Formation and structure of unusual [2 + 1] adducts of citronellal and oligo(hydroxy)benzenes

Bart Forier, Suzanne Toppet, Luc Van Meervelt and Wim Dehaen*

Department of Chemistry, Katholieke Universiteit Leuven, Celestijnenlaan 200F, 3001 Heverlee (Leuven), Belgium. E-mail: wim.dehaen@chem.kuleuven.ac.be

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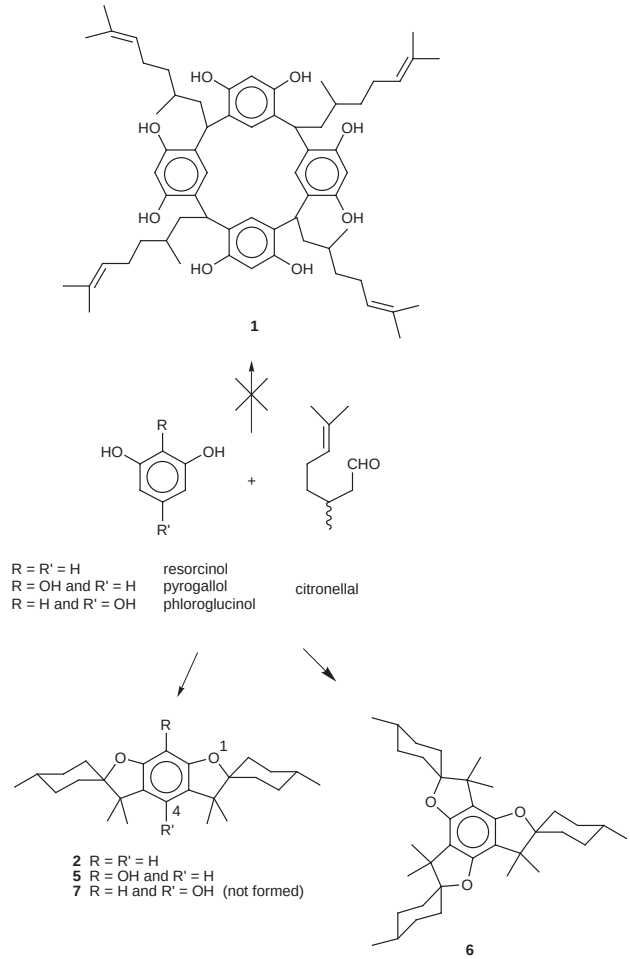
Citronellal reacts with electron rich oligo(hydroxy)benzenes in an acid catalyzed condensation reaction to afford unusual [2 + 1] adducts which are characterized with mass and NMR spectroscopy, and X-ray crystallography.

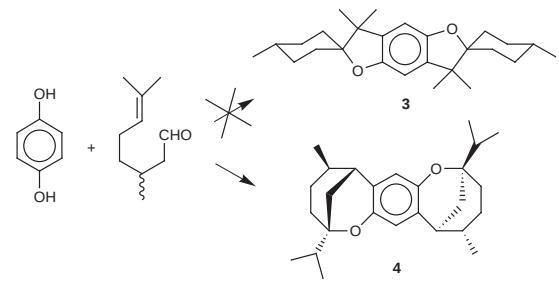
Resorcinarenes are an important class of electron rich cyclophanes, which have been used extensively as hosts for ammonium ions, amino acids, polyols and saccharides.[1] They are also the starting materials for container molecules such as cavitands and carcerands.[2] Their success is to a major extent due to their convenient one step synthesis involving the [4 + 4] acid catalyzed condensation of aldehydes and resorcinol. Both aromatic and aliphatic aldehydes can be used, and in many cases the *rccc* stereoisomer is formed preferentially.

With the goal of introducing chirality to these resorcinarenes in a simple way, we tried the acid-catalyzed condensation of citronellal with resorcinol, following literature procedures.[1] To our joy, large amounts of a white crystalline material were formed. However, the spectral data did not correspond with the desired [4 + 4] adduct **1**. This was clear by the absence of signals corresponding to phenolic hydrogens both in the ^{1}H NMR (taken at 400 MHz) and IR spectra. Moreover, the double bond had disappeared, as was clear from the shift of the methyl groups from δ 2.1 in citronellal to δ 1.1 in the product, and the disappearance of the signal of the vinyl hydrogen in the ^{1}H NMR spectrum. Notably, the product formed was not optically active, and in fact racemic citronellal was used in all subsequent reactions. Very soon it became apparent that a [2 + 1] adduct between citronellal and resorcinol, corresponding to an interesting bis(spirocyclohexane)benzodifuran **2**, had formed. The yield was 66% based on citronellal, rising to 77% when a 2 : 1 ratio of starting materials was used (Scheme 1).[3] The structure of **2** agrees with the mass spectrum (*m/z* 382). The ^{1}H NMR spectrum shows doublet absorptions (6H) at δ 0.9, and a singlet (12H) at δ 1.1 for the hydrogens of the methyl groups. A number of multiplet signals between δ 1.3 and 1.9 (total 18H) correspond to the cyclohexyl protons. Two singlets (each 1H) at δ 6.18 and 6.61 can be assigned to the aromatic H-8 and H-4 of the benzodifuran. Furthermore, in the ^{13}C NMR spectrum the aliphatic quaternary carbons are diagnostic: they show up at δ 45.7 (C-3,6 of benzodifuran) and 91.8 (C-2,7 of benzodifuran). The aromatic signals at δ 93.4 (CH-8 of benzodifuran) and 115.5 (CH-4 of benzodifuran) are within the expected values.

Although citronellal and resorcinol both are very common chemicals, we have found no earlier reference to compound **2** in the literature. To test the generality of this cyclocondensation reaction, other phenols were combined with citronellal. Phenol itself did not give a defined condensation product, but the isomeric hydroquinone gave a [2 + 1] adduct (*m/z* 382) in good yield (72%). However, careful investigation of the ^{1}H and ^{13}C NMR spectra showed that the product is not the (by now) expected benzo[1,2-*b*:4,5-*b*′]difuran **3** but a doubly bridged benzo[1,2-*b*: 4,5-*b*′]dioxocane **4** (Scheme 2). The ^{1}H NMR spectrum shows the methyl groups now all appear as doublets at δ 0.96, 0.97 and 1.10 (each 6H). A multiplet at δ 1.16 (2H) is well separated from the bulk of the aliphatic protons (14 H between δ 1.53 and 1.91). The former signal clearly corresponds to the two hydrogens at C-3,10 which undergo the shielding influence of the aromatic anisotropy. Another well-separated aliphatic signal is the doublet at δ 2.60 corresponding to the benzylic H-6,13. In the aromatic region of the spectrum, the expected singlet (2H) at δ 6.41 is found. In the ^{13}C NMR spectrum the diagnostic signals are from one aliphatic quaternary carbon (C-2,9) at δ 78.2 and one aromatic CH at δ 113.2. The product **4** is not optically active due to its centre of symmetry.



Scheme 1



Scheme 2

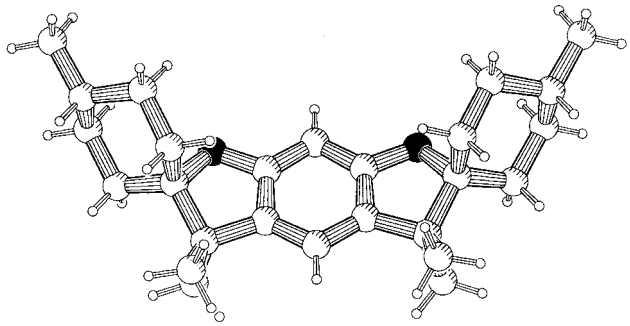


Fig. 1 X-Ray structure of **2**.

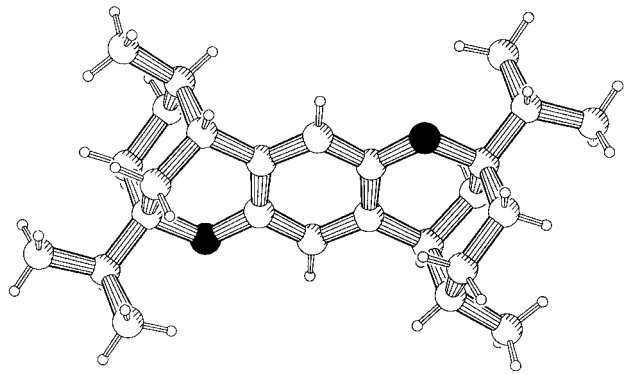
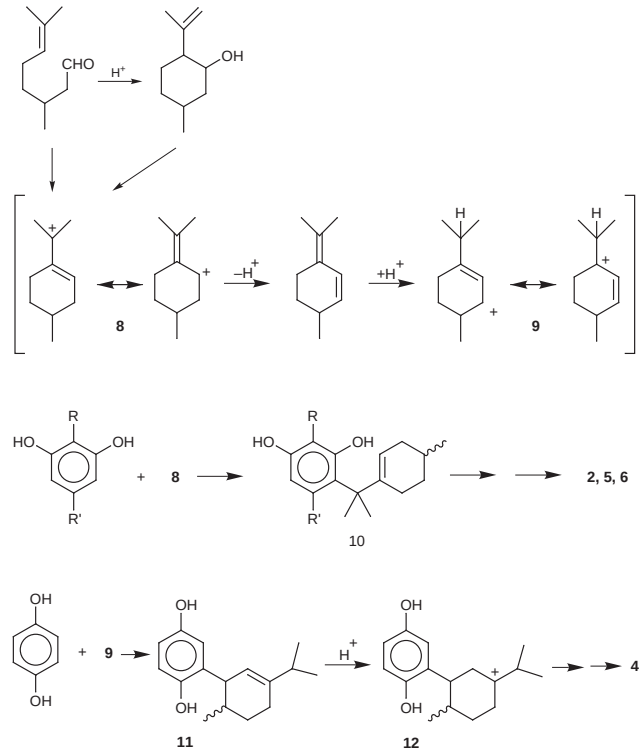


Fig. 2 X-Ray structure of **4**.



Scheme 3

Pyrogallol afforded product **5** with citronellal, having structure and yield (63%) comparable with compound **2**. The isomeric phloroglucinol gave a fair yield (33%) of an inseparable mixture of four diastereoisomers, corresponding to a [3 + 1] adduct **6** (*m/z* 534). The [2 + 1] adduct **7**, which should be theoretically possible, was not present (Scheme 1). The ^{1}H and ^{13}C NMR spectra of this mixture, which was not further investigated, showed similarity to that of the resorcinol adduct **2**.

Crystals of **2** and **4** were grown from an acetone–MeOH mixture and the molecular structures of **2** and **4** were confirmed by X-ray diffraction.[4] The molecular shape of compound **2** is determined to a large extent by the conformation of the different rings (Fig. 1). The central ring system is slightly bent: the angle between the best planes through both tetrahydrofuran rings is 14.5°. Both cyclohexane rings have a chair conformation with the methyl substituent in the equatorial position and the *gem*-dimethyl carbon in the equatorial position in order to reduce possible steric hindrance. Compound **4** possesses an internal centre of symmetry (Fig. 2). The tetrahydropyran ring has a clear envelope conformation with the isopropyl group attached in the equatorial position. The cyclohexane ring, oriented axially with respect to the previous ring, has a chair conformation with the methyl substituent in the axial position.

Citronellal is known to cyclize in acidic medium, in fact this is a way to prepare isopulegol.[5] When the condensations of resorcinol and hydroquinone were carried out with isopulegol, the adducts **2** and **4** were formed in comparable yields (75 and 76%, respectively) as for the reactions based on citronellal.

Via a number of intermediates, involving acid-catalyzed isomerizations, the stabilized cationic species **8** and **9** can form in the reaction mixture (Scheme 3). Obviously, **8** is more stable than **9** and will be preferentially formed. Resorcinol, pyrogallol and phloroglucinol are significantly more reactive than hydroquinone towards electrophilic substitution and, therefore, they can react with the stabilized cation **8** with the formation of the intermediate **10**, which after protonation will cyclize with the phenol function. It is interesting to note that even when the reactants are combined in a 1 : 1 ratio, only the [2 + 1] adduct **2** is obtained. Apparently, the intermediate [1 + 1] adduct is significantly more reactive than resorcinol itself.

Hydroquinone will only react with the less stabilized cation **9**, and the intermediate **11** will be protonated selectively with the formation of the tertiary carbenium ion **12**, and ultimately the bridged compound **4**. A similar singly bridged [2 + 1] condensation product resulting from the acid catalyzed condensation of resorcinol and 2-cyclohexenone was reported recently.[6]

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Notes and references

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2 D. J. Cram and J. M. Cram, *Container Molecules and their Guests*, *Monographs in Supramolecular Chemistry*, ed. J. F. Stoddart, Royal Society of Chemistry, Cambridge, 1994, vol. 4; R. G. Chapman and J. C. Sherman, *Tetrahedron*, 1997, **53**, 15911

3 All new compounds described were characterized by IR, mass, ^{1}H and ^{13}C NMR spectroscopy and gave correct C, H elemental analysis.

4 *Crystal data*: intensity data were collected at 16 °C on a Siemens P4 diffractometer using Mo-Kα radiation (λ = 0.71073 Å). Data were corrected for Lp effects, but not for absorption. For **2**: $C_{26}H_{38}O_2$, M = 382.56, triclinic, $P\bar{1}$, a = 6.604(1), b = 11.265(3), c = 15.797(4) Å, α = 106.96(2), β = 90.41(2), γ = 93.45(2)°, V = 1121.7(4) Å^3, Z = 2, D_c = 1.133 g cm^{-3}, μ(Mo-Kα) = 0.069 mm^{-1}, F(000) = 420, crystal size 0.5 × 0.1 × 0.1 mm, 2716 independent reflections. Final R = 0.0535 for 1912 reflections with $I > 2\sigma(I)$ and $\omega R2$ = 0.1490 for all data. For **4**: $C_{26}H_{38}O_2$, M = 382.56, monoclinic, $P2_1/n$, a = 8.555(2), b = 10.668(2), c = 12.247(2) Å, β = 108.14(1)°, V = 1076.1(4) Å^3, Z = 2, D_c = 1.181 g cm^{-3}, μ(Mo-Kα) = 0.069 mm^{-1}, F(000) = 420, crystal size 0.45 × 0.25 × 0.25 mm, 1893 independent reflections. Final R = 0.0393 for 1598 reflections with $I > 2\sigma(I)$ and $\omega R2$ = 0.1084 for all data. The structures were solved by direct methods (SHELXTL). Refinement on F^2 was carried out by full-matrix least-squares (SHELXTL) with anisotropic displacement parameters for non-H atoms and riding isotropic H atoms (C–H distance free to refine). CCDC 182/1255. See http://www.rsc.org/suppdata/cc/1999/1117/ for crystallographic data in .cif format.

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