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Hydration and Hemiacetal Formation in Oxo-[*m*.*n*]Metacyclophanes

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[*m*.2]Metacyclophanes with an oxo-function in the C_2 bridge exhibit an enhanced carbonyl reactivity towards nucleophiles. The equilibrium constants for hydration and hemiacetal formation markedly decrease as *m* increases and qualitatively correlate with the ring strain present in the parent hydrocarbon. [*m*.*n*]Metacyclophanes with $m,n \geq 3$ are almost free from intraanular steric strain. Accordingly, oxo-functions in the bridges do not exhibit an appreciable enhancement of reactivity.

(Keywords: Oxo-[m.n]metacyclophanes; Hydrates; Hemiacetals; Ring Strain)

Hydrat- und Hemiacetalbildung bei Oxo-[m.n]metacyclophanen

[*m*.2]Metacyclophane mit einer Oxo-Funktion in der C_2-Brücke zeigen eine erhöhte Carbonylreaktivität gegenüber Nucleophilen. Die Gleichgewichtskonstanten für die Hydratisierung und Hemiacetalbildung nehmen mit steigendem *m* ab und korrelieren qualitativ mit der Ringspannung des entsprechenden Kohlenwasserstoffs. Dagegen sind [*m*.*n*]Metacyclophane mit $m,n \geq 3$ weitgehend frei von intraanularen sterischen Spannungen. Oxo-Funktionen in den Brücken besitzen deshalb keine nennenswert erhöhte Carbonylreaktivität.

Introduction

The most intriguing feature of [2.2]metacyclophane-1,10-dione (**1**) is the formation of a stable dihydrate[1]. In many respects there is a great similarity with cyclopropanone, which for long time has been regarded as the only simple ketone exhibiting this outstanding property[2]. For both compounds the driving force for adduct formation can be rationalized solely in terms of relaxation of strain on changing the coordination number from three to four[1,3]. Obviously, strain imposed

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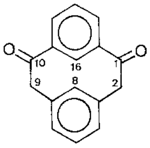

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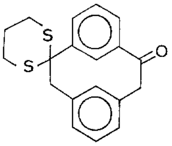

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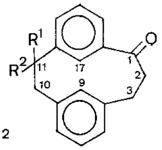
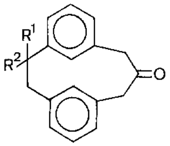
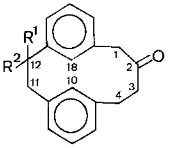
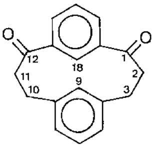






R^1	R^2			
$=O$		3a	4a	5a
OH	OH	3b	4b	5b
OCH_3	OH	3c	4c	5c
OH	OCH_3	3d	4d	5d
$-S(CH_2)_3S-$		3e	4e	5e



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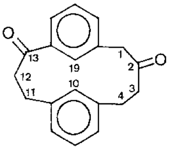

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onto the ring system by introduction of oxo-functions is a prerequisite for the enhanced reactivity observed. As the chain length of [*m* . *n*]metacyclophanes increases the tendency for adduct formation of the parent ketones should decrease. In order to gain more insight into the strain-dependent carbonyl reactivity we have initiated a systematic study on oxo-[*m* . *n*]metacyclophanes. We now report on the behaviour of oxo-[3.2]-, -[3.3]-, -[4.2]-, and -[4.3]-metacyclophanes for which a synthesis has been outlined recently[4,5].

Results and Discussion

The reactions of **3a**, **4a**, and **5a** with water and/or methanol can easily be followed by the time dependent ^{1}H nmr and/or electronic absorption spectra. After 24 h at room temperature equlibrium was attained in all cases. The reactions observed were catalyzed by acids and bases and proved to be fully reversible on evaporation of the solvents *in vacuo* and slight warming. For **5a** only reaction with methanol could be observed, while a hydrate could not be detected by the methods employed.

When a saturated solution of **4a** in dioxane—water (20% *v*/*v*) was kept at room temperature for 24 h a crystalline precipitate of the hydrate **4b** was formed. It was identified by its ^{1}H nmr, electronic absorption spectrum (Fig. 1) and elemental analysis*. **4b** reversibly looses one equivalent of water on heating above its melting point thereby re-forming **4a**. **4b** represents the second isolable hydrate in the [*m* . *n*]metacyclophane-series[1].

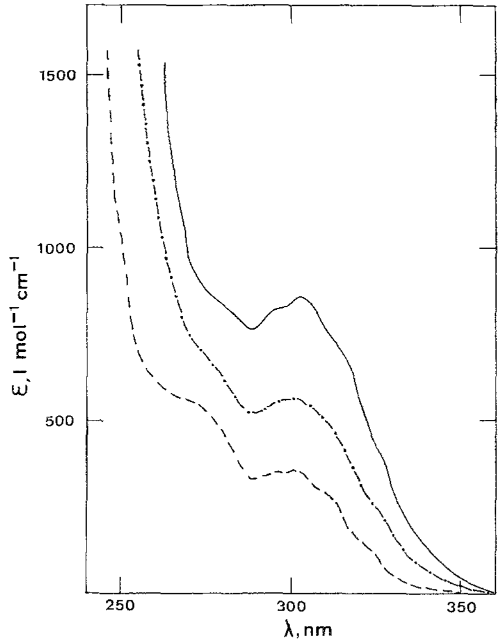

Fig. 1. Electronic absorption spectra of $4.6 \times 10^{-4} M$ solutions of **4a** (———) and the hydrate **4b** (— — —) in dioxane containing 61% *n*/*n* water immediately after solution and after 24 h (—·—·) at equilibrium (room temperature)

The resonance absorption of the intraanular protons and the protons of the C_2 bridge of the species present at the pertinent equilibria

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* Unfortunately, the ir frequencies of the oxo-groups in **4a** are very similar (~ 1 708 cm^{-1})[4]; therefore the ir spectrum of **4b** is not conclusive with respect to the position of the remaining carbonyl group. However for assignment to structure **4b** the same arguments hold true as for the other, not isolable adducts (see below).

Table 1. *^1H nmr parameters (δ, ppm; J, Hz; 250 MHz) and equilibrium population (%) of [3.2]metacyclophan-diones* **3a** *and* **4a** *and adducts formed in dioxane-water (54% n/n) and chloroform-methanol (67% n/n) at 20 °C*

Solvent	Compound	H at C-9 δ	H at C-17 δ	AB-system at C-10 δ_A	δ_B	J_{AB}	%
dioxane-water	**3a**	7.66	7.88	4.29	4.00	16.3	80
	3b	5.13	6.01	3.10	2.56	12.8	20
chloroform-methanol	**3a**	7.59	7.82	4.26	4.03	16.2	36
	3c	5.01	6.08	3.11	2.58	12.6	32
	3d	5.18	5.91	3.23	2.54	12.6	32
dioxane-water	**4a**	6.41	5.62	3.87	3.82	14.7	45
	4b	5.16	5.60	3.11	2.51	12.9	55
chloroform-methanol	**4a**	6.27	5.38	3.90	3.72	14.9	10
	4c	5.09	5.78	3.08	2.56	12.7	45
	4d	5.22	5.48	3.23	2.49	12.5	45

Table 2. *^1H nmr parameters (δ, ppm; 250 MHz) and equilibrium population (%) of [4.2]metacyclophane-2,12-dione* (**5a**) *and adducts formed in chloroform-methanol (67% n/n) at 20 °C**

Compound	H at C-10 δ	H at C-18 δ	H at C-11 δ		%
5a	7.05	7.08	4.07	(A_2)	80
5c, **5d**	5.52	5.81	2.78 2.71	(AB)	20

* Due to the low ring inversion barrier of the [4.2]metacyclophane system[5] the diastereoisomers **5c** and **5d** rapidly interconvert.

are listed in Tables 1 and 2. Accordingly, reaction of the diones with water gives rise to the formation of *one* hydrate while with methanol *two*, almost equipopulated diastereoisomeric hemiacetals are formed. This indicates that only one of the two carbonyl groups present in **3a**, **4a**, and **5a** reacts with the nucleophile, in contrast to the behaviour of [2.2]metacyclophane-1,10-dione (**1**) where both carbonyl groups are subject to nucleophilic attack by water and alcohols[1]. From integration of peak areas the equilibrium populations compiled in Tables 1 and 2 were calculated. The chemical shifts of the protons of the adducts **3b**, **3c**, **3d**, **4b**, **4c**, and **4d** ($\delta_A = 3.08$–3.23 ppm, $\delta_B = 2.49$–2.58 ppm) are characteristic for the absorptions of protons located in α-position to a carbon atom carrying two OH- or one OH- and one OR-group in a C_2 bridge. For comparison, the shift values found for adducts of **1** are $\delta_A = 3.00\text{-}3.24$, $\delta_B = 2.34\text{-}2.40$ ppm[1]. Expectedly, for the rapidly interconverting[5] diastereoisomeric [4.2]metacyclophane-hemiacetals **5c** and **5d** mean values are obtained, proving again the prefential attack of nucleophiles at the carbonyl group in the C_2 bridge.

Clearly, as the C_2-carbonyl group is blocked selectively as in the ketones **3e**, **4e**, and **5e** no reaction with water or methanol takes place anymore. Likewise, the [3.3]metacyclophane-dione **6** and its isomers[4] as well as the [4.3]metacyclophane-dione **7** do not show any tendency for hydrate- or hemiacetal-formation.

In the [4.2]metacyclophane-dione **5a** the carbonyl reactivity is already too weak to cause appreciable population of the hydrate **5b**. However, if stronger nucleophiles such as methanol or diazomethane[5] are used the enhanced reactivity of the C_2-carbonyl group emerges again.

Plausibly, neither reaction of the carbonyl group at the C_m bridge ($m > 2$) of an [m . 2]metacyclophane nor reaction in any bridge of an [m . n]metacyclophane ($m, n > 2$) accounts for an appreciable relaxation of steric strain by changing the co-ordination number.

Table 3. *Hydration- (K_{HYD}) and hemiacetalisation- (K_{HEM}) equilibrium constants of oxo-[m . n]metacyclophanes at 20 °C*

	1[6]	**2**[6]	**3a**	**4a**	**5a**	**6**	**7**
	$m, n = 2$	$m, n = 2$	$m = 3$, $n = 2$	$m = 3$, $n = 2$	$m = 4$, $n = 2$	$m, n = 3$	$m = 4$, $n = 3$
K_{HYD}	28 (K_1) 3 (K_2)	4.5	0.5	2.3	<0.06	<0.06	<0.06
K_{HEM}	~100 (K_1) 18 (K_2)	29.0	2.7	13.4	0.4	<0.06	<0.06

An inspection of the pertinent equilibrium constants K_{HYD} and K_{HEM} (see Table 3) qualitatively reveals the dependence of the equilibrium position upon the ring strain as expected. The finding that a carbonyl group is by far more reactive if located in a C_2 bridge than in any longer bridge is further corroborated by recent investigations of carbene insertion reactions. The regioselectivity of diazomethane attack has thus been the basis for a convenient synthesis of [3.2]-, [3.3]-, [4.2]-, and [4.3]-metacyclophanes[4,5].

Acknowledgement

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Experimental

For general experimental procedures and apparata see Ref. [1] and [4]. Compounds **3a**, **3e**, **4a**, **4e**, **5a**, **5e**, **6**, and **7** have been prepared as described recently[4,5].

11,11-Dihydroxy-[3.2]metacyclophane-2-one (**4b**)

To a solution of 40 mg **4a** in 1.0 ml dioxane, 0.25 ml water was added and the mixture kept over night at room temperature. The crystalline **4b** (25 mg, 58%) deposited was filtered and washed twice with small portions (0.5 ml) of dioxane and ether, and dried quickly (5 min) under reduced pressure (0.3 mm); mp (sealed capillary tube) 148-152 °C; due to dehydration re-melting yielded the mp of **4a** (109-112 °C)[4]. Found: C 76.3, H 6.0, O 18.1%; Calcd. for $C_{17}H_{16}O_3$ (268.30): C 76.1, H 6.0, O 17.9%; ms (50 °C, 70 eV) (*m/e*): 250 (M^+-H_2O); ir (nujol): 3 400, 3 360 (ν O—H); 1 680 cm^{-1} (ν C=O); uv (dioxane) (ε): 323 s (150), 310 s (300), 303 (360), 294 (340), 270 (530), 335 s nm (6 700); ^{1}H nmr (*THF*-d_8, ambient temperature, 250 MHz): $\delta = 7.55$, 7.27, 7.18, and 5.66 (ABCX, 4H, H at C-13, C-14, C-15, and C-17); 7.16, 7.10, 7.06, and 5.18 (ABCX, 4 H, H at C-6, C-5, C-7, and C-9); 5.57 (s, 1 H, O—H); 5.15 (s, 1 H, O—H); 3.44 and 3.38 (AB, 2 H, $J_{AB} = 14.3$ Hz, H at C-3 or C-1); 3.41 and 3.38 (AB, 2 H, $J_{AB} = 14.8$ Hz, H at C-1 or C-3); 2.98 and 2.44 ppm (AX, 2 H, $J_{AX} = 12.7$ Hz, H at C-10).

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