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SELECTIVE CONFORMATIONAL CHANGES OF CYCLIC SYSTEMS—XII[1]

ENHANCED REACTIVITY OF TEN MEMBERED RING KETONES DUE TO TRANSANULAR STERIC COMPRESSION: HYDRATES AND HEMIKETALS FROM OXO-[2.2]METACYCLOPHANES

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Abstract—The rigid, 10-membered ring ketones incorporated in [2.2]metacyclophanes exhibit a pronounced tendency towards adduct formation with nucleophiles. [2.2]Metacyclophane-1,10-dione (1) readily adds water and alcohols, e.g. in dioxane solution containing 20 n/n water an equilibrium is attained between 1 (9%) and the mono- and dihydrates 1' (55%) and 1'' (36%) respectively. In pure water the equilibrium is further shifted towards the adducts, as revealed by an extrapolation. Equilibration of the dihydrate 1'' which can be isolated in crystalline form gives corresponding results. In methanol the equilibrium mixture consists mostly of the diastereomeric bis-hemiketals **1aa**, **1ee** and **1ae**. A similar behaviour is found for the monoketone 2, 1-propylenethioketal of [2.2]metacyclophane-1,10-dione. The reactions studied are fully reversible on evaporation of the solvents and subsequent warming under reduced pressure.

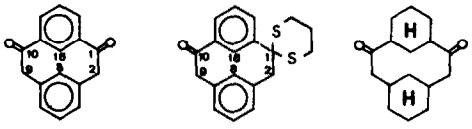
The results are gained from a combinatory evaluation of ^{1}H NMR and absorption spectra of 1 and 2 in solution. The enhanced reactivity of the CO groups in 1 and 2 can be accounted for by a relief of steric strain on rehybridization $sp^2 \rightarrow sp^3$ due to a simultaneous conformational change. In dodecahydro-[2.2]metacyclophane-1,10-dione (3), where a similar relief of strain is not operative an anomalous carbonyl reactivity is not observed.

The reversible addition of water and alcohols to carbonyl compounds yielding hydrates and hemiketals respectively has been a subject of considerable interest in recent years.[2-12] In most cases an enhanced reactivity can be correlated with electronegative substituents in α-position to the CO group.[2] Clearly, adduct formation in simple aliphatic carbonyl compounds is much more familiar with aldehydes than with ketones. Only polyfunctional ketones, e.g. α-di and tri-ketones and some α,β-unsaturated members exhibit a similar behaviour (*cf* Ref. 8 and refs cited therein). In these derivatives one group can likewise be regarded as an electron acceptor.

For ring ketones another aspect must be taken into consideration, i.e. the possibility of a modification of steric strain on changing the coordination number. This may cause either an increase or a decrease of carbonyl reactivity depending on the strain energy bilance of the ketone and the pertinent adducts. Thus, the carbonyl reactivity of cycloalkanones is reduced from cyclopropanone to cyclobutanone; cyclohexanone, however, turns out to be more reactive than cyclopentanone.[4] As a rule the tendency towards adduct formation is less pronounced for larger rings. It may be enhanced, however, if an additional strain is imposed on the ketone which can partially be relaxed on rehybridization $sp^2 \rightarrow sp^3$.[4,13]

Recently it has been shown that the introduction of oxo functions into the bridge of the [2.2]metacyclophane system entails selective conformational changes.[14] Due to the topology of the metacyclophane skeleton oxo-functionalized derivatives can serve as models for strained ten membered ring ketones with fixed geometry.

In this communication we report the equilibria of hydration and hemiketal formation of [2.2]metacyclophane-1,10-dione (1) and its monopropylene thioketal 2 and the conformational changes involved in these reactions.



1 2 3

Scheme 1.

RESULTS

The reactions of 1 and 2 with water and alcohols can easily be observed from the time dependent decrease of the CO electronic absorption band (*cf* Fig. 1). The ratios OD_∞/OD_0 refering to the initial optical density (OD_0) and the value attained at equilibrium (OD_∞) are summarized in Table 1. The reactions studied are accelerated by addition of acids and bases without influencing the equilibrium position.

The phenomena observed can be attributed to the hydration and hemiketalization equilibria (1)–(4) outlined in Scheme 2 rather than to an enolization, as quite different band maxima are to be expected for [2.2]metacyclophanes unsaturated in the bridge.[15] Moreover, the ^{1}H NMR spectra of the products formed do not reveal any indication to enol formation (see below). Since 1

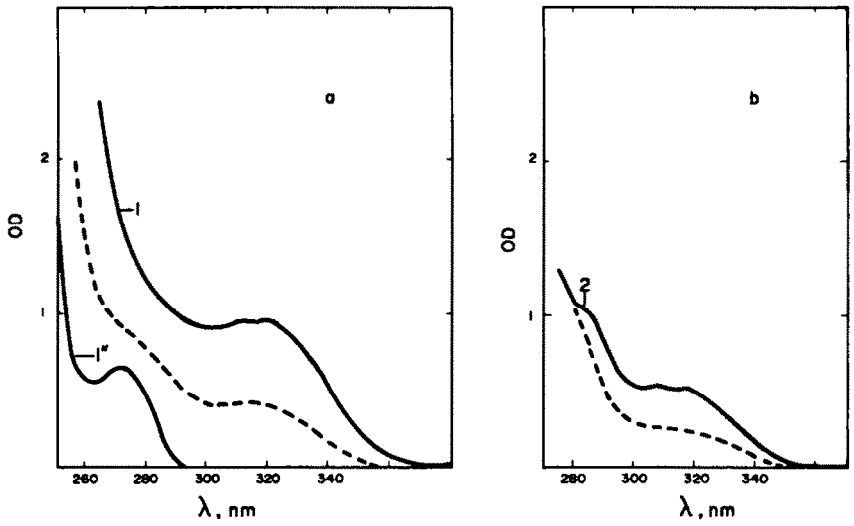


Fig. 1. Absorption spectra of 1 and 1" (a) and 2 (b) in dioxane containing 20 n/n water (both 1 cm path length; 1.24×10^{-3} M). The full lines refer to the initial band shape, the dotted lines to the band shape at equilibrium at 20°.

Table 1. Ratio OD_∞/OD_0 between the optical densities of freshly prepared solutions (OD_0) of 1 and 2 and after reaching of equilibrium (OD_∞) at the wavelength λ [nm] in various solvents at 20°C. t_∞ [h] refers to the time after which no further spectral changes could be observed

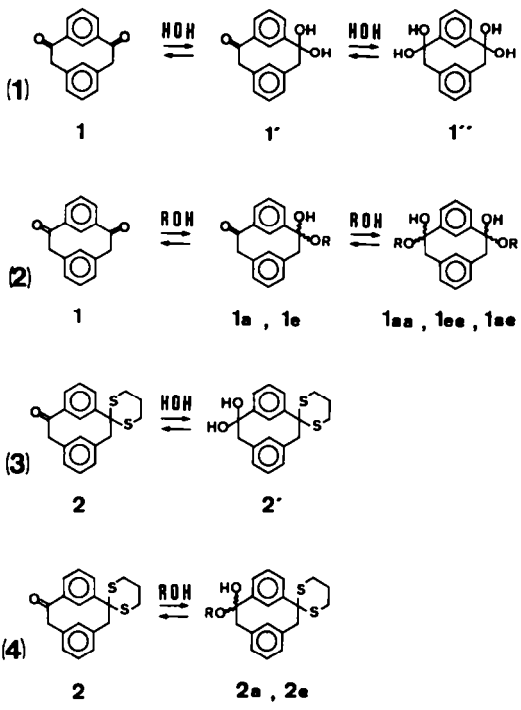
	1			2		
Solvent	λ	OD_∞/OD_0	t_∞	λ	OD_∞/OD_0	t_∞
Ethanol	315	0.10	25[a]	308	0.07	50
Methanol	315	0.03[b]	0.5	308	0.03[b]	1
Methanol (67 n/n) $CHCl_3$				308	0.07	2
Methanol (20 n/n) Dioxane	319	0.15	20	308	0.10	20
Water (20 n/n) Dioxane	319	0.43	24	308	0.49	72
Water	319	0.1_5[c]	<0.1	308	0.1_5[c]	<0.1

[a] In 96% ethanol the rate is greatly enhanced.
[b] Due to the fast reaction OD_0 could not be evaluated accurately. The value was taken from ethanol.
[c] Estimated value from an extrapolation to pure water.

carries two oxo functions and the CO absorption can thus be attributed to more than one species no quantitative conclusions can be drawn with respect to the populations involved in the equilibria (1) and (2). In the case of equilibrium (4) the OD_∞/OD_0 ratio reflects the portion of unreacted ketone but no distinction can be made concerning the distribution of the diastereoisomers **2a/2e**. Hence, the abosrption data are quantitatively sufficient only for reaction (3).

It should be mentioned that the absorption spectrum of 1 in ethanol given in the experimental section was recorded immediately after preparation of the solution and differs from that reported in Ref. 16. Presumably the absorption spectrum in Ref. 16 originates from an aged solution where hemiketal formation had already taken place.

The absorption spectra of 3 in ethanol, methanol and dioxane/water remained constant within ten days. They were not changed by addition of catalytic amounts of acids and bases.



Scheme 2. Hydration and hemiketal formation of 1 and 2 and the species involved in the equilibria (1)–(4). The scripts a and e refer to the axial and equatorial position of the alkoxy groups (R = Me, Et). The enantioners of the chiral species 1', 1a, 1e, 1ae, 2, 2', 2a and 2e are not shown.

Further insight into the equilibria (1)–(4) can be gained from a study of the ^{1}H NMR spectra of the equilibrium mixtures under consideration. Since the interconversion rate of species turned out to be slow on the NMR time scale, product formation and the distribution at equilibrium could be observed directly.

The pertinent parameters of the individual spectra (*cf* Figs. 2 and 3 and Tables 2–5) and their assignment to the species formed follow from a shift comparison with appropriate model compounds, the time dependence of resonance absorptions and double resonance experiments (selective decoupling). A complete analysis of the aromatic region of the mixtures and of the dithiane resonance absorptions of 2 and its adducts was not accomplished. The equilibrium distributions were evaluated from the integration of the intraanular protons at C-8 and C-16. The experimental error for these values given in Tables 2–5 amounts to 10–20%. In those cases where the resonance absorptions of the AB-systems of the bridges were sufficiently resolved a reasonable agreement with the values gained from the intraanular protons was found. No H–D exchange at these sites was detected. The signals of the intraanular protons at C-8 and C-16 in ^{1}H NMR spectra at 60 MHz of equilibrated solutions of 1 and 2 in ethanol-d_6 give evidence that the equilibrium compositions attained in this solvent correspond roughly to those determined for methanol.

The solvents and solvent mixtures employed for both absorption- and ^{1}H NMR spectral recordings were chosen mainly for reasons of solubility.

Reversible loss of water or alcohol can be accomplished with equilibrated samples of 1 and 2 on evaporation of the solvents and subsequent slight warming under reduced pressure. The compounds thus obtained are identical in all respects with the starting materials 1 and 2.

On keeping solutions of 1 in a dioxane–water mixture at room temperature the dihydrate 1'' deposits as a white crystalline solid within 24–48 hr. It was identified as dihydrate by elemental analysis, IR, ^{1}H NMR, and absorption spectra. On slight warming or on standing in open air 1'' looses water and is reconverted to the parent diketone 1. Accordingly, the mass spectrum of 1'' is not conclusive. Even at room temperature dehydration takes place in the ionization chamber yielding the spectrum of 1.

DISCUSSION

The data compiled in Tables 1–5 reveal a striking tendency of 1 and 2 towards adduct formation with alcohols and water. The results obtained by means of ^{1}H NMR and absorption spectroscopy corroborate and supplement each other. In order to draw a comparison between the hydration and hemiketalization equilibria absorption spectra were recorded under analogous conditions and an extrapolation to pure water was performed. The OD_m/OD_0 values for dioxane containing 20 n/n methanol and water respectively and for pure methanol, ethanol and water contained in Table 1 do not reveal striking differences with respect to the relation of equilibria (1)/(2) and (3)/(4) respectively. Comparable values differ by less than a factor five in all cases so that the free enthalpy differences for the two types of adduct formation have to be quite similar. Moreover an interpretation of the differences observed would be rather problematic, since the equilibrium positions are governed by various factors. Thus, e.g. due to the number of

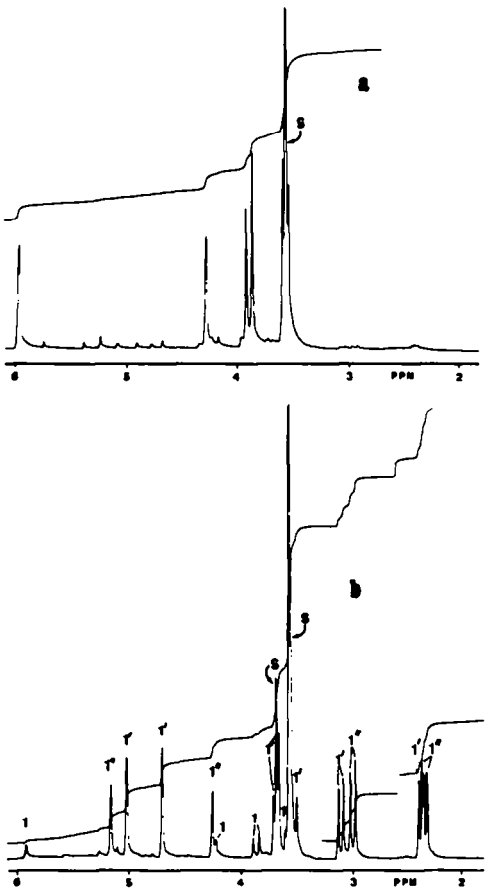


Fig. 2. ^{1}H NMR spectrum (270 MHz) of 1 (a): in dioxane-d_8; the spectrum reveals traces of adducts already formed during measurement, (b): at equilibrium after addition of 20 n/n D_2O. The resonance absorptions of the individual species 1, 1′ and 1″ are indicated. S refers to dioxane-d_8 and D_2O respectively.

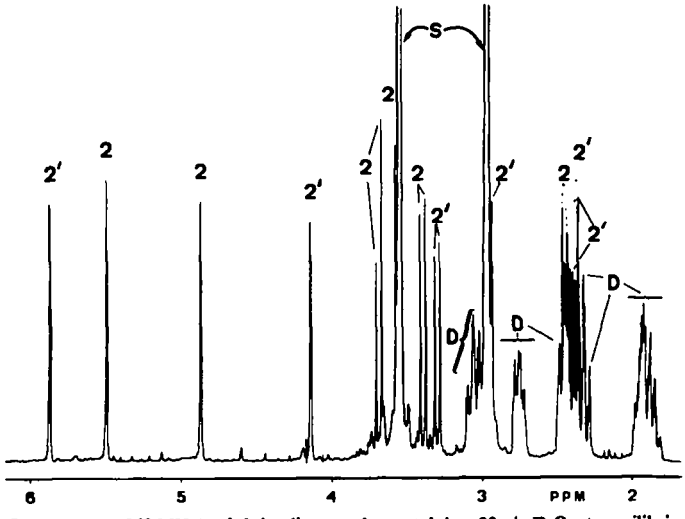


Fig. 3. ^{1}H NMR spectrum (360 MHz) of 2 in dioxane-d_8 containing 20 n/n D_2O at equilibrium. The resonance absorptions of the individual species 2 and 2′ are indicated. D refers to the signals from the dithiane moiety and S to dioxane-d_8 and D_2O respectively.

species involved and the changes in symmetry, hemiketalization is favoured entropically in relation to hydration. Our discussion will therefore be restricted to a general interpretation of the equilibria (1)–(4). The phenomenon in itself seems to merit an explanation.

Prima facie no reason for an enhanced carbonyl reactivity is evident in 1–3. Moreover, aromatic ketones as represented by 1 and 2 are in general much less disposed to form adducts than aliphatic carbonyl compounds.[8] Even if a partial loss of conjugation due to the non-

Table 2. ^{1}H NMR parameters (δ [ppm]; J [Hz]; 270 MHz) of 1, 1' and 1'' in dioxane-d_8/D_2O (20 n/n) and their population (%) at hydration equilibrium (1)

	proton at		AB-system at				
	C-8	C-16	C-2		C-9		
	δ	δ	δ	J	δ	J	%
1	5.91	4.22	3.85 3.57	14.0	3.85 3.57	14.0	9
1'	5.02	4.71	3.11 2.40	12.5	3.69 3.55	13.5	55
1''	4.25	5.32	3.00 2.36	12.4	3.00 2.36	12.4	36

Table 3. ^{1}H NMR parameters (δ [ppm]; J [Hz]; 270 MHz) of 1, 1a, 1e, 1aa, 1ee and 1ae in methanol-d_4 and their population at hemiketalization equilibrium (2). Note that the assignment of 1a/1e and 1aa/1ee respectively is tentative

	proton at		AB-system at				
	C-8	C-16	C-2		C-9		
	δ	δ	δ	J	δ	J	%
1	5.97	4.20	3.85 3.62	14.3	3.85 3.62	14.3	<3
1a	5.23	~4.8	3.10 2.39	12.5	3.64 3.56	13.5	<3
1e	5.07	4.54	3.24 2.37	12.5	3.68 3.56	13.5	<3
1aa	4.15	5.41	3.02 2.38	12.4	3.02 2.38	12.4	18
1ae	4.22	5.17	3.04 2.39	12.6	3.16 2.34	12.4	53
1ee	4.32	4.93	3.19 2.34	12.4	3.19 2.34	12.4	29

Table 4. ^{1}H NMR parameters (δ [ppm]; J [Hz]; 360 MHz) of 2 and 2' in dioxane-d_8/D_2O (20 n/n) and their population (%) at the hydration equilibrium (3)

	proton at		AB-system at				
	C-8	C-16	C-2		C-9		
	δ	δ	δ	J	δ	J	%
2	4.89	5.33	3.42 2.49	12.2	3.71 3.58	13.5	55
2'	4.17	5.89	3.33 2.48	12.4	2.89 2.47	12.3	45

Table 5. ^{1}H NMR parameters (δ [ppm]; J [Hz]; 270 MHz) of 2, 2e and 2a in $CDCl_3$/methanol-d_4 (67 n/n) and their population at hemiketalization equilibrium (4). Due to the limited solubility pure methanol-d_4 could not be employed. Note that the assignment of 2a and 2e respectively is tentative

	proton at		AB-system at				
	C-8	C-16	C-2		C-9		
	δ	δ	δ	J	δ	J	%
2	4.94	5.60	2.35 3.49	12.5	3.62 3.78	14.0	5
2a	4.12	6.08	~2.51 3.37	12.5	~2.49 3.07	12.5	50
2e	4.21	5.81	~2.55 3.33	12.5	2.47 3.22	12.4	45

planar arrangement is taken into account, one would expect the aliphatic diketone 3 to show a greater tendency towards addition of nucleophiles than 1 and 2. Instead, as opposed to the behaviour of 1 and 2 no adducts of 3 could be traced by absorption and ^{1}H NMR spectroscopy.

In the case of 1 it might be argued that electronic factors due to a mutual influence of the two CO groups across the aromatic ring could be responsible for adduct formation. The reason for the enhanced carbonyl reactivity in the monoketones 1', 1a, 1e and 2 where such arguments are not applicable is however certainly the same.

Therefore, for an interpretation of the phenomena observed we bestow our attention upon the geometries of the molecules and the conformational changes involved in the equilibria (1)–(4).

In [2.2]metacyclophane the nonbonded distance between positions 8 and 16 amounts to 2.63 Å,[17] a value which falls short of the sum of the Van-der-Waals-radii. This critical parameter is responsible for the distorted geometry of the metacyclophane skeleton. Thus, e.g. the benzene rings are forced in a boat shaped conformation.[17,18] Any structural modification imposed on the system will enhance the strain energy, if it impedes this distance to be kept.

The introduction of oxo-functions into the bridge of [2.2]metacyclophane to give 1 entails an increase of the bond angles in positions 1 and 10 with a simultaneous change of the torsion angles of the bridge.[14] Thus, due to an inward rotation of the intraanular position 8 the two benzene rings in 1 are no longer situated in parallel planes (*cf* Fig. 4). These conformational changes predicted in Ref. 14 have been fully corroborated by a recent X-ray investigation.[19] Even if these conformational changes are transmitted across the system so as to maintain the critical intraanular distance C-8–C-16, the transanular steric compression has to be enhanced in 1 as compared to [2.2]metacyclophane. A rehybridization of the sp^2 carbons in positions 1 and 10 of 1 via adduct formation with water and alcohols will inversely induce a more parallel orientation of the two benzene rings resulting in a relief of steric strain.

In the monoketone 2 the CO and propylenethioketal groups will exert quite different influences on the conformation of the metacyclophane skeleton and the overall geometry of the molecule cannot be predicted accurately.[14] The observed disposition of 2 for hydrate and hemiketal formation may serve as a proof that a transanular steric compression—similar to that in 1—is operative. Evidently, the same arguments hold for the mono-hydrate and mono-hemiketals of 1 (1', 1a and 1e) as adduct formation of 1 does not stop at the monoketone stage.

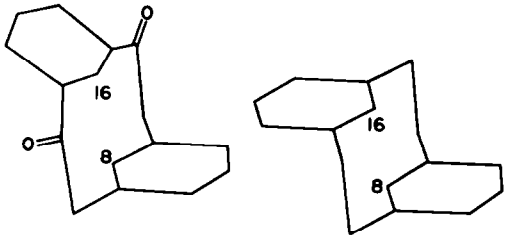


Fig. 4. Geometry of 1 and [2.2]metacyclophane. (Schematic representation; the distorsions of the benzene rings are not shown.)

Regardless of the strain energy of 3 the failure to trace any hydrates or hemiketals indicates that in this case a similar relief of strain due to rehybridization does not occur. A detailed conformational analysis of 3 will be given elsewhere.[20]

The tendency of 1 and 2 for adduct formation is reminiscent of the corresponding behaviour of cyclopropanone[3,21] in which the driving force for rehybridization has been accounted for by means of the I-strain hypothesis.[13]

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EXPERIMENTAL

General. IR spectra were recorded with a Perkin–Elmer 377 in spectrograde CCl_4 (Merck) or Nujol. Low resolution mass spectra were taken on a Varian MAT CH7 with spectrosystem 166. The following spectrometers were employed for the ^{1}H NMR measurements: Varian EM 360 (60 MHz, CW-mode), Bruker WH 270 (270 MHz, FT-mode) and Bruker WH 360 (360 MHz, FT-mode) using spectrograde dioxane-d_8, methanol-d_4, ethanol-d_6, $CDCl_3$, THF-d_8 and D_2O. Electron absorption spectra were taken with a Cary 15 spectrometer employing 0.1, 0.5, 1 and 2 cm thermostated (20 ± 1°C) quartz cuvettes. For absorption measurements cyclohexane (Uvasol, Merck), methanol (Uvasol, Merck), dioxane (Uvasol, Merck, distilled twice from $LiAlH_4$), ethanol (p. A., Merck), $CHCl_3$ (Uvasol, Merck) and bidistilled water were used.

Dihydrate of [2.2]*metacyclophane*-1,10-*dione* (1''). 93 mg 1[14,22,23] were dissolved in 0.9 ml dioxane containing 0.12 ml H_2O. After two days the white, crystalline ppt of 1'' was sucked off (70 mg, 65%), washed with a minimum amount of dioxane, and dried quickly (5 min) under reduced pressure (1 mm). m.p. (sealed capillary tube) 100–140° (under dehydration). Found: C, 69.1; H, 5.4; O, 23.8. Calcd. for $C_{16}H_{16}O_4$ (272.29): C, 70.57; H, 5.92; O, 23.50%. ms (25°, 70 eV) *m/e* 236 (M^+ of 1); IR (Nujol): 3250–3500 cm^{-1} (broad, s, ν-OH); 1112, 1080, 1062 and 1025 cm^{-1} (m, ν-C–O). UV (dioxane) λ(ε): 272 (527), 208 (42,000). NMR (THF-d_8, 60 MHz): 7.6–7.0 (m, 6 H, aromatic protons at C-4–C-6 and C-12–C-14), 5.4 (s, 2 H, O–H), 5.27 ("t", 1 H, proton at C-16), 4.88 (s, 2 H, O–H), 4.28 ("t", 1 H, proton at C-8), 2.93 and 2.35 (AB-system, J_{AB} = 12.5 Hz, 4 H, protons at C-2 and C-9).

[2.2]*Metacyclophane*-1,10-*dione* (1). For preparation and characterization *cf* Refs. 14, 22, 23. ^{1}H NMR *cf* Tables 2 and 3. UV (cyclohexane) λ(ε): 337 (513) s, 322 (706), 313 (697), 302 (657), 217 (28,900), 194 (30,300); UV (EtOH) λ(ε): 330 (619) s, 316 (747), 205 (30,500); UV (dioxane) λ(ε): 330 (644) s, 319 (773), 310 (764) s, 210 (32,400).

Monopropylenethioketal of [2.2]*metacyclophane*-1,10-*dione* (2). For preparation and characterization *cf* Refs. 23, 24. ^{1}H NMR *cf* Tables 4 and 5. UV (cyclohexane) λ(ε): 330 (224) s, 320 (340), 310 (360), 280 (830) s, 207 (39,000); UV (EtOH) λ(ε): 330 (222) s, 315 (351), 308 (370), 285 (620) s, 206 (38,000); UV (dioxane) λ(ε): 328 (287) s, 317 (417), 308 (426), 282 (837) s.

Dodecahydro-[2.2]*metacyclophane*-1,10-*dione* (3). For preparation and characterization *cf* Ref. 20. UV (EtOH) λ(ε): 290 (39); UV (dioxane) λ(ε): 290 (41).

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