atropisomerization barriers in dependence of the substituents R is presently in progress.

EXPERIMENTAL

Multiple scattering X-ray experimental investigation of **2**:[18]

The determination of the absolute structure was preceded by a complete data collection with 8147 reflections. The unique data set consisted of 1457 (1436 with $I \geq 0$) reflections. The crystal was a suitable sample with dimensions: 0.3 x 0.3 x 0.4 mm^3. Structure parameters were: space group $P2_12_12_1$, Z=4, a = 16.1299(4) Å , b = 10.1859(3) Å , c = 9.6648(3) Å , $\alpha, \beta, \gamma = 90°$. The results of the structure determination agree with the data previously obtained.[6] The used diffractometer for the structure determination was a modified PW1100 with $Mo - K_{\alpha 1}$ radiation.

The number of least squares parameters was 246, the weighting scheme was $w = 1/\sigma(F)$ and $(\Delta/\sigma) \leq 0.01$. The difference density minimum and maximum values were: $(\Delta\varrho)_{min} = -0.31 e\text{Å}^{-3}$ and $(\Delta\varrho)_{max} = +0.17 e\text{Å}^{-3}$. Structure refinement led to $R = 0.040$ and $R_w = 0.037$. Table 1 shows the structure factors and their phases used for the determination of the absolute configuration and the changes of the recorded intensities on an arbitrary scale. All measurements are in accordance with the triplet phases calculated on the basis of the refined coordinates. The plots represent the relative changes of the intensity of the primary reflection. Notice that the full width at half maximum of the intensity does not exceed 0.03 degrees for any of the triplets. The triplets Φ_3, Φ_4 and Φ_5 were corrected for Umweganregung and Aufhellung.

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REFERENCES

1. "Novel Concepts in Directed Biaryl Synthesis", part 54; for part 53, see Bringmann, G.; Ledermann, A.; Stahl, M.; Gulden, K.-P. *Tetrahedron* **1995**, *51*, 9353–9360.
2. Bringmann, G.; Hartung, T.; Göbel, L.; Schupp, O.; Ewers, C.L.J.; Schöner, B.; Zagst, R.; Peters, K.; von Schnering, H.G.; Burschka, C. *Liebigs Ann. Chem.* **1992**, 225-232.
3. a) Bringmann, G.; Göbel, L.; Schupp, O. *GIT Fachz. Lab.* **1993**, 189-200; b) Bringmann, G.; Schupp, O. *South African J. Chem.* **1994**, *49*, 83-102; c) Bringmann, G.; Harmsen, S.; Schupp, O.; Walter, R. in *Stereoselective Reactions of Metal-Activated Molecules*; Werner, H.; Sundermeyer, J., Eds.; Vieweg: Braunschweig, 1995, pp. 137-142.
4. Bringmann, G.; Hartung, T. *Tetrahedron*, **1993**, *49*, 7891-7902.
5. Lactone **2** was synthesized according ref. 2; spectroscopic details (IR, NMR, MS and combustion analysis) can be obtained from the authors on request.
6. Peters, K.; Peters, E.-M.; von Schnering, H.G.; Bringmann, G.; Schupp, O. *Z. Kristallogr.* **1995**, *210*, 49-50.
7. Bringmann, G.; Hartung, T.; Kröcher, O.; Gulden, K.-P.; Lange, J.; Burzlaff, H. *Tetrahedron* **1994**, *50*, 2831-2840.
8. Hümmer, K.; Billy, H. *Acta Cryst.* **1986**, *A42*, 127-133.
9. Billy, H.; Burzlaff, H.; Hümmer, K. *Acta Cryst.* **1984**, *A40, Suppl. C*, 409-410.
10. Hümmer, K.; Weckert, E.; Bondza, H. *Acta Cryst.* **1989**, *A45*, 182-187.
11. Hümmer, K.; Billy, H. *Acta Cryst.* **1986**, *A42*, 127-133.
12. Moon, R.M.; Shull, C.G. *Acta Cryst.* **1964**, *17*, 805-812.
13. Burzlaff, H.; Hümmer, K.; Rothammel, W.; Schäfer, G.; Weckert, H.; Bestmann, J.; Roth, D. *Acta Cryst.* **1989**, *B45*, 303-306.
14. Weckert, E.; Hümmer, K.; Addae-Mensah, I.; Achenbach, H. *Phytochemistry* **1992**, *31*, 2170-2172.
15. Weckert, E.; Hümmer, K.; Dominguez, X.A.; Horn, K.; Achenbach, H. *Phytochemistry* **1993**, *33*, 447-448.
16. Krow, G. *Top. Stereochem.* **1970**, *5*, 31-68.
17. Bringmann, G.; Gulden, K.-P.; Busse, H.; Fleischauer, J.; Kramer, B.; Zobel, E. *Tetrahedron* **1993**, *49*, 3305-3312.
18. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 IEW. Any request should be accompanied by the full literature citation for this communication.

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