Structure and Dynamics of Free and Metallated Benzonaphthopyranones and -Pyranes

Gerhard Bringmann*, Holger Busse, Stefan Güssregen, Bernd Schöner, and Rainer Zagst

Institute of Organic Chemistry, Am Hubland, W-8700 Würzburg, Germany

Christian Burschka

Institute of Inorganic Chemistry, Am Hubland, W-8700 Würzburg, Germany

Summary

First calculations of the structures of metal-free and complexed biaryl lactones and their confirmation by X-ray crystallography, the search for the transition states of their helimerization processes, and the spectroscopic determination of the helimerization barriers of related cyclic ethers by DNMR are reported.

Introduction

The directed, stereoselective ring opening of "axially prostereogenic" biaryl lactones is not only of high synthetic value [1], but also of great mechanistic importance, since it is based on an unprecedented novel principle in stereocontrol: A biaryl axis that is already present in the molecule but that does not yet constitute a stable element of chirality is transformed into a configurationally stable axis in a stereocontrolled, atropisomer-selective way. For a better mechanistic understanding of this novel directed "twisting process", a detailed knowledge of the structural and energetic properties of the involved species and the determination of the transition states of the interconversion are of high interest.

Calculation of "Axially Prostereogenic" Biaryl Lactones

In the previous paper, we have reported on the synthesis of a whole series of new lactones **1**, with a broad variety of residues R. Despite the fact that most of these bridged biaryls are not differentiated into stable atropisomers, they are not flat at all: As our semiempirical calculations (MNDO-AM1 [2]) show, they are severely, helicene-like distorted. The extent of this distorsion depends on the size of the *ortho*-substituent R. The high reliability of these calculations can be seen by the comparison with the structures of the actual compounds measured by X-ray diffraction [3], showing a nearly perfect match with the calculated structures, *e.g.* for **1b** (see fig.; solid line: calculated structure; dotted line: structure in the crystal).
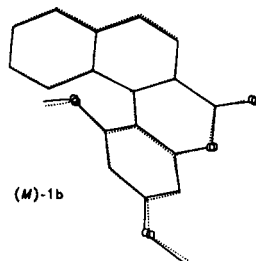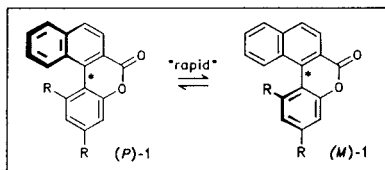
1-3	a	b	c	d	e	f
R	H	OMe	Me	Et	i Pr	t Bu

Calculation of Transition States
for Helimerization Processes of the Lactones 1

In the simplest possible case, a planar geometry of the ring atoms might be expected for the transition state of the interconversion of the two helimeric conformers (P)-1 and (M)-1. The SADDLE option, as included in MOPAC [2], allowed a localization of a planar transition state for the lactones 1a-c. In order to test whether the obtained structures are suited as transition states, the force constant matrix was calculated after optimization of the structure gradients. Yet, only in the case of the unsubstituted lactone 1a, exactly *one* negative normal mode could be attributed, supporting the chemical relevance of this transition state. The lactones with higher steric hindrance exhibit several non-allowed negative normal modes, though with a dominance of rotation of the substituents. Should future calculations to lower the number of those negative modes (IRC, DRC, EF [2]) still not be satisfying, a non-planar transition state, far more difficult to locate, must be postulated. With reference to the geometric similarity of the helimers and the transition state, this would lead to an asymmetric reaction path.

Determination of the Activation Barrier
for Helimerization Processes of Ether-Bridged Biaryls 2

Regrettably, lactones of type 1a-c do not offer the possibility for investigating the rate of the helimerization process, due to the lack of diastereotopic nuclei that become enantiotopic at higher temperatures. Only the lactones 1d and 1e, bearing ethyl and isopropyl groups next to the biaryl axis, show this property, but they normally have no *synthetic* significance in natural products synthesis. For this reason, we aimed at an initial investigation of the corresponding cyclic ethers 2, since they all have diastereotopic/enantiotopic benzylic protons. By comparison of the helimerization barriers of the cyclic ethers 2d and 2e with those of the corresponding energies for the lactones 1d and 1e, a rescaling also for the simple lactones 1a-c should be possible. As a first step in this direction, the activation barrier for the atropiso-merization process of the ether 2c was investigated. Under additional incorporation of long
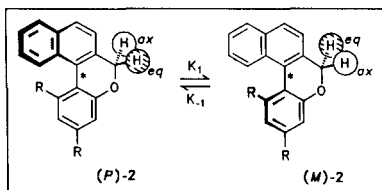
for R = CH₃:

$\Delta G^\dagger = 20.6 \pm 0.1$ kcal mol⁻¹ (298 K)

(by DNMR)

range couplings, the spectra were simulated using the program DNMR5 by Binsch *et al.* [4]. Based on the Eyring-equation, the free activation enthalpy $\Delta G^\ddagger$ for the dimethyl compound **2c** was determined to be 20.47 ± 0.14 kcal mol⁻¹ at 298 K.

Calculation of the Intermediate Lactols and Metal Lactolates 3

The calculation of structures and activation barriers for lactones and cyclic ethers is simultaneously considered as simplified preliminary models for the really relevant species: the intermediate lactols and metal lactolates - the compounds that are directly involved in the interesting stereoselective ring opening process. Besides the helical ring system, they contain an additional stereocenter, so that no longer an enantiomerization process is being investigated, but the interconversion of diastereomers, which makes their investigation far more complex. Semiempirical calculations give access to the structures of these stereoisomers, as well as their energies and their dipole moments, including hydrogen bonds and stability in different solvents. Thus, the structure of **(M)-3a** ("ML$_n$" = H; pseudoaxial position of OH) was calculated to be ~1.8 kcal mol⁻¹ more stable than **(P)-3b** ("ML$_n$" = H; pseudoequatorial position of OH), predicting an anomeric-like effect.

(P)-3b
(calculated for ML$_n$ = H)

(M)-3b
(calculated for ML$_n$ = H)
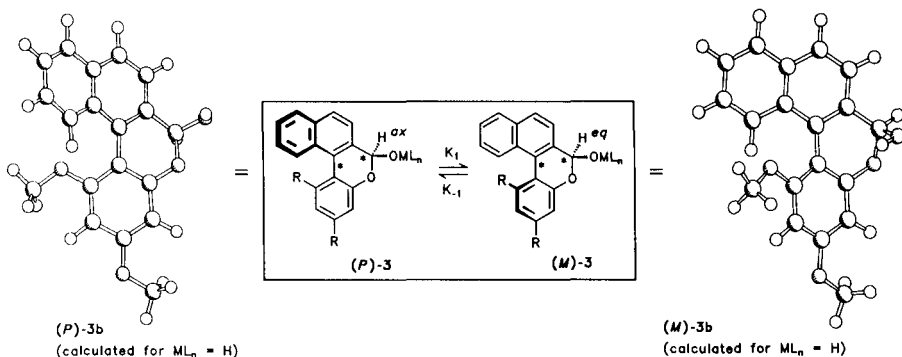
First calculations of metal lactolates, exemplarily starting with Zn and Li species, are under investigation.

Acknowledgements

References

Part 7 in the series "Novel Concepts in Directed Biaryl Synthesis"; for part 6, see the preceding paper of this volume.

[1] a) G. Bringmann, R. Walter, R. Weirich, *Angew. Chem.* **1990**, *102*, 1006-1019; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977-991. - b) G. Bringmann, R. Walter, R. Weirich, *Methods of Org. Chem. (Houben-Weyl)*, E22, in press.

[2] QCPE #455 MOPAC: A General Molecular Orbital Package (Version 6.0) J.J.P. Stewart, J. Frank Seiler Research Laboratory, United Air Force Academy, CO 80840. See handbook and lit. cited therein.

[3] G. Bringmann, T. Hartung, L. Göbel, O. Schupp, Ch.L.J. Ewers, B. Schöner, R. Zagst, K. Peters, ᵀ.G. von Schnering, Ch. Burschka, *Liebigs Ann. Chem.*, submitted.

[4] D.S. Stephenson, G. Binsch, *J. Magn. Reson.* **1978**, *32*, 145-152, and lit. cited therein.