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Concave Reagents -17. Steric Effects on the Acidity of Concave Sulfinic Acids and Concave Benzoic Acids[1]

Ulrich Lüning*, Heiko Baumgartner and Carsten Wangnick

Institut für Organische Chemie der Christian-Albrechts-Universität zu Kiel, Olshausenstr. 40
D-24098 Kiel, Germany, fax: +49-431-880-1558, e-mail: noc03@rz.uni-kiel.d400.de

Abstract: Bimacrocyclic and acyclic *m*-terphenylsulfinic acids **5**, **7** and **9** have been synthesized. Acidities have been measured in 2-methoxyethanol/water (80:20 w/w) and have been compared to the acidities of analogous benzoic acids. Tetra-*ortho*-substitution of the outer aryl rings of a *m*-terphenyl-2'-acid leads to a decrease in acidity which is probably caused by hindered solvation of the corresponding anions.

The incorporation of acidic and basic functionalities into bimacrocyclic structures has lead to concave acids and bases.[2] These concave reagents have already been used in model reactions leading to improved selectivities due to the concave shielding.[2]

As acid/base centers, nitrogen atoms or carboxylic acids have been used so far.[2] 2'-substituted *m*-terphenyls are good building blocks for the construction of concave reagents because many reactive centers can be incorporated easily,[3-5] e. g. sulfur containing functional groups. This has been shown by the synthesis of a bimacrocyclic thiol acetate and *m*-terphenylic precursors like the sulfinic acid **5**.[4] Recently our concept of concave reagents was adopted for the construction of a concave sulfenic acid.[6]

Figure 1 depicts the synthesis of concave sulfinic and benzoic acids. Starting from the *m*-terphenyl-2'-iodide **1**, reaction with *n*-butyllithium gave the lithium compound **2**. The sulfur functionality could be introduced by reaction with liquid SO_2. Hydrolysis gave the *m*-terphenylsulfinic acid **5**.[4] In a reaction sequence similar to the generation of concave benzoic acids,[7] the tetra-*ortho*-methyl derivative was functionalized by a fourfold NBS bromination of the *ortho*-methyl groups to form **7** in 52% yield. The reactive intermediate **7** then was doubly cyclized with 1,4-bis(mercaptomethyl)-benzene[8] to form bimacrocycle **9** in 10 % yield.

The new bimacrocyclic sulfinic acid **9** was characterized by IR, ^{1}H NMR, MS spectra and elemental analysis. In contrast to the concave benzoic acids, no purification problems occurred.[7] In an 80 : 20 (w/w) mixture of 2-methoxyethanol and water, the pK_a values for the bimacrocycle **9**, its precursor **5**, benzenesulfinic acid (**11**) and the benzoic acid analogs **6**, **10** and benzoic acid (**12**) were determined at 25°C. In *Table 1* the results are listed and compared with data for the benzoic acids derivatives **6**, **10** and **12** in ethanol obtained by photometric titration against 4-nitrophenolates.

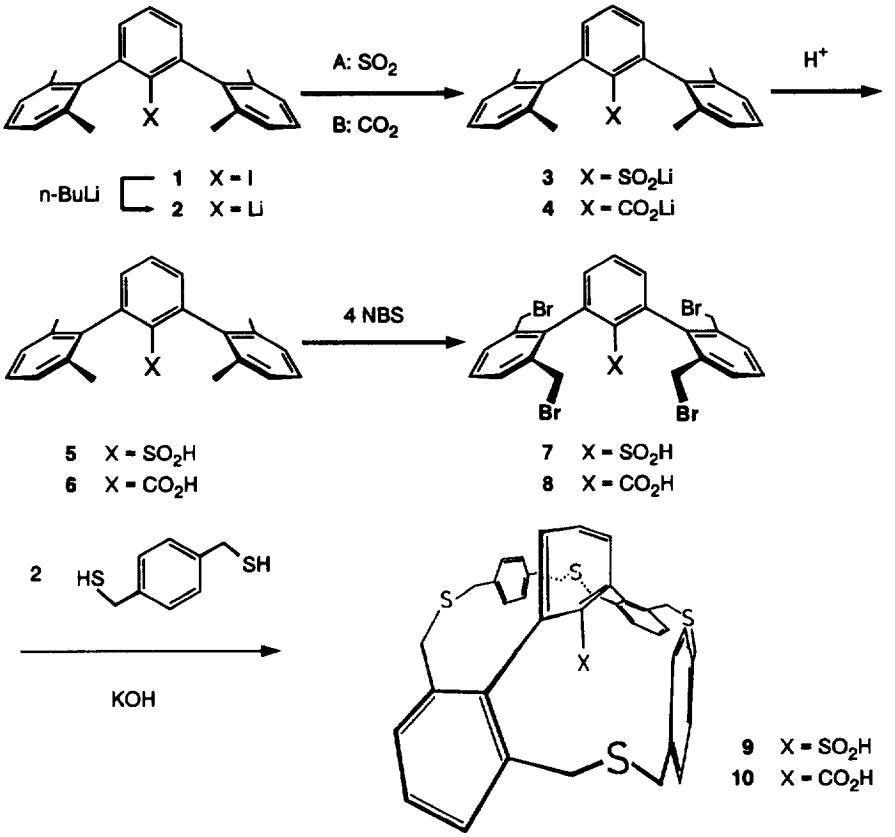
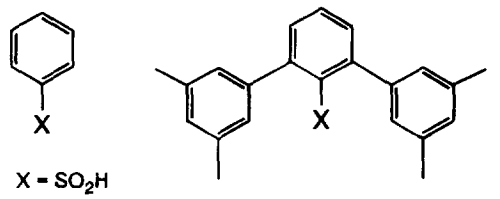


Figure 1: Synthesis of sulfinic acids **5**, **7** and **9**, and benzoic acids **6**, **8** and **10** starting from the iodide **1** by reaction with SO_2 (sequence A) or with CO_2 (sequence B).

Table 1: pK_a values of sulfinic acids **5**, **9** and **11** and of benzoic acids **6**, **10** and **12** in 2-methoxyethanol/water (80 : 20) and in ethanol at 25°C.

	pK_a **11/12**	pK_a **5/6**	pK_a **9/10**	solvent
X = SOOH	3.9	5.25	5.7	$MeOCH_2CH_2OH/H_2O$ (80/20)
X = COOH	6.45 [a]	8.1	7.9	$MeOCH_2CH_2OH/H_2O$ (80/20)
X = COOH	10.25	11.9	11.8	EtOH

[a] 6.63.[9,10]



11 X = SO_2H
12 X = CO_2H

13 X = CO_2H

A comparison of the pK_a values for the benzoic acids and the sulfinic acids shows a sharp decrease in acidity when going from the phenyl derivatives **11** and **12** to the *m*-terphenyl compounds **5**, **6**, **9** and **10** regardless whether they are bimacrocyclic or open chain. The differences in acidity between the open chain and bimacrocyclic *m*-terphenyls were smaller than 0.5 pK_a units both in 2-methoxyethanol/water and in ethanol.

For benzoic acids some pK_a values in methoxyethanol/water (80:20 w/w) are known. A comparison between 4-phenylbenzoic acid (pK_a = 6.47),[10] 2,6-diphenylbenzoic acid (*m*-terphenyl-2'-carboxylic acid, pK_a = 6.39)[11] and the acids of *Table 1* reveals that the tetra-*ortho*-substitution of the *m*-terphenyl system is responsible for the change in acidity.

In ethanol the acidities of the two tetramethyl-*m*-terphenyl-2'-carboxylic acids **6** and **13**[7] which only differ in the position of the four methyl substituents have been compared with benzoic acid: pK_a (**6**): 11.9, pK_a (**12**): 10.25, pK_a (**13**): 9.95. Also in ethanol, a distinctly smaller acidity has been found for the tetra-*ortho*-substituted acid **6** while the tetra-*meta*-substituted acid **13** is even more acidic than benzoic acidic (**12**). This may be caused by the electron withdrawing effect of the aryl rings which can only turn into the plane of the central aryl ring if *m*-substituted. The *ortho*-substituents in **6** prohibit a conjugation and may as well hinder the solvation of the resulting anion leading to the lower acidities.

A comparison between the arylsulfinic acids and the benzoic acids proves that sulfinic acids are more acidic than the carbon analogs (ΔpK_a = 2.16 - 2.84). This is in agreement with data for crown ether based acids[12] where sulfinic acids also were the stronger acids by two to three orders of magnitude.

The acidities of the benzoic acids **6**, **10** and **12** were determined in ethanol and in 2-methoxyethanol/water. The solvent change from the water containing mixture to the less polar ethanol leads to a decrease in acidity by almost four orders of magnitude. But it is remarkable that the differences in acidity ΔpK_a between **6**, **10** and **12** hardly changed.

EXPERIMENTAL

2,2",6,6"-Tetramethyl-m-terphenyl-2'-sulfinic acid (**5**): Under nitrogen, a solution of *n*-butyllithium in *n*-hexane (26.0 ml, 15 %, 40.2 mmol) was added to a solution of *m*-terphenyl iodide **1** (16.6 g, 40.2 mmol) in 100 ml of dry diethyl ether and the mixture was stirred for 15 h at room temp. At -50°C, this solution was added within 20 min to ca. 40 ml of liquid and well stirred sulfur dioxide with a syringe through a septum. The solution turned yellow and was stirred for 2 h at -50°C. Within the next 2 h, the mixture was warmed to

room temp. and excess sulfur dioxide was evaporated. After addition of 100 ml of 5 N HCl, **5** was extracted with 200 ml of diethyl ether, washed twice with 100 ml of water and dried with $CaCl_2$. Evaporation of the solvent gave a solid which was recrystallized from *n*-hexane yielding 6.9 g (49%)[13] of **5**, m. p. 172°C (dec.). - IR (KBr): $\tilde{\nu}$ = 3650 - 3300 (OH), 2919 (CH_3), 1459 (CH_3), 1084 (S=O), 806 (S-OH), 766 (arom.). - ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.08 (s, 12 H), 5.28 (s, 1 H), 7.09 - 7.27 (m, 8 H), 7.60 (t, J = 7.4 Hz, 1 H). - MS (EI, 70 eV): m/z (%) = 350 (M^+, 36), 315 (24), 284 (31), 271 (100), 165 (44). - $C_{22}H_{22}SO_2$ (350.49), calcd. C 75.40, H 6.33, found C 75.29, H 6.23.

2,2",6,6"-Tetrakis(bromomethyl)-m-terphenyl-2'-sulfinic acid (**7**): Under nitrogen, *m*-terphenylsulfinic acid (**5**) (5.83 g, 16.6 mmol), *N*-bromosuccinimide (14.57 g, 80.7 mmol) and dibenzoyl peroxide (ca. 40 mg) were added to 500 ml of CCl_4 p. a. After 15, 25, 60 and 95 min of refluxing, four portions of 30 mg of dibenzoyl peroxide were added. The mixture was refluxed for additional 25 min and filtered at room temp. The succinimide was washed well with CCl_4. The combined CCl_4 layer was washed with water (3 x 100 ml) and dried with $MgSO_4$. Evaporation of the solvent gave an orange to yellow solid which was stirred with 40 ml of CCl_4 for 10 min at 30°C. After cooling to -18°C the mixture was filtered and the solid was dried in vacuo yielding 5.8 g (52%) of **7**, m. p. 188°C (dec.). - IR (KBr): $\tilde{\nu}$ = 3650 - 3310 (OH), 2913 (CH), 1455 (CH), 1081 (S=O), 805 (SO-OH), 551 (Br). - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.45 (d, J = 10.5 Hz, ca. 4 H), 4.13 (d, J = 10.5 Hz, ca. 4 H), 7.2 - 8.0 (m, ca. 9 H). - MS (EI, 70 eV): m/z (%) = 670, 668, 666, 664, 662 (M^+, <3, 4, 6, 4, <3), 589, 587, 585, 583 (M^+ - Br, <3, 3, 3, <3), 441, 439, 437 (M^+ - SO_2H, - 2 Br, 13, 30, 23), 359, 361 (72, 72), 281 (100), 265 (75). - HR-MS: $C_{22}H_{18}{}^{79}Br_3{}^{81}BrO_2S$, calcd. 663.7722, found 663.7704; $C_{22}H_{18}{}^{79}Br_2{}^{81}Br_2O_2S$ calcd. 665.7702, found 665.7686; $C_{22}H_{18}{}^{79}Br{}^{81}Br_3O_2S$ calcd. 667.7685, found 667.7670.

3,10,18,25-Tetrathiaheptacyclo[14.14.7.2^{5,8}.2^{20,23}.1^{32,36}.0^{12,37}.0^{27,31}]-dotetraconta-1(31),5,7,12 (37),13,15,20,22,27,29,32(42),33,35,38,40-pentadecaene-42-sulfinic acid (**9**): Under nitrogen within 8 h, a solution of tetrabromide **7** (2.84 g, 4.27 mmol) and 1,4-bis(mercaptomethyl)-benzene (1.45 g, 8.53 mmol)[8] in 500 ml of dry toluene was added to a well stirred boiling solution of KOH p.a. (12.0 g, 214 mmol) in 400 ml of dry ethanol. The yellow to brown solution was refluxed for additional 60 min and the solvents were evaporated. 500 ml of dichloromethane and 150 ml of 2 N HCl were added to the brown residue, insoluble particles were filtered off, and the dichloromethane layer was washed with 100 ml of water and dried with $MgSO_4$. Evaporation of the solvent yielded 1.5 g of an orange to brown solid which was purified by chromatography [silica gel, dichloromethane/ethanol/water (50 : 10 : 1), R_f 0.73], yield: 290 mg (10%) of **9**, m. p. >300°C. - IR (KBr): $\tilde{\nu}$ = 3640 - 3300 (OH), 2909 (CH), 1429 (CH), 1099 (S=O), 801 (SO-OH), 756 (arom). - ^{1}H NMR (200 MHz, $CDCl_3$): δ= 2.20 (d, J = 10.2 Hz, 4 H), 3.13 (d, J = 10.2 Hz, 4 H), 3.20 (br. s, $SO_2H{\cdot}H_2O$, exchanges with D_2O, ca. 3 H), 3.63 (d, J = 13.5 Hz, 4 H), 3.71 (d, J = 13.5 Hz, 4 H), 6.80 (br. s, 4 H), 7.12 - 7.22 (m, 8 H), 7.24 (br. d, J = 7.0 Hz, 2 H), 7.40 (br. d, J = 7.0 Hz, 2 H), 7.52 (ABB'-System, J = 8.5 Hz, J = 7.0 Hz, 1 H). - MS (EI, 70 eV): m/z (%) = 664 (M^+ - H_2O, 5), 618 (M^+ - SO_2, 34), 481 (17), 311 (53), 64 (100). - $C_{38}H_{34}O_2S_5 \cdot H_2O$ (701.04) calcd. C 65.11 H 5.18, found C 64.99 H 5.09.

Titrations

In 2-methoxyethanol/water: The pK_a values were determined by potentiometric titration of 1 mM solutions of the acids with a standardized sodium hydroxide solution (0.1 N) in 80 % (w/w) 2-methoxyethanol/water at 25°C. Each titration was reproduced at least three times. Reproducibility: 0.1 pK_a units for the bimacrocyclic acids, 0.05 pK_a units for all other acids.

In ethanol: 3 ml of a 100 mM solution of a phenolate (for **12**: sodium 4-nitro-2,6-diphenylphenolate,[14] bromokresol green; for **6**: sodium 4-nitrophenolate,[14] sodium 4-nitro-2,6-diphenylphenolate, sodium 4-nitro-2,6-bis(3,5-dimethoxyphenyl)-phenolate;[14] for **10**: sodium 4-nitrophenolate[15]) in ethanol was titrated with small volumina (1 - 100 µl) of a 20 - 70 mM solution of **6**, **10** or **12** in ethanol or acetone. Via the change in UV-absorption, relative acidities were determined. The relative acidity scale was attached to the pK_a scale by using the known pK_a of bromokresol green in ethanol (10.30).[16]

REFERENCES AND FOOTNOTES

1. Concave Reagents 16: Ross, H.; Lüning, U. *Angew. Chem.*, in press.
2. Lüning, U. *Top. Curr. Chem.* **1995**, *175*, 57 - 99, and ref.
3. Vinod, T. K.; Hart, H. *Top. Curr. Chem.* **1994**, *172*, 119 - 178.
4. Lüning, U.; Baumgartner, H. *Synlett* **1993**, 571 - 572.
5. Even gallium has been incorporated into the 2'-position of a 2,2",6,6"-tetramethyl-*m*-terphenyl: Li, X.- W.; Pennington, W. T.; Robinson, G. H. *Organometallics* **1995**, *14*, 2109 - 2111.
6. Goto, K.; Tokitoh, N.; Okazahi, R. *Angew. Chem.* **1995**, 107, 1202 - 1203; *Int. Ed. Engl.* **1995**, *34*, 1124 - 1126.
7. a) Lüning, U.; Wangnick, C.; Peters, K.; v. Schnering, H. G. *Chem. Ber.* **1991**, *124*, 397 - 402.
   b) Lüning, U.; Wangnick, C. *Liebigs Ann. Chem.* **1992**, 481 - 484.
8. Brink, M. *Synthesis* **1975**, 807 - 808.
9. Simon, W.; Lyssy, G. H.; Mörikofer, A.; Heilbronner, E. *Zusammenstellung von scheinbaren Dissoziationskonstanten im Lösungsmittelsystem Methylcellusolve/Wasser*, vol. 1, Juris-Verlag, Zürich **1959**.
10. Bowden, K.; Hojatti, M. *J. Chem. Soc. Perkin Trans. II*, **1990**, 1201 - 1203.
11. Chen, C.-T.; Siegel, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 5959 - 5960.

12 . a) Lüning, U. *Adv. Phys. Org. Chem. 30*, in press. - b) Skowronska-Ptasinska, M.; Telleman, P.; Aarts, V. M. L. J.; Grootenhuis, P. D. J.; van Eerden, J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* **1987**, *28*, 1937 - 1940.

13 . With isolation and purification of the lithium salt **3** and for smaller batches yields up to 70% are possible, see [4].

14 . Wangnick, C. *Dissertation*: *"Konkave Säuren", Synthese von sterisch extrem gehinderten Carbonsäuren*, Universität Freiburg **1991**.

15 . Analogous to: Goddard, D.; Goddard, A. E. *J. Chem. Soc.* **1922**, 54 - 58.

16 . Bishop, E. in *Analytical Chemistry, Vol. 51, Indicators* (Ed. Belcher, R.; Frieser, H.) 1. ed., Pergamon Press, Braunschweig **1972**.

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