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Restricted Helix Inversion in Chiral 2,18-Bridged Biliverdins

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Summary. The energy barrier to helix inversion in biliverdin is doubled if the pyrrolinone rings are bonded by a four-link chain as present in the chiral diastereoisomers of 2,18-(1′,4′-dimethoxybutane-1′,4′-diyl)-8,12-bis(2″-methoxycarbonylethyl)-3,7,13,17-tetramethyl-1,19-(21 *H*,24 *H*)-bilindion **1** and its hydroxy derivative **2**. The torsional restrictions thus imposed on the bilatriene moiety provide the basis for resolution by first-order asymmetric transformation with optically active mandelic acid. Interconversion barriers at 293 K range from 85 to 90 kJ mol^{-1} and were determined monitoring the rate of isomerization processes (*M*-*RR*)-**1 b** $\rightleftharpoons$ (*P*-*RR*)-**1 a**, (*P*-*SS*)-**1 b** $\rightleftharpoons$ (*M*-*SS*)-**1 a**, and the racemization process (*P*-*RS*)-**1 c** $\rightleftharpoons$ (*M*-*RS*)-**1 c** by c.d. spectroscopy. Similar results were obtained with the bridged biliverdins **2**.

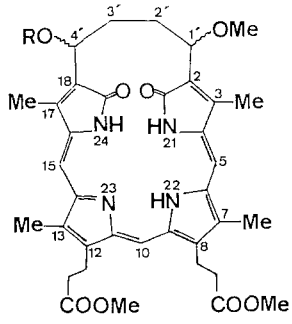
Keywords. Helix inversion; Bridged biliverdins; Interconversion barrier; Circular dichroism.

Behinderung der Helix-Interkonversion in 2,18-überbrückten Biliverdinen

Zusammenfassung. Die Energiebarriere für die Helixinversion von Biliverdinen läßt sich durch Überbrücken der Pyrrolinonringe mit einer C-4 Einheit auf das Doppelte erhöhen. Derartige Verhältnisse liegen in den chiralen Diastereomeren des 2,18-(1′,4′-Dimethoxybutan-1′,4′-diyl)-8,12-bis(2″-methoxycarbonylethyl)-3,7,13,17-tetramethyl-1,19-(21 *H*,24 *H*)-bilindions **1** und seines Hydroxyabkömmlings **2** vor. Die dadurch bedingten Torsionsrestriktionen im Bilatrienteil stellen die Grundlage für eine Spaltung durch asymmetrische Umwandlung erster Art mit optisch aktiver Mandelsäure dar. Die Barrieren liegen zwischen 85 und 90 kJ mol^{-1} (293 K) und wurden aus der Geschwindigkeit der Isomerisierungsprozesse (*M*-*RR*)-**1 b** $\rightleftharpoons$ (*P*-*RR*)-**1 a**, (*P*-*SS*)-**1 b** $\rightleftharpoons$ (*M*-*SS*)-**1 a**, sowie des Razemisierungsprozesses (*P*-*RS*)-**1 c** $\rightleftharpoons$ (*M*-*RS*)-**1 c** mittels Circulardichroismus bestimmt. Ähnliche Ergebnisse wurden für die Isomeren von **2** erhalten.

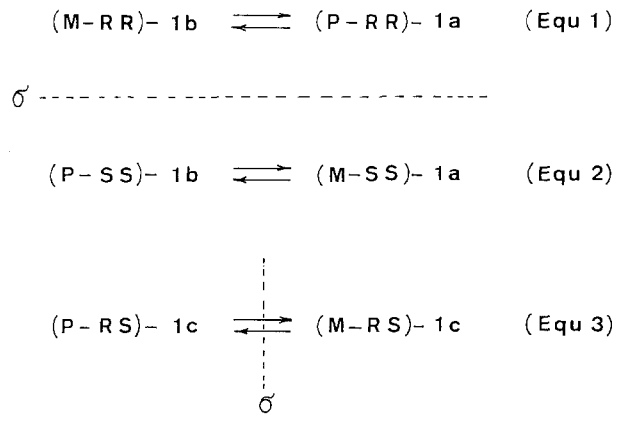
Introduction

In a previous paper [1] we described the synthesis and isolation of three diastereoisomeric pairs of enantiomers predicted for the bridged biliverdin **1**, viz. *rac.* **1 a**, *rac.* **1 b**, and *rac.* **1 c**. Since *rac.* **1 a** and *rac.* **1 b** are homochiral at positions C-1′ and C-4′ configurational change of the third chirality element—the helical shaped bilatriene backbone—results in mutual conversion (equilibria 1 and 2). In contradistinction $M \rightleftharpoons P$ helix inversion in the disastereoisomer **1 c** directly affords the corresponding antipode (equilibrium 3) [2]. Interconversion is thermally induced and at ambient temperatures equilibria 1–3 are attained within less than 30



1	2
R = *Me*	*R* = H
(*M-SS*)-**1a**	(*M-SS*)-**2a**
(*P-RR*)-**1a**	(*P-RR*)-**2a**
(*M-RR*)-**1b**	(*M-RR*)-**2b**
(*P-SS*)-**1b**	(*P-SS*)-**2b**
(*M-RS*)-**1c**	
(*P-RS*)-**1c**	

minutes. Nevertheless at moderate low temperatures (258 K) isomers *rac.* **1a** and *rac.* **1b** can be separated by t.l.c. [1]. This implies the interconversion barrier of the bilatriene helix in compounds **1** to be drastically enhanced if compared with non-bridged derivatives. For the latter rates have been found to be rapid on the n.m.r. time scale even at 258 K. Only if the temperature is drastically decreased down to ca. 200 K appropriate derivatives exhibit two different spectra indicating the interconversion barrier to be as low as 42 kJ mol^{-1} (200 K) [3]. In contrast mixtures composed from *rac.* **1a** and *rac.* **1b** show individual spectra even at temperatures up to 403 K [1]. In continuing our efforts into the stereochemistry of bridged biliverdins we also succeeded in the resolution of *rac.* **1a** and *rac.* **1b** into four stereoisomeric entities (*M-SS*)-**1a**, (*P-RR*)-**1a**, (*M-RR*)-**1b**, and (*P-SS*)-**1b** by first order asymmetric transformation techniques [4]. In this notation configurational symbols *R* and *S* refer to positions C-1′ and C-4′, respectively. These compounds display considerable optical activity which comprises an outstanding feature of the inherently chiral bilatriene helix, in common with non-bridged derivatives [5]. Since isomers **1a** and **1b** are pairwise related through equilibria 1 and 2 optically active species offer the opportunity for a convenient determination of the energy barrier to helix inversion via c.d. The investigations performed on **1a** and **1b** are supplemented by a kinetic study of the racemization process of **1c** isomers (equation 3) and by results with the hydroxy derivative **2**, a synthetic precursor of **1**.



Results and Discussion

Determination of the barrier to helix inversion succeeded with a kinetic investigation of respective equations (1)–(3). At an initaial stage of this study the rate of isomerization *rac.* **1b** $\rightleftharpoons$ *rac.* **1a** [equilibria (1) and (2)] was followed by u.v.-visible spectroscopy and therefore did not require an optically active auxiliary.

However, the reliability of this seemingly most convenient method critically depends on spectral differences between diastereoisomers. Since u.v.-visible spectra of *rac.* **1a** and *rac.* **1b** closely resemble each other [1] relatively large errors inherent to the mode of detection prevent a meaningful temperature dependence to be performed. In Table 1 the $\Delta G^{\neq}$ values obtained starting from different isomer ratios are compiled.

The second approach to the investigation of inversion rates used is likewise based on a combination of equations 1 and 2 but different in that starting materials contained the *M*-helical species (*M-SS*)-**1a** and (*M-RR*)-**1b** in excess (h.e. [6] ca. 50%, by ^{1}H n.m.r.). This overpopulation was generated by first-order asymmetric transformation at room temperature adding (*R*)-(−)-mandelic acid to a mixture of *rac.* **1a** and *rac.* **1b** in benzene. Thereby equilibria 1 and 2 are shifted to opposite sides due to the kinetic lability of the bilatriene helix and the discriminating influence of (*R*)-(−)-mandelic acid favouring the *M*-helical species. If this influence is removed by addition of ethanol [7] or by neutralization with triethylamine equilibria are re-established and c.d. decreases with time until a value of zero is reached [8]. This process was monitored at λ = 653 nm over the temperature range from 277.1 to 311.8 K. The kinetic data obtained are compiled in Table 2. Individual parameters for helix inversion of **1a** and **1b** type species have been evaluated taking into account their equilibrium constants K in ethanol (Table 2). Since c.d. values are large before re-inversion takes place the temperature dependence of $\Delta G^{\neq}$ could be performed quite accurately.

By the same method interconversion barriers of diastereoisomers **2** were established (Table 3). Attainment of equilibria 1 and 2 has also been followed separately starting from (*M-SS*)-**1a** and (*M-RR*)-**1b**, respectively (Table 3). Helix inversion in the third diastereoisomer **1c** results in formation of the respective antipode [Equ.

Table 1. Kinetics of isomerization *rac.* **1b** $\rightleftharpoons$ *rac.* **1a** and barriers to helix interconversion $\Delta G^{\neq}$ at 293.5 K as monitored by u.v.-visible spectroscopy at λ = 662 nm in ethanol of ca. $1.2 \cdot 10^{-4} M$ solutions

Initial isomer ratio	k_{obs}[a]	$t_{1/2}$[b]	k_a	k_b	$\Delta G_a^{\neq}$[c]	$\Delta G_b^{\neq}$[c]
rac. **1a** : *rac.* **1b**	$s^{-1} \cdot 10^3$	s	$s^{-1} \cdot 10^3$		kJ mol^{-1}	
1 : 0	3.14	221	0.897	2.24	89.0	86.7
0 : 1	4.27	162	1.22	3.05	88.2	86.0
3 : 7[d]	3.69	188	1.05	2.63	88.6	86.3

[a] Mean values from at least three measurements; error $\pm 0.6 \cdot 10^{-3}$ s^{-1}; correlation 0.97–0.99; individual parameters followed from the equilibration constant in ethanol (see Table 2)

[b] Half-time of equilibration

[c] Error ± 0.5 kJ mol^{-1}

[d] Obtained by equilibration in benzene prior to injection

Table 2. Kinetics of helix interconversion and barriers $\Delta G^{\neq}$ starting with a mixture **1a**:**1b** in which the *M*-helical species are in excess (h.e. ca. 50%) at various temperatures as monitored by c.d. at $\lambda = 653$ nm in ethanol of ca. $5 \cdot 10^{-5} M$ solutions[a]

T(K)	K[b]	k_{obs}[c]	$t_{1/2}$[d]	k_a	k_b	$\Delta G_a^{\neq}$	$\Delta G_b^{\neq}$
		$s^{-1} \cdot 10^3$	s	$s^{-1} \cdot 10^3$		kJ mol^{-1}	
277.1	2.6	0.425	1630	0.118	0.307	88.53	86.33
293.5	2.5	3.01	230	0.860	2.15	89.07	86.83
302.6	2.4	7.97	87	2.34	5.63	89.39	87.18
311.8	2.3	18.7	37	5.67	13.0	89.89	87.74
200[e]						85.3	83.1

[a] A plot $\Delta G^{\neq}/T$ versus $1/T$ for **1a** and **1b** species gave straight lines. From corresponding slopes and intercepts $\Delta H_a^{\neq} = 77.7$ kJ mol^{-1}, $\Delta S_a^{\neq} = -38$ J mol^{-1}K^{-1} (correlation = 0.9998) and $\Delta H_b^{\neq} = 75.1$ kJ mol^{-1}, $\Delta S_b^{\neq} = -40$ J mol^{-1}K^{-1} (correlation = 0.9999) was obtained

[b] Determined by ^{1}H n.m.r.

[c] Correlation = 0.9998

[d] See footnote b to Table 1

[e] Extrapolated values

(3)]. After partial resolution with (*R*)-(−)-mandelic acid in benzene (h.e. ca. 50%) (*M-RS*)-**1c** was subjected to conditions for racemization by neutralizing, the influence of the optically active auxiliary (Table 3).

An inspection of interconversion barriers $\Delta G^{\neq}$ of **1a** and **1b** species summarized in Table 3 reveals independence from both method and source the values ranging from 86 to 89 kJ mol^{-1} (293.5 K). Results obtained by c.d. spectroscopy are almost superimposable. Moreover barriers for isomer **1c** and even for the hydroxy derivatives **2a** and **2b** excellently conform with the above values.

Since positions of equilibria 1 and 2 can be controlled by the solvent [1, 4] an interpretation of differences in $\Delta G^{\neq}$ between **1a** and **1b** species seems less meaningful. Similar values as obtained for ethanol are also found for chloroform and dichloromethane solutions favouring the population of the **1a** species (Table 4). If solvents are considered in which the **1b** species predominate (benzene, tetrahydrofurane, carbon tetrachloride) $\Delta G^{\neq}$ values are simply interchanged. No increase of *both* barriers occurs and neither a decrease. This implies that external influence are of minor importance. Moreover, values remain invariably for pure and acidic ethanol suggesting that hydrogen bonding between nitrogens does not contribute to the enhancement of barriers observed. The inversion path most likely proceeds via slight changes of torsional angles thus rendering the possibility for the pyrrolinone entities to pass each other.

If extrapolated to 200 K (Table 2) the barriers found for **1a** and **1b** are still twice as large as those reported for non-bridged compounds ($\Delta G^{\neq}$ ca. 42 kJ mol^{-1} (200 K)) [3]. However, though inversion is markedly hindered the helix geometry in the ground state is not altered significantly by the four-membered bridge as follows from a comparison of u.v.-visible spectra [1]. This implies that **1** and **2** essentially represent strain-free molecules. Therefore the *N*-21–*N*-24 bridged biliverdin reported in Ref. [9] markedly differs from the bridged derivatives investi-

Table 3. Interconversion barriers $\Delta G^{\neq}$ of the bilatriene helix[a] in 2,18-bridged biliverdins as obtained by kinetic studies of different equilibria as monitored by u.v.-visible[b] or c.d.[c] spectroscopy in ethanol of ca. $5 \cdot 10^{-5} M$ solutions at 293.5 K (starting isomers in excess underlined)

Equilibrium	Observable	$\Delta G_a^{\neq}$	$\Delta G_b^{\neq}$
		kJ mol^{-1}	
rac. **1b**⇌*rac.* **1a**	u.v.-visible	89.0	86.7
rac. **1b**⇌*rac.* **1a**	u.v.-visible	88.2	86.0
(*M-RR*)-**1b**⇌(*P-RR*)-**1a** (*P-SS*)-**1b**⇌(*M-SS*)-**1a**	c.d.	89.1	86.8
(*M-RR*)-**1b**⇌(*P-RR*)-**1a**	c.d.	89.1	86.8
(*P-SS*)-**1b**⇌(*M-SS*)-**1a**	c.d.	89.0	86.7
(*P-RS*)-**1c**⇌(*M-RS*)-**1c**	c.d.	86.2	
(*M-RR*)-**2b**⇌(*P-RR*)-**2a** (*P-SS*)-**2b**⇌(*M-SS*)-**2a**	c.d.	88.2	85.7

[a] Equilibrium constants needed for evaluation of individual parameters were taken from Refs. [1] and [4]
[b] Error ± 0.5 kJ mol^{-1}
[c] Error ± 0.1 kJ mol^{-1}

Table 4. Equilibrium constants K (**1a** : **1b**)[a], kinetics, and interconversion barriers $\Delta G^{\neq}$ (293.5 K)[b] of the bilatriene helix in various solvents of ca. $5 \cdot 10^{-5} M$ solutions[c]

Solvent	K	k_{obs}[d]	$t_{1/2}$[e]	$\Delta G_a^{\neq}$	$\Delta G_b^{\neq}$
		$s^{-1} \cdot 10^3$	s	kJ mol^{-1}	
Dichloromethane	4.0	2.85	243	90.1	86.8
Chloroform	2.7	1.88	368	90.4	88.0
Ethanol[f]	2.5	3.01	230	89.1	86.8
Benzene	0.45	4.68	148	85.9	87.9
Tetrahydrofurane	0.37	6.08	112	85.1	87.6
Carbon tetrachloride	0.21	3.87	178	85.9	89.8

[a] Values taken from Ref. [4]
[b] Error ± 0.1 kJ mol^{-1}
[c] Method applied see caption to Table 2
[d] Correlation > 0.9997
[e] See footnote b to Table 1
[f] If equilibration is performed in acidic ethanol containing five equivalents of hydrochloric acid no change in rates occur

gated here in that enhancement of interconversion barrier is associated with appreciable deviations from the geometry of non-bridged compounds.

Experimental

Synthesis [1, 10] and resolution [4] of diastereoisomers *rac.* **1a** and *rac.* **1b** has been described elsewhere. Enrichment of *M*-helical species in the hydroxy compounds *rac.* **2a** and *rac.* **2b** was

performed by first-order asymmetric transformation in analogy to *rac.* **1a** and *rac* **1b**. The same procedure was used for resolution of *rac.* **1c.** H.e.s. achieved for **2** (h.e. ca. 30%, $\Delta\varepsilon$ (653 nm) = −40) and **1c** (h.e. ca. 50%, $\Delta\varepsilon$ (653 nm) = −67) were estimated by matching with the c.d. parameters reported for optically active **1a** and **1b** [4]. ^{1}H N.m.r. spectra (250 MHz) were obtained with a Bruker WM 250 spectrometer in [$^2H_6$] benzene and [$^2H_6$] ethanol with $SiMe_4$ as internal reference. C.d. and u.v.-visible spectra were performed with a Jobin Yvon Mark III and a Perkin Elmer Lambda 7 instrument (equipped with data station 3600), respectively in thermostatted (±0.1 K) quartz cuvettes of variable path length (0.01–1 cm) in spectroscopic grade (Uvasol, Merck) benzene, chloroform, carbon tetrachloride (all chromatographed on alumina prior to use), dichloromethane, ethanol, and tetrahydrofurane (distilled from $LiAlH_4$ prior to use). (*R*)-(−)-mandelic acid [Fluka, $[\alpha]_D^{20}$ = −142.2° (*c* 5, H_2O)] showed satisfactory optical rotation (Perkin Elmer 241 polarimeter).

Kinetic Measurements of Racemic Species

Stock solutions of *rac.* **1a** and *rac.* **1b** (each ca. $10^{-2}M$, dichloromethane) were kept at −30°C. Then ca. 25 µl of the respective solution were injeted in pre-thermostatted cuvettes containing 2 ml ethanol and the absorbance at λ = 662 nm was followed with time.

Kinetic Measurements of Optically Active Species

Ca. 10 µl of the respective solution of **1a**+**1b** [h.e. = 54%, $\Delta\varepsilon$ (653 nm) = −72], **2a**+**2b** [h.e. ca. 30%, $\Delta\varepsilon$ (653 nm) = −40], and **1c** [h.e. ca. 50%, $\Delta\varepsilon$ (653 nm) = −67] in benzene (each ca. $10^{-2}M$) enriched in *M*-helical species due to the presence of three equivalents of (*R*)-(−)-mandelic acid were injected into the pre-thermostatted c.d. cuvette containing 2 ml of the appropriate solvent and stoichiometric amounts of triethylamine to neutralize the discriminating influence of (*R*)-(−)-mandelic acid. In the case of ethanol and tetrahydrofurane addition of the amine may be omitted [7]. The c.d. at λ = 653 nm was then followed with time. No influence of the base occasionally added on rates could be observed.

For kinetic studies on individual isomers (*M-SS*)-**1a** [h.e. > 95%, $\Delta\varepsilon$ (653 nm) = −141] and (*M-RR*)-**1b** [h.e. > 95%, $\Delta\varepsilon$ (652 nm) = −126] stock solutions (each ca. $10^{-2}M$, dichloromethane) were kept at −30°C and injected into ethanol as described above.

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References and Notes

[1] Krois D., Lehner H. (in press) J. Chem. Soc. Perkin Trans. I
[2] Note that (*P-RS*)-**1c** ≡ (*P-SR*)-**1c** and (*M-RS*)-**1c** ≡ (*M-SR*)-**1c**
[3] Lehner H., Riemer W., Schaffner K. (1979) Liebings Ann. Chem. **1979**: 1798
[4] Krois D., Lehner H. (in press) J. Chem. Soc. Perkin Trans. II
[5] Krois D., Lehner H, (1985) J. Chem. Soc. Perkin Trans. II **1985**: 421; Krois D., Lehner H. (1987) J. Chem. Soc. Perkin Trans. II **1987**: 219, 1523
[6] The term h.e. (helical excess) used throughout this paper bears the advantage to be applicable to *both* enantiomers *and* diastereoisomers
[7] Many oxygenated solvents severely compete with chiral discriminating forces built up between (*R*)-(−)-mandelic acid and the bilatriene entity. Thus addition of ethanol or tetrahydrofurane leads to a complete breakdown of discriminatory efficiency

[8] Since the amount of species of (*RR*) configuration always equals that of (*SS*) configuration irrespective of the h.e. achieved the relation $\times_{(M\text{-}RR)-\mathbf{1b}} - \times_{(P\text{-}SS)-\mathbf{1b}} = \times_{(M\text{-}SS)-\mathbf{1a}} - \times_{(P\text{-}RR)-\mathbf{1a}}$ follows which means that the ratio of **1 a** and **1 b** type species *detected by c.d.* remains invariant during attainment of equilibria. This seems important in view of the slight differences in c.d. spectra of diastereoisomers [4]. The same arguments apply for the isomers of **2**

[9] Falk H., Thirring K. (1981) Tetrahedron **37**: 761

[10] Krois D., Lehner H. (1989) Monatsh. Chem. **120**: 575

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