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Cyclooligomeric Condensation Products. IV.* Formation of Stereoisomeric [1_4](2,5)Furanophanes

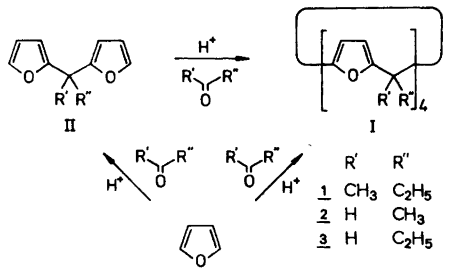
A. G. SVERKER HÖGBERG** and MICHAEL WEBER

Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

^{13}C NMR and HPLC analyses were used to show that the acid-catalyzed condensation of acetaldehyde with 1,1-di(2-furyl)ethane gives a mixture, m.p. 127–140 °C, of the four geometrical isomers of 1,7,13,19-tetramethyl[1_4](2,5)furanophane. Quantitatively, there is a small but significant deviation from a random statistical distribution between the four isomers, mainly evident from the relative enrichment in the mixture of the all-*cis* isomer, m.p. 191.0–192.0 °C. Similarly, the condensation of propanal with 1,1-di(2-furyl)propane gives a mixture, m.p. 83–88 °C, of the stereoisomers of 1,7,13,19-tetraethyl[1_4](2,5)furanophane from which the all-*cis* isomer, m.p. 152.0–153.0 °C was isolated by recrystallization. Finally the 1,7,13,19-tetraethyl-1,7,13,19-tetramethyl[1_4](2,5)furanophane, m.p. 170.0–172.0 °C, obtained by the condensation of butanone with furan, was found to be a mixture of stereoisomers too.

The formation of [1_4](2,5)furanophanes I (R′ and R″ = alkyl) by the acid-catalyzed condensation of ketones with furan or difurylalkanes II (R′ and R″ = alkyl) (see Scheme 1) has been studied extensively by W. H. Brown and co-workers.[1–7]

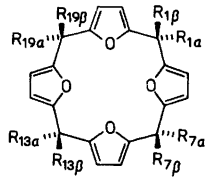
Interest in these macrocycles was further stimulated by the report that increased yields could be obtained in the presence of soluble lithium salts, suggesting the presence of a metal ion templating effect.[8] However, recently an alternative explanation was forwarded by Rest, who was able to correlate the yield of the macrocycles, not with the metal ion content but with the amount of acid added to the reaction mixture.[9]



Scheme 1.

When the furanophanes are unsymmetrically substituted (I, R′ ≠ R″) the macrocycle may exist in four different configurations Ia–Id (see Table 1). Brown observed that the reaction of butanone with

Table 1. Stereostructures Ia–Id. Configurations and number of ^{13}C NMR Peaks. R = R′ or R″ (see Scheme 1).



Position of R′ [a]		No. of peaks [b]
Ia	α,α,α,α	1/1
Ib	α,α,α,β	4/3
Ic	α,α,β,β	2/1
Id	α,β,α,β	1/1

[a] Relative positions of R′ at carbons 1,7,13 and 19 (cyclophane numbering) or 2,7,12 and 17 (IUPAC numbering). [b] Calculated number of ^{13}C NMR peaks for each type of aromatic/aliphatic carbon.

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** Present address: Boliden Kemi AB, Box 902, S-251 09 Helsingborg, Sweden.

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furan unexpectedly gave a single product *1* (I: R′ = CH_3; R″ = C_2H_5) m.p. 174 °C, while the reaction between butanone and 2,2-di(2-furyl)propane (or acetone with 2,2-di-2-furylbutane) gave the expected mixture of *cis* and *trans* isomers, m.p. 204 and 178.5 °C, respectively, in a ratio of 1:8.[1] Recently, the reaction between acetaldehyde and 1,1-di(2-furyl)ethane was reported to give a product *2* (I: R′ = H; R″ = CH_3), m.p. 140 – 142 °C, in a yield of 13%.[10,11]

A similar reaction, the acid-catalyzed condensation of various aldehydes with resorcinol, gives tetrasubstituted [1₄]metacyclophanes with a high degree of stereoselectivity.[12-14] These macrocycles, which may be obtained in yields exceeding 80%, are related to the furanophanes not only by their mode of synthesis but also by their size and symmetry properties. Initially only two out of the four possible geometrical isomers are formed, one of which is quantitatively converted into the other (the all-*cis* isomer) as the reaction proceeds. In addition, this final single stereoisomer exists in a single stable conformation out of several possible.

The stereoselectivity of the reaction was attributed to the effect of intra-molecular non-bonded interactions leading to conformational control of the intermediates. In view of the similarities between the [1₄]metacyclophanes and the [1₄](2,5)furanophanes and the lack of stereochemical information on the latter compounds, a reinvestigation of the furanophanes seemed worthwhile in order to extend and further develop the stereocontrol concept advanced for the former system.

EXPERIMENTAL

^1H and ^{13}C NMR data of the compounds in $CDCl_3$ solutions were obtained using a Bruker WP 200 FT instrument at 200 MHz and 50.3 MHz, respectively. For the low-temperature spectra an equal mixture of $CDCl_3$ and CH_2Cl_2 was used as a solvent. The dipole moment of *2a* was calculated from determinations at three different concentrations (0.031 – 0.124 M in benzene) using a dipolemeter DM 01 (Wissenschaftlich-Technishen Werkstätten GmbH). HPLC analyses were performed on a Spectra Physics SP 8000 chromatograph equipped with a 4.6 × 200 mm Spherisorb 5 μm silica column, and a UV-detector (280 nm) using cyclohexane – methylene chloride (2:1 v/v) as an eluent at a pumping rate of 2 ml/min. R_f-values are given in seconds. The microanalyses were performed by Alab, Uppsala.

Furanophane (1). It was prepared according to the literature procedure,[1] m.p. 170 – 172 °C (lit.[1] m.p. 174 °C). ^{13}C NMR: δ 157.81, 157.69, 157.57 (C-arom), 104.15, 104.09, 103.97, 103.87 (CH-arom), 40.57, 40.55 (C), 30.00, 29.93, 29.87, 29.82, 29.77 (C-CH_3), 21.91, 21.87, 21.82, 21.70, 21.64 (CH_2), 8.28, 8.22, 8.15 (CH_2-CH_3).

Furanophane (2). 1,1-Di(2-furyl)ethane[3,10] (5.0 g, 31 mmol) was added to a stirred, ice-chilled solution of aq. acetaldehyde (5 ml 90% (v/v), 90 mmol) dissolved in 105 ml of a 2*M* solution of $LiClO_4 \cdot 3H_2O$ (32.0 g) in a mixture of 60% $HClO_4$, H_2O and EtOH (1:4:16 v/v). After 25 min the ice-bath was removed and the mixture was stirred for another 41 h and then poured into a mixture of 10% $NaHCO_3$ (100 ml) and water (300 ml). The product was taken up in 400 ml of diethyl ether, 50 ml of light petroleum was added and the organic solution was washed two times with 200 ml of water and finally with brine before it was dried over anhydr. $MgSO_4$. Evaporation yielded 6.84 g of crude product which was first purified by flash chromatography[15] on 180 g of silica gel using an equal mixture of toluene and light petroleum as eluent. The final fraction eluted, gave upon evaporation 2.27 g of a yellow powder which was further purified by sublimation at 120 °C/10 Pa yielding 31% (1.83 g, 4.9 mmol) of a mixture of stereoisomers *2*, m.p. 127 – 140 °C. Anal. $C_{24}H_{24}O_4$: C, H. IR and MS as published.[10] ^1H NMR:[11] δ 5.97, 5.95(5), 5.95 (8H, three s, arom), 4.04, 4.01, 4.00, 3.99 (4H, four q, rel. int. 1.1:1.4:1.0:2.0, *J* 7 Hz, CH), 1.51, 1.50, 1.49 (12H, three d, *J* 7 Hz, CH_3). ^{13}C NMR: δ 155.53, 155.51, 155.44, 155.40, 155.39, 155.31 (C-arom), 104.89, 104.84, 104.77, 104.75, 104.67, 104.66, 104.55, 104.51 (CH-arom), 32.90, 32.80, 32.69 (CH), 17.56, 17.48, 17.29, 17.24, 16.99, 16.94 (CH_3) (rel. area: 1.5:1:2.4:3.2:1.7:2.5).[16] HPLC (R_f-value in s, rel. area): 214(29), 242(49), 376(22).

Furanophane (2a).[17a] Recrystallization of the isomer mixture *2* three times from hexane and seven times from light petroleum yielded 150 mg (2.5%) of the pure stereoisomer *2a*, m.p. 191.0 – 192.0 °C. Anal. $C_{24}H_{24}O_4$: C, H. IR and MS as *2*. ^1H NMR: δ 5.95(6) (8H, s, arom), 4.04 (4H, q, *J* 7 Hz, CH), 1.52 (12H, d, *J* 7 Hz, CH_3). ^{13}C NMR: δ 155.54 (C-arom), 104.48 (CH-arom), 32.65 (CH), 16.95 (CH_3). HPLC (R_f in s, rel. area): 376(100).

The combined mother-liquors were evaporated and recrystallized from light petroleum yielding a mixture *2′*, m.p. 133.0 – 134.5 °C. Anal. $C_{24}H_{24}O_4$: C, H. IR and MS as *2*. Partial ^{13}C NMR:[18] δ 17.56, 17.47, 17.29, 17.22, 16.97 (CH_3) (Ref. area: 1.0:1:3.8:2.7:1.4). HPLC (R_f in s, rel. area): 217(46), 251(54).

Furanophane (3). It was prepared in a manner similar to *2* from 1,1-di(2-furyl)propane (5.25 g, 30 mmol) and propanal (4.5 g, 77 mmol). However, the eluent used for flash chromatography was a mixture

of toluene and light petroleum 3:10 v/v). The yield of *3*, m.p. 83–88 °C was 25% (1.62 g, 3.8 mmol). Anal. $C_{28}H_{32}O_4$. IR. (KBr) 2955, 2925, 2870, 1565, 1460, 1185, 1010, 970, 955, 790, 770 cm^{-1}. MS [IP 70 eV] $m/z = 432(M^+)$. ^1H NMR δ 5.94(4), 5.94, 5.93 (8H, three s, arom), 3.70, 3.69 (12H, two t, J 7.8 Hz, CH), 1.93(5), 1.92, 1.91(5) (8H, three quintets, J 7.8 Hz, CH_2), 0.87, 0.86(7), 0.86, 0.85, 0.84(5) (12H, five t, J 7.3 Hz, CH_3). ^{13}C NMR δ 154.42, 154.34, 154.32, 154.25, 154.21 (C-arom), 105.51, 105.48, 105.46, 105.40, 105.32 (CH-arom), 40.62, 40.58, 40.56 (CH), 24.36, 24.32, 24.26, 24.21, 24.18 (CH_2), 12.15, 12.08, 12.01 (CH_3). HPLC: three peaks.[18]

*Furanophane (*3a*).*[17b] The mixture *3* was recrystallized four times from light petroleum to yield 16 mg (0.2%) of the pure stereoisomer *3a* m.p. 152.0–153.0 °C. Anal. $C_{28}H_{32}O_4$: C, H. IR and MS as *3*. ^1H NMR δ 5.94 (8H, s, arom), 3.70 (4H, t, J 7.8 Hz, CH), 1.93 (8H, quintet, J 7.6 Hz, CH_2), 0.84(6) (12H, t, J 7.3 Hz, CH_3). ^{13}C NMR: δ 154.23 (C-arom), 105.45 (CH-arom), 40.60 (CH), 24.32 (CH_2), 11.98 (CH_3). HPLC: one peak with the same R_f-value as the last peak of *3*.[18]

RESULTS

The reaction of acetaldehyde with the difurylethane was quite facile at room temperature in the presence of perchloric acid and lithium perchlorate. From the mixture of condensation products a macrocyclic fraction *2* ($C_{24}H_{24}O_4$), m.p. 127–140 °C, was isolated in a fairly good yield (31%) by flash chromatography followed by sublimation *in vacuo*. Its ^1H NMR spectrum exhibited multiple overlapping resonances. The ^{13}C NMR showed multiple resonances too for each type of carbon with eight and six separate singlets for the aromatic CH-carbons and the aliphatic CH_3-carbons, respectively.

TLC analysis (silica plates) of *2* did not give any indication of the presence of more than one compound. However, after extensive optimization of the elution parameters, HPLC analysis of *2* gave three well-resolved peaks with a relative area of 29:49:22. In one chromatogram, using a somewhat less polar eluent mixture, the first peak was slightly resolved, indicating the presence of two components in a relative ratio of 1:3.

Repeated recrystallization of *2* gave a small (2.5%) fraction *2a* ($C_{24}H_{24}O_4$), m.p. 191.0–192.0 °C. Its ^1H NMR showed a singlet in the aromatic region and a single AX_3 system in the aliphatic. The ^{13}C NMR consisted of a single peak for each type of carbon. Its ^1H and ^{13}C low temperature NMR spectra, recorded at −75 and −65 °C, respectively, exhibited only minor changes relative to the spectra recorded at room temperature. (The methyl doublet of the ^1H NMR spectrum was slightly more broadened than the TMS-singlet.) The dipole moment of *2a* was also measured and found to be zero. HPLC analysis of *2a* gave one peak with the same R_f-value as the last fraction of the mixture *2*.

The combined mother-liquors from the recrystallization of *2a* were evaporated and recrystallized to yield a fraction *2'* ($C_{24}H_{24}O_4$), m.p. 133.0–134.5 °C. Its HPLC analysis showed two peaks with the same R_f-values as those of the first two of the original mixture *2* (rel. ratio 46:54). The ^1H and ^{13}C NMR spectra were similar to those of *2* with respect to the shift values, but with all peaks belonging to *2a* missing. However, the relative intensities of the peaks were different from those of *2*.

The corresponding tetraethyl substituted furanophanes were obtained by the reaction of propanal with 1,1-di(2-furyl)propane. The product *3* ($C_{28}H_{32}O_4$), m.p. 83–88 °C, was obtained in 25% yield. Its ^1H and ^{13}C NMR spectra exhibited multiple resonances too but were less well resolved than those of *2*. HPLC analysis gave three separate peaks, the first two slightly overlapping each other. A small fraction (0.2%) *3a* ($C_{28}H_{32}O_4$), m.p. 152.0–153.0 °C, was obtained by recrystallization of *3*. Its ^1H and ^{13}C NMR spectra showed similar symmetry properties to those of *2a*. HPLC analysis gave a single peak with the same R_f-value as that of the last peak of *3*.

Finally the butanone–furan condensation product *1*, m.p. 170.0–172.0 °C, prepared according to the literature procedure,[1] was investigated by ^{13}C NMR analysis. The spectrum exhibited multiple resonances for each type of carbon.

DISCUSSION

Both HPLC and NMR analyses show that the products *1*–*3* indeed are mixtures of stereoisomers. The minute structural differences between the isomers, resulting in very similar physical properties, prevented their complete separation. Interestingly several of the mixtures exhibited fairly narrow melting point ranges, a feature also experienced by earlier workers in the field.

The ^{13}C NMR spectra were particularly useful in determining the compositions of the mixtures. The spectrum of *2* contains the full number of aromatic

CH (eight) and aliphatic CH_3 (six) resonances calculated for a mixture of all four stereoisomers possessing structures Ia–Id; (R′=H; R″=CH_3), while there is some accidental overlapping of the signals of the other two types of carbons. *A priori* these shift differences might be expected to have a twofold origin; anisotropic aromatic ring-current effects (conformational differences) and the shielding effects of the methyl groups (configurational and conformational differences). Qualitatively the relative shift differences of the six CH_3 singlets can be rationalized by evoking non-bonded through-space shielding effects from the methyl groups alone (*vide infra*).

The symmetry properties of the ^{13}C NMR spectrum of *2a* (as well as of *3a*) reveal that this isomer possesses either configuration Ia or Id. A further analysis of the ^{13}C shifts of the methyl carbons shows that the peak corresponding to *2a* has the lowest chemical shift out of the six in the mixture *2* containing all four stereoisomers. This suggests that in *2a* each methyl group experiences the maximum cumulative through-space shielding effects from the remaining three methyl groups *i.e.* the methyl groups are all on the same side of the macrocycle as in configuration Ia.

Independent support for this assignment is obtained from the result of the HPLC-analysis. Most likely the macrocycles bind to the silica surface through the intra-annular ether oxygens. Both hydrogen bonding and dipole–dipole interactions are possible. The relative binding energies depend on the number of ether oxygen of the macrocycle that simultaneously can be oriented into binding positions. The number of methyl groups that sterically interfere with binding to the surface depends on the configuration of the macrocycle. The maximum binding strength is attained in the all-*cis* isomer in which all four ether oxygens can participate in the binding. All four methyl groups are then on the opposite side of the macrocycle pointing away from the silica surface. The remaining three isomers will have one or two methyl groups poking into the silica surface. They will thus exhibit correspondingly lower binding strengths due to the decreased number of ether oxygens being able to simultaneously participate in the binding. From these considerations follows that upon chromatography the all-*cis* isomer, which is the most strongly absorbed one, will be eluted last of the four. Thus this supports the assignment of structure Ia (R=H; R=CH_3) to isomer *2a*. It can further be argued by similar reasoning that the second last peak is due to the isomer possessing the *cis-cis-trans* configuration Ib. The first peak which seems to contain two components would then be comparised of the two most hindered isomers possessing configurations Ic and Id.

Independent of the HPLC determination the relative composition of *2* can also be calculated from the peak areas of the CH_3 singlets of the ^{13}C NMR spectrum. By this method the ratio between the isomers possessing configuration Ia–Id was 20:52:20:8, in close agreement with the HPLC data (22:49:21:8). These numbers should be compared with the statistically expected distribution 12.5:50:25:12.5 and point to a small but significant enrichment of the all-*cis* isomer *2a*. By the NMR method the composition of the mixture *2′* was calculated to be 0:51:39:10. The effect of the repeated recrystallization of the combined mother-liquors from the recrystallization of *2a* thus led to a relative enrichment with respect to the isomer possessing configuration Ic. This enrichment was, however, insufficient to obtain it in a pure state.

A key factor, which was suggested to govern the stereochemistry in the formation of the [1_4]metacyclophanes, was the conformational control originating from intra-molecular non-bonded interactions at first in the triphenylmethane or diphenylalkane units and then subsequently in the higher condensation intermediates. Inspection of CPK-models indicates that these interactions decrease when the resorcyl groups are replaced by the furyl groups. We suggest that the low degree of stereoselectivity in the formation of the [1_4](2,5)furanophanes is a consequence of this lowering of the conformational barriers.[19] Also, for the same reason, the activation energy for pseudorotation of a macrocycle possessing the all-*cis* configuration Ia is expected to be lower than for the corresponding [1_4]metacyclophane isomer ($\Delta G^{\ddagger}_{306K} = 60.3$ kJ mol^{-1}). Thus the result of the low-temperature NMR of *2a*, which failed to demonstrate the presence of such a conformational barrier, does not rule out the proposed all-*cis* configuration. The lack of any measurable dipole moment of *2a* indicates either that the method is too insensitive to the small structural effects or that it is the result of the combined configurational and conformational effects.

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16. Calculated intensities for a statistically formed mixture (*i.e.* Ia – Id = 1:4:2:1): 1:1:2:2:1:1.
17. Systematic names: (a) *r*-2,*c*-7,*c*-12,*c*-17-tetramethyl-21,22,23,24-tetraoxapentacyclo[16.2.1.-$1^{3,6}.1^{8,11}.1^{13,16}$]tetracosane. (b) *r*-2,*c*-7,*c*-12,*c*-17-tetraethyl-21,22,23,24-tetraoxapentacyclo-[16.2.1.1^{3,6}.1^{8,11}.1^{13,16}]tetracosane.
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