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Synthesis of Tetraoxygenated Terephthalates via a Dichloroquinone Route: Characterization of Cross-Conjugated *Liebermann* Betaine Intermediates

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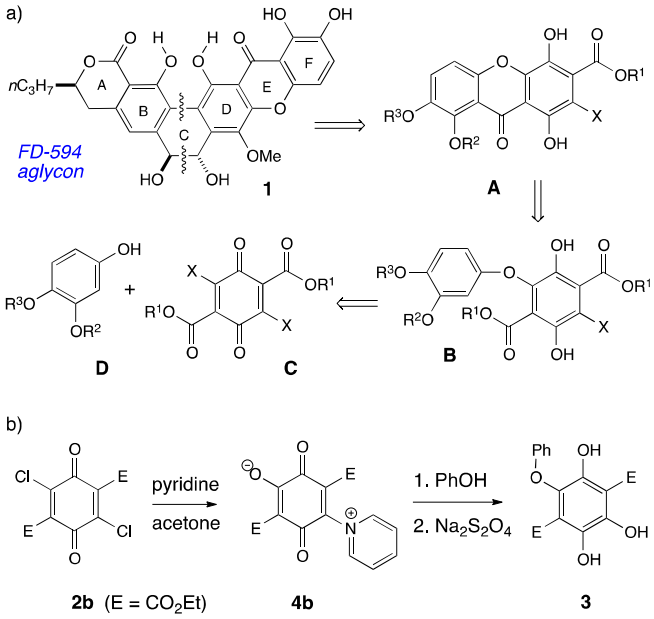
Dedicated to the memory of Hans Liebermann and David Lisser

Cross-conjugated quinoid betaines **4** (2,5-bis(alkoxycarbonyl)-3,6-dioxo-4-(1-pyridinium-1-yl)cyclohexa-1,4-dien-1-olates; *Liebermann* betaines) were synthesized from 2,5-dichloro-3,6-dioxo-cyclohexa-1,4-diene-1,4-dicarboxylates (**2**) and pyridines in acetone containing water. Their structure was secured by NMR spectroscopy and by X-ray diffraction analysis of **4f** (alkoxy = OEt, pyridine = 4-$Me_2NC_5H_4N$). Betaines **4** show comparatively high reactivity towards nucleophiles as a consequence of their cross-conjugated character. Betaine **4a** and hydroxy-3,4-methylenedioxybenzene (sesamol) condense to give a pyridinium quinolate salt **14** which has a bifurcate hydrogen bond from a pyridinium N^+–H donor to both carbonyl (C=O) and olate (C–O^-) acceptors in the solid state. Betaine **4b** hydrolyzes in aqueous solution to give diethyl 2,5-dihydroxy-3,6-dioxocyclohexa-1,4-diene-1,4-dicarboxylate (**11**) as a pyridinium salt, or as polymeric zinc(II) complex of the dianion of **11** in the presence of $ZnCl_2$. Dihydroxyquinone **11** was analytically differentiated from its independently prepared hydroquinone form, diethyl 2,3,5,6-tetrahydroxy-terephthalate (**12**), by NMR analysis in solution and X-ray crystal structure determination of both compounds.

Keywords: betaines • conjugation • nitrogen heterocycles • quinones • structure elucidation

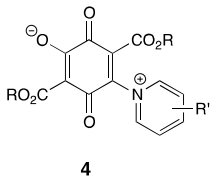
Introduction

The regioselective composition of fully substituted, highly oxygenated aromatic cores needs to be addressed in the total synthesis of oxygenated natural products, a leading example being polycyclic xanthones.[1] Such challenges were presented in synthetic approaches towards aglycon **1** of the xanthoquinone antibiotic FD-594[2][3] with its hexasubstituted aromatic D-ring with six different substituents (Scheme 1a).



Scheme 1. a) Retrosynthetic disconnection of xanthone **A** to dihaloquinone terephthalate **C**. b) Synthesis of a tetraoxygenated terephthalate.

Based on a chirality transfer strategy already successfully implemented in total syntheses of the pradimicin, benanomicin and TAN-1085 structures,[4] FD-594 aglycon (**1**) was disconnected to a xanthone **A** (Scheme 1a). The latter reveals a hidden symmetry[5] after disconnection to *O*-aryl ether **B**, since this compound might result from an S_NAr reaction of quinone **C** (X = leaving group) with phenol **D**. The approach took inspiration from work by *Liebermann* and *Lisser*[6] who had coupled dichloroquinone **2b** with phenols in the presence of pyridine to give derivatives of type **3** (Scheme 1b), and had proposed the mesomeric betaine **4b** (*Liebermann's* betaine) as isolable reaction intermediate (Scheme 1b, Figure 1).



	R	R'
4a	Me	H
4b	Et	H
4c	Bn	H
4d	(1*R*)-menthyl	H
4e	Et	3,5-Me_2
4f	Et	4-NMe_2

Figure 1. Structures of *Liebermann* betaines discussed in this work.

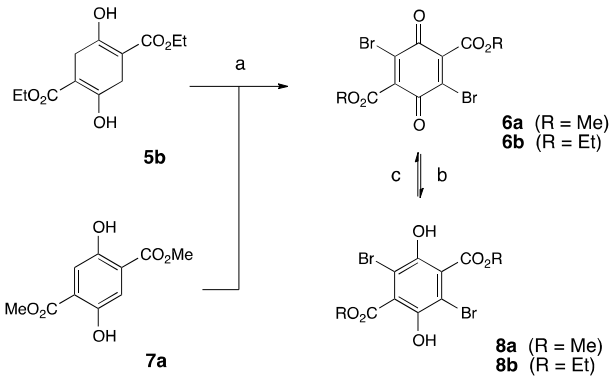
Mesomeric, heterocyclic betaines possess intriguing electronic structures that present challenges to theories of electronic structure and systems of classification alike.[7][8] They serve as intermediates in the synthesis of aromatic and heterocyclic compounds,[7][9] and some have been isolated from natural sources.[10] *Liebermann* and *Lisser* had reported the single representative **4b** in 1934 and assigned its structure based on indirect arguments.[6][11] While syntheses of targets corresponding to **A** starting from dichloroquinone esters **2** have eventually been realized via slightly different routes,[3][12] we wish to report here the result of experiments undertaken to explore the option of using the fascinating betaines **4** as synthetic entry into tetraoxygenated terephthalates. In the course of those studies, we have determined spectral, structural and reactivity properties of several betaines **4** (Figure 1).

Results and Discussion

Dichloroquinones **2** are conveniently prepared on laboratory scale from succinylosuccinates **5** and *N*-chlorosuccinimide in acetic acid.[13] The analogous reaction of **5b** with *N*-bromosuccinimide (NBS) gives bromoquinone ester **6b** (Scheme 2a). However, the latter compound results in higher yield from direct bromination of **5**.[14][15] Compound **6a** is likewise obtained by direct bromination of **7a**, which is conveniently prepared from **5a** and NCS.[13] The last step of the multistep conversion from either **5** or **7** to **6**:

8 + Br_2 ⇌ **6** + 2 HBr (eq 1)

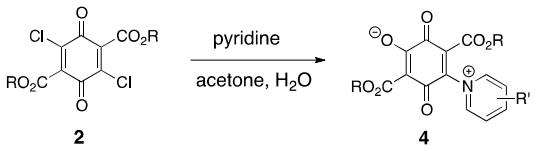
is reversible; therefore, mixtures of **6** and **8** are obtained unless an excess of Br_2 is applied. The reversibility of reaction (1) was proven by heating **6b** with HBr in acetic acid: bromine vapors are liberated, and **8b** is isolated from the reaction mixture (Scheme 2b). However, reference samples of dibromohydroquinones **8** are best obtained by dithionite reduction of quinones **6** (Scheme 2c).

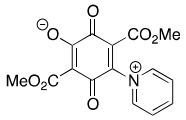
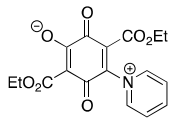
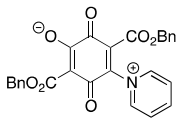
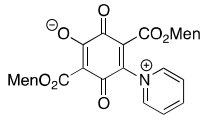
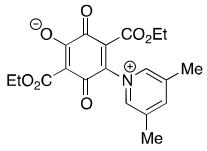
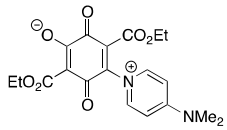


Scheme 2. a) Br_2, HOAc, r.t. (**6a**, 82% from **7a**) or NBS, HOAc, 80 °C→ r.t. (**6b**, 46% from **5b**). b) $Na_2S_2O_4$, H_2O, CH_2Cl_2 (**8a**, 94%), or HBr·HOAc, 85 °C (**8b**, 73%). c) NBS, HOAc, or Br_2, HOAc, r.t.

According to *Liebermann* and *Lisser*, diethyl 2,5-dichloroquinone-1,4-dicarboxylate **2b** reacts with excess pyridine in acetone to give dark crystals of betaine **4b** (Table 1).[6] Based on the plausible stoichiometry, this reaction consumes an equivalent of water, which may have come either from residual water present in commercial acetone, or from water generated through a pyridine induced aldol condensation of acetone itself. We prefer to add a few drops of water to the reaction mixture to render the precipitation of betaines more reliable. The crude betaine crystals were often contaminated with pyridinium chloride, as indicated by a positive Ag^+-test for chloride. Due to their limited stability in protic solvents, and low solubility in most other solvents, the crude betaines could not be readily purified by recrystallization. Specific purification protocols were thus developed, including washing sequences with ethanol or isopropanol, or chemical removal of hydrogen chloride by stirring with Ag_2O, followed by filtration, evaporation and crystallization (see *experimental part* for details). *Liebermann*-betaines **4** derived from various chloroquinone esters **2** and pyridines were thus obtained in analytically pure form (Table 1), except for dimethyl ester **4a**, whose solubility properties prevented the isolation of the pure compound (Table 1, entry 1).

Table 1. Synthesis of *Liebermann* betaines.[a]



entry	quinone	pyridine	product	yield [%]
1	**2a** (R = Me)	Py	 **4a**	–
2	**2b** (R = Et)	Py	 **4b**	59–62
3	**2c** (R = Bn)	Py	 **4c**	53
4	**2d** (R = Men)[b]	Py	 **4d**	76
5	**2b** (R = Et)	3,5-Me_2Py	 **4e**	66
6	**2b** (R = Et)	DMAP	 **4f**	76

[a] See experimental part for reaction condition details. [b] Men = (1*R*)-menthyl = (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl. Py = pyridine.

Betaines **4b–d** were obtained by reaction of the starting esters **2** with pyridine (Table 1, entries 2–4). Ethyl ester **3b** also reacts with 3,5-dimethylpyridine or 4-*N,N*-dimethylaminopyridine (DMAP) to give betaines **4e** or **4f**, respectively (Table 1, entries 5,6). Reactions of **2b** with quinoline, isoquinoline or 2,4-dimethylpyridine showed low conversion and gave impure reaction products, pointing to a steric limitation of the reaction. Methyl ester betaine **4a**, which is readily generated from **2a** or **6a**, has not been obtained free from halide salt impurities, but its *in-situ* solutions could be used for further reactions (*vide infra*). Betaines **4** are either rust-red powders or dark violet solids, depending on particle size. Fresh solutions in hydroxylic solvents are red, but those in aprotic solvents are intensely dark-violet. Compound **4b** crystallizes from hot acetonitrile as dark-red dendritic microcrystals. The more lipophilic menthyl ester betain **4d** crystallized from CH_2Cl_2–hexane, but twinning along the largest crystal face beset a structural characterization of the plate-like, thin, dark-violet crystals. Crystals suitable for X-ray diffraction were obtained from dark-violet solutions of **4f** in CH_2Cl_2–hexane. The crystallographic analysis (Figure 2) confirms the structure proposed by *Liebermann*, which had relied on elemental analysis data and reactivity considerations.[6] The dimethylamino-group of **4f** is coplanar and fully conjugated to the heterocyclic ring, while the pyridinium substituent itself is rotated relative to the plane of the quinoid core by 63°. The bonding angles of the exocyclic substituents around the fully substituted six-membered quinoid core ring deviate from the idealized 120° geometry. Notably, the angle O(3)-C(5)-C(4) amounts to 125.7°, N(1)-C(2)-C(3) to 115.8°, and O(2)-C(3)-C(2) to 115.6°. While it is tempting to ascribe part of this deviation to electrostatic

attraction between O(2) and N(1), it should be noted that the observed deviations are always directed towards the longer intra-ring C–C bonds and thus may also represent an equilibration of steric repulsion among the exocyclic substituents. In the supramolecular structure of **4f**, four equivalent molecules meet with their ethyl end groups in the center of the unit cell, allowing for relatively large librations in this "hydrophobic region", hence the observed disorder. The molecules are tiled with their quinoid rings along the α-axis.

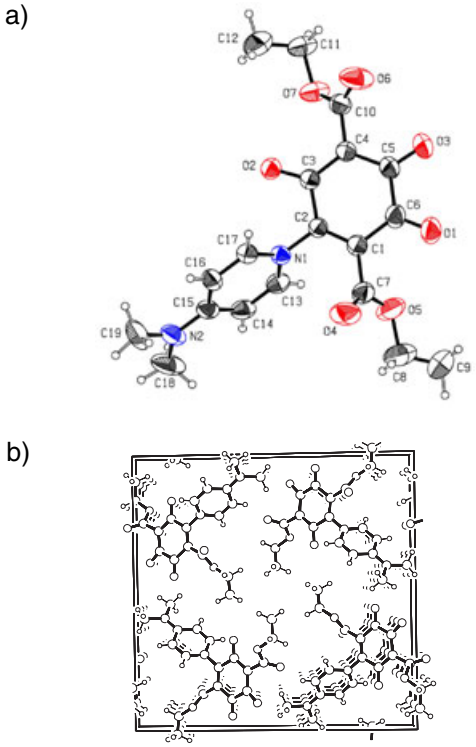
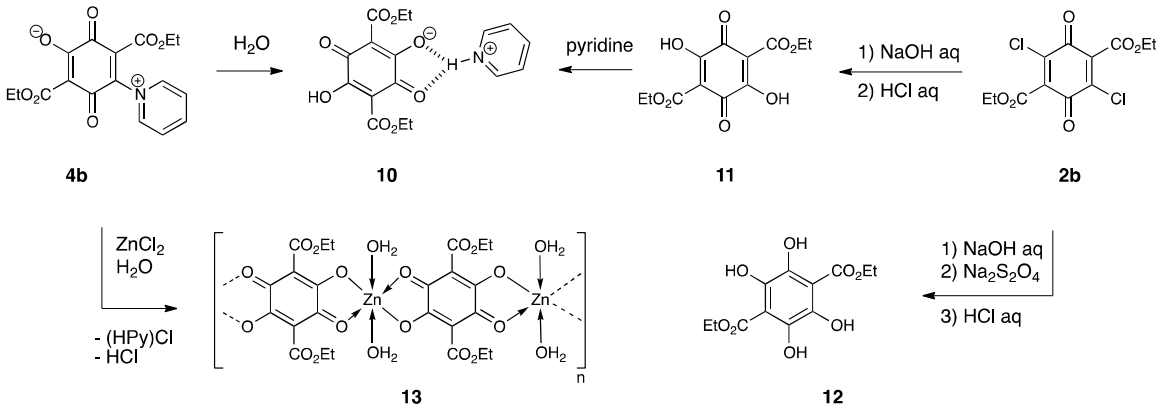


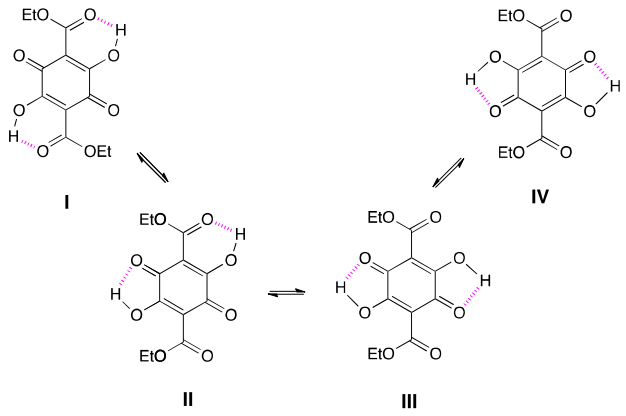
Figure 2. a) ORTEP representation of a single molecule of **4f** with ellipsoids at the 30% probability level. Nitrogen atoms are colored blue, oxygen atoms red. b) Unit cell view showing the center, where four ethyl groups meet in a hydrophobic, disordered region.

Betaines **4** are notably electrophilic; they slowly hydrolyze in solution in the presence of moisture. Dark-red aqueous solutions of **4b** turn brown-yellow over a day at room temperature, or within 3 h at 60 °C. Evaporation of such hydrolysates to dryness gives a brown-red residue that is soluble in CH_2Cl_2 or $CDCl_3$; its NMR data are consistent with pyridinium salt **10** of dihydroxyquinone ester **11** (Scheme 3a).



Scheme 3. Syntheses of quinone **11**, hydroquinone **12** and derivatives of **11** from *Liebermann*'s betaine **4b**.

A corresponding ^{1}H-NMR spectrum was obtained by mixing 2,5-dihydroxyquinone **11** with pyridine in $CDCl_3$. The latter was prepared by dissolving chloroquinone **2b** in aqueous base, followed by acidification (Scheme 3).[16] If the basic solution was treated with sodium dithionite prior to acidification, hydroquinone ester **12** precipitated instead.[17] Both compounds had been described in the late 19th century, but there is little recent work on them in spite of their potential relevance as ligands for metal-organic frameworks.[18] In 1989, dimethyl tetrahydroxyterephthalate was claimed as the side-product of reactions of chloroquinone dimethylester **2a** with basic nucleophiles in DMSO,[19] but comparison of the reported ^{13}C-NMR data with those of **11**/**12** shows that the compound in question must have been the dihydroxyquinone dimethylester.[1] The ^{1}H-NMR spectrum of dihydroxyquinone **11** in $CDCl_3$ solution displays two broadened singlets in the high frequency region at δ13.73 and 15.00 in a ratio of ≈12:1, which could correspond to two hydrogen-bond tautomers like **I** and **II** (Scheme 4),[2] whereas the (D_6)-DMSO solution features a single signal for the OH group at $\delta(^1H)$ = 9.53 that could be hydrogen bonded to the solvent. Dynamics of **11** in $CDCl_3$ are evident from observation of only one carbon signal ($\delta(^{13}C)$ = 106.6, C-1/4) for the quinoid core; the second signal for C-2/3/5/6 is presumably invisible due to line broadening. In DMSO solution, signals for both C-1/4 (110.2) and C-2/3/5/6 (163.3) are apparent; the equivalency of C-2 with C-6 and of C-3 with C-5 points to fast tautomeric exchanges via structures **III** and **IV**.



Scheme 4. Tautomeric structures of **11**.

The X-ray crystal structure for **11** shows the molecule to have a planar structure with all non-hydrogen atoms in one plane (Figure 3). Both phenolic hydroxy groups are involved in intramolecular hydrogen bonds with ester carbonyl oxygens, representing tautomer **I** (cf. Scheme 4). The quinoid carbonyl bond C(1)–O(1) is shortened to 121.5 pm, the ester carbonyl C(4)–O(3) at 123.1 pm, and the C(3)–O(2) single bond to hydroxyl at 131.1 pm. The C–C bonds separating the conjugated 3-hydroxy-2-alken-1-one subunits C(1)–C(3a) and C(1a)–C(3) are only slightly shorter (152.2 pm) than a regular C–C single bond.

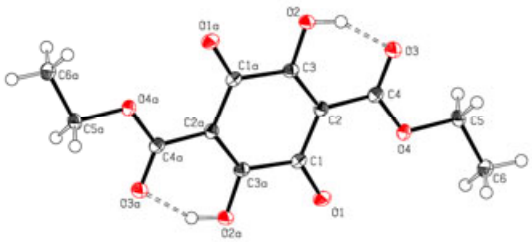


Figure 3. ORTEP representation of dihydroxyquinone **11**. Ellipsoids are shown at 50% probability.

[1] The missassignment was probably caused by the observation of 4 peaks in the ^{13}C-NMR spectrum (DMSO; δ= 52.15, 110.37, 163.77, 168.56) rather than the 5 peaks expected for a static structure. The actual symmetry is higher due to a dynamic proton exchange, *vide infra*.

[2] The high frequency shift of the minor tautomer should be due to a salicylate type 6-membred ring hydrogen bond, and not a hydroxyquinone type 5-membered ring H-bond; compare $\delta(^1H)$ in $CDCl_3$ of the OH-group in methyl salicylate (10.74) relative to that of 2,5-dihydroxyquinone (7.74).

A sample solution of the tetrahydroxyphthalate **12** in $CDCl_3$ evaporated to leave a rather large single crystal (see Figure S-1). Any ambiguity as to whether oxidation to quinone **11** might have occurred in air was resolved when X-ray crystallography revealed the crystal to be composed of **12**. All hydroxy groups are involved in intramolecular hydrogen bonds to their proximal ester group, either to carbonyl or alkoxy oxygen (Figure 4). The hydrogen binding to alkoxy oxygen is also involved in another hydrogen bond to a phenolic oxygen of a neighboring molecule as acceptor.

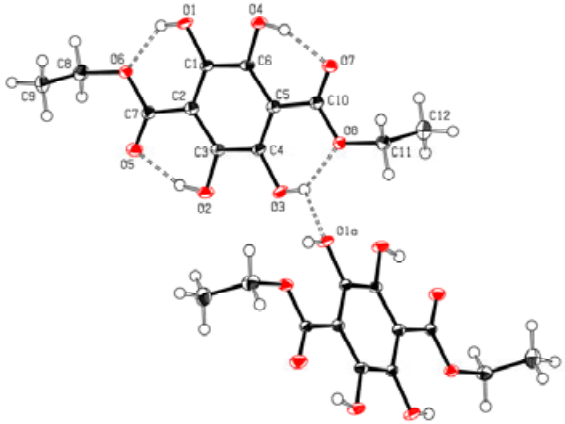
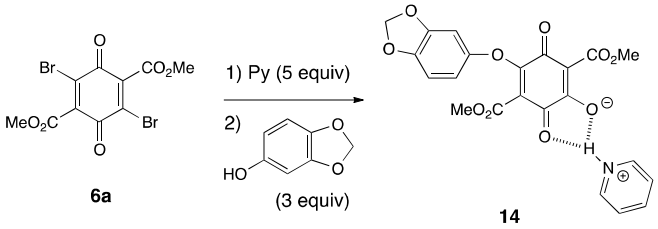


Figure 4. Representation of two molecules of **12** showing intramolecular and intermolecular hydrogen bonding schemes. Ellipsoids are shown at 50% probability.

Returning to the topic of hydrolysis of betaine **4b**, it was found that some metal ions (Ca^{2+}, Ag^{+}, Mg^{2+}, Zn^{2+}) accelerate the process, which is then accompanied by precipitation of metal containing solids. Among these, the Zn(II) complex **13** resulting from reaction of **4b** with excess aqueous $ZnCl_2$ was isolated as insoluble, brown-orange powder. This material analyzed as $[Zn^{2+}(C_{12}H_{10}O_8^{2-})(H_2O)_2]$ and must be a coordination polymer involving the bridging dianion of **11** as doubly chelating ligand (Scheme 3). Related complexes of 2,5-dihydroxyquinones are known and can assume a variety of oligomeric or polymeric structures.[20] The generation of such complexes by *in situ* release of the ligand through hydrolysis of a water-soluble precursor is notable. Finally, the reactivity of *Liebermann's* betaines towards phenols as nucleophiles was explored. While the reaction of dihaloquinones **2** and **6** with phenols and pyridine in acetone leads to symmetric, doubly substituted 2,5-diaryloxyquinones,[6][15] *in situ* generation of betaine **4** and coupling with phenols gives access to asymmetric mono-*O*-arylated quinone dicarboxylates.[6] With an intent to use this reaction towards a xanthone precursor **A** for the FD-594 aglycon synthesis (Scheme 1), methyl ester betaine **4a** was generated *in situ* from bromoquinone **6a** and pyridine in acetone, and coupled with sesamol (benzo[*d*][1,3]dioxol-5-ol; Scheme 5). From the non-uniform product mixture, a crystalline material could be separated after two recrystallizations, which was identified as hydroxyquinone pyridinium-salt **14** by X-ray crystal-structure analysis (Scheme 5).



Scheme 5. Coupling of sesamol with an in situ prepared betaine. Py = pyridine.

The pyridinium cation of **14** binds to the hydroxyquinone anion through a three-centered hydrogen bond [N(1)–H = 92.8 pm, N(1)···O(1) = 285.6 pm, N(1)–H(17)···O(1) = 119.0°; N(1)···O(3) = 270.1 pm, N(1)–H(17)···O(3) = 161.4°]. The quinone ring is essentially planar (*rmsd* = 0.02 Å) and inclined 75.7° to the plane of the 1,3-benzodioxol-5-yloxyl moiety. The smaller angle at the oxygen bridge C(2)–O(4)–C(11) amounts to 120°. The methoxycarbonyl groups are rotated out of the plane of the central ring by 75.6° [C(7)–O(5)–O(4)] and 41.4° [C(10)–O(6)–O(7)]. The larger rotation of the carboxymethyl group at C(1) is related to a stacking interaction of its π-system with the benzodioxol moiety, possibly in a donor-acceptor fashion. The formal single bond C2–O8 (134.1 pm) is conjugated to the formal double bond C(6)–

O(1) (121.3 pm; compare to standard C(sp^2)–O and C=O values of ca. 135 and 121 pm, respectively), whereas C5–O3 (124.8(2) pm) and C3–O2 (122.9(2) pm) are part of a fully delocalized system bearing the negative charge, which is asymmetrically distorted towards O(3). The overall conjugated system resembles a *para*- rather than an *ortho* quinoid one. In the crystal unit cell of **14** (Fig. 4), two structurally equivalent molecules are π-π stacked *via* the aromatic rings of the 1,3-benzodioxol-5-yloxyl substituents across the center-of-symmetry (C---C = 372–377 pm). Pyridine-hydroxyquinone adducts such as **10** or **14** can take the form of either hydrogen bridged adducts or salts with complete proton-transfer, depending on the components or the medium.[21] The full proton transfer in **14** is assisted by the acidifying effect of the methoxycarbonyl substituents on the hydroxy-quinone.

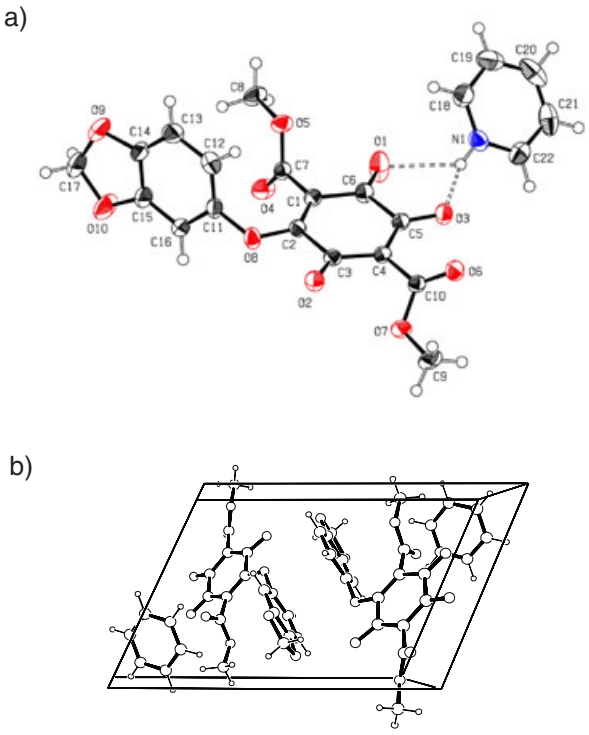


Figure 5. Figure a) ORTEP representation of **14** at the 50% probability level. b) Unit cell view showing the intermolecular stacking of benzodioxole units.

Liebermann-betaines **4** are cross-conjugated heterocyclic mesomeric betaines that are isoconjugate to an odd, alternant hydrocarbon mono-anion (class 9), according to the classification scheme of Ollis et al.[7][22] The term cross-conjugated indicates that the positive and negative charges are delocalized into separate parts of the conjugated system, which follows from an analysis of the energetically most plausible dipolar canonical structures. Betaines **4** can be compared to some related pyridinium-olates for further clarification (Figure 6).[23] *Ullmanns* betaine (**15**)[24] is comparable to **4** in that the charges are mainly located in fragments that correspond to a pyridinium cation and a 1,3-diketonate anion, but they are connected in such a way that the negative charge is also conjugated into the pyridine unit. Three carbons bear both positive and negative charges in suitable canonic resonance structures, which means that in contrast to **4**, **15** is a *conjugated* mesomeric betaine. Further analysis of the dipolar canonical structures shows that it is a conjugated *N*-ylide, as the 1,2-polar resonance form contributes considerably to the true molecule, and it is isoconjugate to an odd alternant hydrocarbon anion (class 5 of Ollis et al).

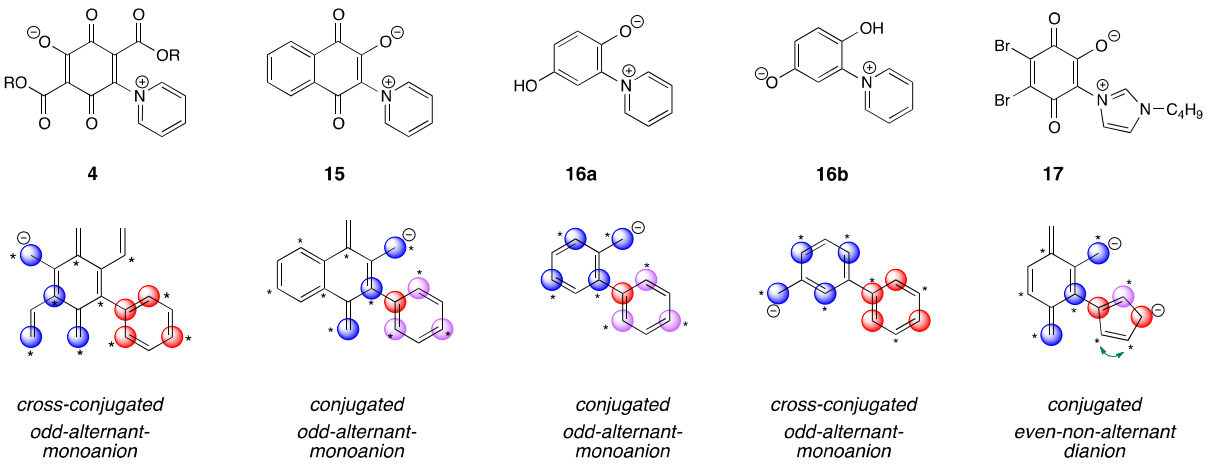


Figure 6. Selected betaines and their classifications, with major limiting structure (top) and isoconjugate hydrocarbon anions (below). The sites of delocalization of positive (red), negative (blue) or both (purple) charges in the canonic resonance forms are also indicated in the formula below.

The case of *Diels'* betaine **16** [25]), which has also been identified as the alkaloid punicine from *Punica granatum*, [26] is interesting as it could principally occur in two tautomeric forms **16a**/**b**, of which **16a** is a conjugated mesomeric betaine, isoconjugate to an odd alternant hydrocarbon anion (class 1), and **16b** is a cross-conjugated betaine, isoconjugate to an odd, alternant hydrocarbon monoanion (class 9). The more recently reported betaine **17** [3c] combines a 1,3-diketoenolate anion with an imidazolium cation. The system is isoconjugate to an even non-alternant hydrocarbon dianion and is a conjugated mesomeric betaine (class 4).

Conclusions

Syntheses of tetraoxygenated terephthalates have been performed starting from the readily availalbe dichloroquinone esters **2** via pyridine-induced S_NAr reactions with oxygen nucleophiles. The intermediary mesomeric pyridinium quinolate betaines **4** (*Liebermann* betaines) have been fully characterized by X-ray crystal structure analysis and NMR spectroscopy. The components **11** and **12** of the dihydroxyquinone dicarboxylate/tetrahydroxyterphthalate redox-system have been synthesized via hydrolysis of dichloroquinone **2** or betaine **4b** and unequivocally characterized by spectral and X-ray crystallographic methods. An application of betaines **4** to serve as ligand precursors for the synthesis of metal-organic coordination polymers in aqueous solution has been suggested.

Appendix

This paper is dedicated to the memory of *Hans Liebermann* and *David Lisser*, who first prepared and described betaine **4b**. *Hans Liebermann* (26.3.1876 – 11.9.1938) was a lecturer and professor of organic chemistry at Technische Hochschule Berlin, where he established a research program on the synthesis of organic dyes using succinylosuccinates (cyclohexane-1,4-dione-2,5-dicarboxylates) as versatile starting materials. [27] In 1934, he was removed from his position due to racial (antisemitic) and political reasons, which led to his eventual suicide. [28] *David Lisser* (28.11.1906 – 15.8.1942) was born in Jaroslawl (Russia) into a (Jewish) family that was forced to emigrate to Germany in 1920 for political reasons. [11] He studied chemistry at TH Berlin and worked towards a doctoral degree with *H. Liebermann* in 1931/2. The synthesis of betaine **4b** was described in his dissertation as part of work clarifying the role of pyridine in reactions of **2b** with nucleophiles. [11] He later moved to France, but was deported to the Auschwitz concentration camp during World War II, where he died. [29]

Experimental Section

General

Reaction temperatures refer to oil-bath temperatures. Melting points were measured on a metal block with a mercury thermometer and are not corrected. [30] TLC were performed on coated plates (F254 indicator) and detected by UV and phosphomolybdate stain. Preparative chromatography (CC = column chromatography) was performed on silica gel 60 (0.040–0.063 mm) using pressured air (0.2

bar) for flash elution. NMR spectra were recorded at room temperature (ca 24 °C). Proton chemical shifts are given relative to internal tetramethylsilane in $CDCl_3$ or referenced against residual solvent signal ([D_5]-DMSO = δ2.50, [D_2]-MeCN = δ1.94). ^{13}C-NMR chemical shifts are referenced relative to solvent signals ($CDCl_3$ = δ77.00; [D_6]-DMSO = δ39.52; [D_3]-MeCN = δ1.32). Unless otherwise mentioned, chemicals were obtained from commercial suppliers and used as received. The starting chloroquinone esters **2** and terephthalate **7a** were obtained as earlier reported.[13]Succinylosuccinates **5a**/**b** re commercially available. Solvents were used as received from suppliers. Acetone used for the preparation of betaines must contain residual water as discussed in the text.

Abbreviations

aq = aqueous solution of; *t*BuOMe = *tert*-butyl-methyl ether; CC = column chromatography; DMAP = 4-(*N*,*N*′-dimethylamino)pyridine; DMF = *N*,*N*-dimethylformamide; (1*R*)-menthyl-(oxy) = (1*R*,2*S*,5*R*)-(2-isopropyl-5-methyl)-cyclohexyl-(oxy)]; NBS = *N*-bromosuccinimide; NCS = *N*-chlorosuccinimide; Py = pyridine; sat = saturated solution of.

Crystallography

CCDC 230927 (**4f**), 230928 (**14**), 1506150 (**11**) and 1506151 (**12**) contain supplementary crystallographic information for this work. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for information on the structure solution.

Bromoquinones and derived compounds

Dimethyl 2,5-dibromo-3,6-dioxo-cyclohexa-1,4-diene-1,4-dicarboxylate (6a): Bromine (5.2 mL, 102 mmol, 10 equiv.) was added in portions to a suspension of **7a** (2.28 g, 10.0 mmol) in HOAc (40 mL) with stirring. A dark brown solution formed with warming. A few mL of water were added, and the reaction mixture was stirred for 1 d at r.t. The resulting yellow suspension was filtered and the solid washed with a little HOAc to give yellow crystals (3.15 g, 82%). M.p. 249–251 °C (lit. 250–251 °C).[31] IR (KBr): 2958w, 2847w, 1742s, 1676s, 1602m, 1437m, 1298s, 1235m, 1112s, 963m, 912m, 826m, 730w. ^{1}H-NMR (395 MHz, $CDCl_3$): 3.99 (s, 6 H, 2 OMe). ^{13}C-NMR (99 MHz, $CDCl_3$): 53.5 (CH_3); 134.1 (C); 141.2 (C); 162.1 (C); 173.8 (C). Anal. calc. for $C_{10}H_6Br_2O_6$ (381.96): C 31.44, H 1.58; found C 31.31, H 1.49.

Diethyl 2,5-dibromo-3,6-dioxo-cyclohexa-1,4-diene-1,4-dicarboxylate (6b): While this compound is probably best synthesized by reaction of either **5b** or **7b** with Br_2,[14][15] a non-optimized procedure using NBS as brominating reagent is given here: To a suspension of **5b** (5.685 g, 22.2 mmol) in HOAc (25 mL) at 80 °C, NBS (4.2 g, 23.6 mmol) was added in portions. After 1.5 h at 85 °C, additional NBS (12.5 g, 70.2 mmol) was added in portions, causing evolution of Br_2-vapors. The reaction mixture was stirred for 6 h at 70 °C. During this time, a suspension formed (presumably of the product), but later the material dissolved again (reduction to **8b**). Another portion of NBS (5.0 g, 28.1 mmol) was added to the reaction solution, which turned to a suspension over 15 min. Heating was discontinued and the vessel set aside for crystallization. Filtration and washing with HOAc (20 mL) and water (2 × 20 mL) gave yellow crystals (4.171 g, 46%) of **6b** after drying in high vacuum. M.p. 223–227 °C (lit. 227 °C).[27d] IR (KBr): 2991w, 2971w, 2944w, 2906w, 1733s, 1676s, 1605m, 1559w, 1472w, 1444w, 1364m, 1287s, 1243m, 1126s, 1106s, 1013m, 862m, 845m, 729w. ^{1}H-NMR (395 MHz, $CDCl_3$): 1.40 (t, ^3J(H,H) = 7.1, 6 H, 2 CH_3 of OEt); 4.47 (q, ^3J(H,H) = 7.1, 4 H, 2 OCH_2). ^{13}C-NMR (99 MHz, $CDCl_3$): 13.7 (CH_3); 63.3 (CH_2); 137.6 (C); 140.3 (C); 160.7 (C); 174.3 (C). Anal. calc. for $C_{12}H_{10}Br_2O_6$ (410.01): C 35.15, H 2.46; found C 35.31, H 2.44.

Dimethyl 2,5-dibromo-3,6-dihydroxy-terephthalate (8a): A suspension of **6a** (1.776 g, 4.65 mmol) in CH_2Cl_2 (20 mL) and a solution of $Na_2S_2O_4$ (85%; 2.17 g, 9.3 mmol) in water (30 mL) were combined and vigorously stirred for 30 min at r.t. The CH_2Cl_2 was carefully removed (foaming may occur!) in vacuum at a rotatory evaporator to give an aqueous suspension of colorless crystals. Filtration, washing of the solid with water and drying in high vacuum gave white crystals of **8a** (1.679 g, 94%). This colorless material dissolves with yellow-green color in CH_2Cl_2 (*solvatochromism*). M.p. 204–206 °C (lit. 205 °C).[32] ^{1}H-NMR (395 MHz, $CDCl_3$): 4.04 (s, 6 H, 2 OMe); 8.88 (s, 2 H, 2 OH). ^{13}C-NMR (99 MHz, $CDCl_3$): 53.1 (CH_3); 109.7 (C); 121.7 (C); 149.1 (C); 167.6 (C). IR (KBr): 3239m br., 1696s, 1438m, 1414m, 1319m, 1286m, 1209m, 972m, 821m. Anal. calc. for $C_{10}H_8Br_2O_6$ (383.98): C 31.28, H 2.10; found C 31.17, H 1.98.

Dimethyl 2,5-dibromo-3,6-dimethoxy-terephthalate: The dimethylether derivative of hydroquinone **8a** was prepared for further characterization: To a solution of **8a** (775 mg, 2.02 mmol) in DMF (2 mL) and MeI (1.0 mL, 16 mmol), NaH (60% in oil; 170 mg, 4.25 mmol) was added in portions. Gas evolved, and the reaction mixture turned into a thick slurry with warming. After dilution with DMF (2 mL) and stirring for 1 h at 60 °C, the mixture was diluted with *t*BuOMe and quenched with water. The organic phase was washed with sat aq NaCl (2 ×) and evaporated to dryness. CC (*t*BuOMe/hexanes 1:5) resulted in incomplete separation, thus all fractions containing product were combined and evaporated to dryness. The crude product was dissolved in CH_2Cl_2 and MeOH. CH_2Cl_2 was slowly evaporated in vacuum

using a rotatory evaporator. The resulting crystal suspension was filtered and the solid washed with MeOH to give colorless, sugar-like crystals (771 mg, 93%). M.p. 162.5–164.5 °C. IR (KBr): 2946m, 2859w, 1731s, 1458m, 1440m, 1377s, 1262s, 1138m, 1014s, 961m, 808w. ^{1}H-NMR (395 MHz, $CDCl_3$): 3.88 (s, 6 H, 2 OMe); 3.99 (s, 6 H, 2 OMe). ^{13}C-NMR (99 MHz, $CDCl_3$): 53.0 (CH_3); 62.6 (CH_3); 114.1 (C); 134.3 (C); 151.5 (C); 165.3 (C).

Diethyl 2,5-dibromo-3,6-dihydroxy-terephthalate (8b): To a suspension of **6b** (315.5 mg, 0.77 mmol) in HOAc (0.5 mL) at 85 °C, HBr·HOAc (0.57 mL, 3.2 mmol) was added dropwise with stirring. The bromine vapors that developed were occasionally removed by an air-stream. After 15 min, the reaction mixture was diluted with more HOAc (1 mL). Stirring was continued for 1 h at 85 °C. The reaction mixture was cooled and diluted with *t*BuOMe. The reaction solution was washed with water (2 ×), sat aq $NaHCO_3$ (1 ×) and water (2 ×). The organic phase was dried (Na_2SO_4), filtered, and evaporated to give a crude product, which was recrystallized by dissolving in CH_2Cl_2/hexane and slowly evaporating to ca. 2 mL volume. Filtration and washing of the solid with a little hexane gave colorless needles (231.6 mg, 73%). M.p. 156–157 °C (lit. 156 °C,[33] 157 °C[34]). IR (KBr): 3221s br., 2993w, 1694s br., 1473m, 1425s, 1370m, 1316s, 1299s, 1284s, 1205s, 1151m, 1098m, 1011m, 862m, 842m. ^{1}H-NMR (395 MHz, $CDCl_3$): 1.45 (t, ^3J(H,H) = 7.1, 6 H, 2 CH_3); 4.51 (q, ^3J(H,H) = 7.1, 4 H, 2 OCH_2); 8.94 (s, 2 H, 2 OH). ^{13}C-NMR (99 MHz, $CDCl_3$): 14.0 (CH_3); 63.1 (CH_2); 109.6 (C); 121.5 (C); 148.7 (C); 166.7 (C). Anal. calc. for $C_{12}H_{12}Br_2O_6$ (412.03): C 34.98, H 2.94; found C 34.89, H 2.85.

Synthesis of Liebermann's betaines

2,5-Bis(ethoxycarbonyl)-3,6-dioxo-4-(1-pyridinium-1-yl)cyclohexa-1,4-dienolate (4b): *Small scale reaction*: A suspension of **2b** (1.312 g, 4.085 mmol) in technical grade acetone (50 mL)[a] was heated to 45–50 °C to effect complete dissolution. While the solution was still warm, a solution of pyridine (1.32 mL, 16.35 mmol) in acetone (5 mL) was added dropwise over 10 min at r.t., causing a color change to red-violet. Stirring was discontinued and the reaction flask kept at 4 °C overnight. The product crystallized in dark red-violet crystals, which were isolated by filtration and washed with acetone. In the dry state, the color of the product is brown-red. The crude product (1.12 g, 79%) still contained chloride[b] and was purified as follows: The solid was finely suspended in *i*PrOH (5 mL), lumps being broken up with a spatula and using ultrasonication. The suspension was filtered and the product washed with *i*PrOH and Et_2O. Drying in high vacuum gave a fine red-brown powder (880 mg, 62%) containing only traces of chloride. *Larger scale reaction with alternative purification*: The reaction was performed as above on a 26 mmol scale in technical grade acetone (320 mL).[a] The crude product was suspended in acetone (20 mL) at 0 °C and abs. EtOH (20 mL) was added. The suspension was stirred for 15 min at 0 °C, and the product isolated by suction filtration and washing with acetone. The yield was 59%, and the product entirely free of chloride.[b] Recrystallization of the material is possible by preparing filtered, warm (50 °C) solutions of the material in acetonitrile and cooling them to 0 °C (or –20 °C) for several hours. *Notes*: [a]) For the reaction to proceed it is necessary that the acetone contains traces of water, which is often the case if "aged" solvent is used, but may not be the case with a freshly opened bottle. To ensure that the reaction takes place, a few equivalents of water (relative to starting material) may be added to the solvent at the outset of the reaction. [b]) The presence of chloride was tested as follows: a sample of the product was dissolved in a little deionized water with addition of a few drops of dilute 10% aqueous HNO_3. Upon addition of aqueous $AgNO_3$, generation of a turbidity or precipitation of AgCl indicated the presence of chloride. M.p. >171 °C dec. (lit. 194 °C, dec.).[6] IR (KBr): 3121w, 3090w, 3061w, 2996w, 1740s, 1718s, 1676s, 1624s, 1577s, 1555s, 1473m, 1400m, 1375m, 1314m, 1282m, 1234m, 1193m, 1060w, 1019w, 783w, 745w, 677w. ^{1}H-NMR (395 MHz, [D_3]-MeCN): 1.00 (t, ^3J(H,H) = 7.1, 3 H, CH_3 of Et); 1.22 (t, ^3J(H,H) = 7.1, 3 H, CH_3 of Et); 4.10 (q, ^3J(H,H) = 7.1, 2 H, OCH_2); 4.14 (q, ^3J(H,H) = 7.1, 2 H, OCH_2); 8.14–8.19 (m, 2 H-Py); 8.66–8.70 (m, 2 H-Py); 8.71 (tt, ^3J(H,H) = 7.9, ^4J(H,H) = 1.4, 1 H-Py). ^{1}H-NMR (395 MHz, [D_6]-DMSO): 0.93 (t, ^3J(H,H) = 7.1, 3 H, CH_3 of Et); 1.17 (t, ^3J(H,H) = 7.0, 3 H, CH_3 of Et); 4.07 (ψ-quint, ^3J(H,H) = 7.1, 4 H, 2 OCH_2); 8.30–8.36 (m, 2 H-Py); 8.84 (tt, ^3J(H,H) = 7.9, ^4J(H,H) = 1.3, 1 H-Py); 9.15–9.21 (m, 2 H-Py). ^{13}C-NMR (99 MHz, [D_6]-DMSO): 13.4 (CH_3); 14.2 (CH_3); 59.3 (CH_2); 62.7 (CH_2); 109.7 (C); 127.9 (CH); 130.0 (C); 145.8 (C); 146.1 (CH); 149.1 (CH); 161.0 (C); 167.0 (C); 169.4 (C); 170.1 (C); 181.8 (C). Anal. calc. for $C_{17}H_{17}NO_7$ (345.30): C 59.13, H 4.38, N 4.06; found C 59.37, H 4.54, N 3.90.

2,5-Bis(benzyloxycarbonyl)-3,6-dioxo-4-(1-pyridinium-1-yl)cyclohexa-1,4-dienolate (4c): To a solution of **2c**[13] (455 mg, 1.02 mmol) in acetone (10 mL) and CH_2Cl_2 (10 mL), a solution of pyridine (0.42 mL, 5.2 mmol) in acetone (5 mL) was added dropwise. A reddish-brown suspension resulted, which was stirred for 1 h at r.t. Solvents were removed in vacuo and the residue stirred with MeOH (10 mL) for 5 min. Filtration and washing of the solid with a little MeOH and *t*BuOMe gave brown powder (255 mg, 53%). The material is soluble in DMSO, not very soluble in MeCN or MeOH. *Note*: The yield is low due to losses into the mother liquor. Less MeOH might be used for the pre-

filtration step. M.p. 152–157 °C dec. IR (KBr): 3063w, 3029w, 1740m, 1696s br., 1623m, 1565s br., 1473m, 1548w, 1399m, 1363m, 1297s, 1175m br., 1064w, 736w, 696w. ^{1}H-NMR (395 MHz, [D$_6$]-DMSO): 5.10 (s, 2 H, OCH$_2$); 5.12 (s, 2 H, OCH$_2$); 7.10–7.18 (m, 2 H-Ph); 7.23–7.47 (m, 8 H-Ph); 8.14 (br. t, ^3J(H,H) ≈ 7, 2 H-Py); 8.68 (t × m, ^3J(H,H) ≈ 7.9, 1 H-Py); 9.10 (br. d, ^3J(H,H) = 6.4, 2 H-Py). ^{13}C-NMR (99 MHz, [D$_6$]-DMSO): 64.8 (CH$_2$); 67.9 (CH$_2$); 108.6 (C); 127.7 (CH); 128.0 (CH); 128.1 (CH); 128.8 (CH); 129.1 (CH); 129.1 (CH); 129.2 (CH); 129.8 (C); 135.0 (C); 137.7 (C); 145.8 (CH); 145.9 (C); 148.8 (CH); 160.9 (C); 166.6 (C); 169.9 (C); 170.3 (C); 181.6 (C). Anal. calc. for $C_{27}H_{19}NO_7$ (469.44): C 69.08, H 4.08, N 2.98; found C 68.79, H 4.12, N 2.72.

2,5-Bis(((1*R*)-menthyloxy)carbonyl)-3,6-dioxo-4-(1-pyridinium-1-yl)cyclohexa-1,4-dienolate (4d): A solution of pyridine (202 µL, 2.50 mmol) in acetone (5 mL) was added dropwise to a solution of **2d**[13] (273.8 mg, 0.506 mmol) in acetone (4 mL). The resulting deep-violet solution was kept 1 h at r.t., then stored overnight at –20 °C for crystallization. The solid was isolated by filtration and re-dissolved in MeCN (10 mL) and acetone (20 mL). Silver oxide (200 mg, 0.86 mmol) was added and the suspension vigorously stirred for 30 min at r.t. Filtration through Celite (washing with acetone) gave a deep-violet solution, which was evaporated to dryness. The resulting dark solid was dissolved in MeCN (2 mL) and CH_2Cl_2 (10 mL). The solution was filtered, evaporated to a small volume (ca. 3 mL), and overlayered with Et_2O (4 mL). Crystallization by standing at 0 °C for several hours gave dark crystals which were washed with Et_2O (217 mg, 76%). The material is insoluble in water, soluble in MeOH (red color). Water precipitates the product from a MeOH-solution. A silver test (see above; in MeOH/H_2O solution) was negative. M.p. 185–189 °C dec. IR (KBr): 2956m, 2871w, 1734m, 1696m, 1624w, 1561s br., 1472m, 1303m, 1195m, 962w. ^{1}H-NMR (395 MHz, $CDCl_3$): 0.58 (d, ^3J(H,H) = 6.9, 3 H); 0.67–1.02 (m, 5 H); 0.76 (d, ^3J(H,H) = 6.9, 3 H); 0.78 (d, ^3J(H,H) = 7.0, 3 H); 0.83 (d, ^3J(H,H) = 6.6, 3 H); 0.87 (br. d, ^3J(H,H) = 6.7, 6 H); 1.02–1.14 (m, 2 H); 1.19–1.29 (m, 1 H); 1.29–1.73 (m, 8 H); 2.07–2.16 (m, 1 H); 2.28 (sept × d, ^3J(H,H) = 6.9, 2.6, 1 H); 4.66 (td, ^3J(H,H) = 10.9, 4.3, 1 H); 4.85 (td, ^3J(H,H) = 10.9, 4.3, 1 H); 8.22 (ψ-t, ^3J(H,H) ≈ 7.4, 2 H); 8.71 (tt, ^3J(H,H) = 7.9, ^4J(H,H) = 1.3, 1 H); 8.75 (br. s, 2 H). ^{13}C-NMR (99 MHz, $CDCl_3$): 15.4 (CH$_3$); 15.7 (CH$_3$); 20.4 (CH$_3$); 20.7 (CH$_3$); 21.5 (CH$_3$); 21.8 (CH$_3$); 22.5 (CH$_2$); 22.7 (CH$_2$); 25.0 (CH); 25.5 (CH); 31.0 (CH); 31.3 (CH); 33.5 (CH$_2$); 34.1 (CH$_2$); 40.1 (CH$_2$); 40.9 (CH$_2$); 46.5 (CH); 46.8 (CH); 74.1 (CH); 78.2 (CH); 110.4 (C); 127.6 (br., CH); 131.3 (C); 144.3 (C); 145.5 (CH); 148.1 (CH); 160.7 (C); 166.6 (C); 169.0 (C); 169.7 (C); 180.5 (C). Anal. calc. for $C_{33}H_{43}NO_7$ (565.70): C 70.06, H 7.66, N 2.48; found C 69.76, H 7.46, N 2.37; sample recryst. from MeCN–*t*BuOMe: found C 69.88, H 7.69, N 2.32.

4-(3,5-Dimethyl-1-pyridinium-1-yl)-2,5-bis(ethoxycarbonyl)-3,6-dioxocyclohexa-1,4-dienolate (4e): Quinone **2b** (963 mg, 3.0 mmol) was dissolved in warm acetone (30 mL) and the solution cooled to r.t. A solution of 3,5-dimethylpyridine (1.37 mL, 12.0 mmol) in acetone (10 mL) was added with gentle stirring. The resulting deep-violet reaction mixture was stored at 0 °C overnight to yield mixed dark violet and colorless crystals. The solids were isolated by filtration and washed with some acetone. The material was finely divided in absolute EtOH (10 mL) at 0 °C and stirred for 5 min. Filtration and washing of the solids with cooled EtOH (3 mL) and drying gave brown-red powder (737.7 mg, 66%). The EtOH-wash is accompanied by losses, but removes chloride salts (negative Ag^+-test, see above). M.p. 186 °C dec. IR (KBr): 3042m, 2978w, 1727m, 1696s br., 1618m, 1566s br., 1477m, 1402m, 1368m, 1319m, 1290m, 1198m, 1096w, 1036w. ^{1}H-NMR (395 MHz, [D$_3$]-MeCN): 1.02 (t, ^3J(H,H) = 7.1, 3 H, CH$_3$ of OEt); 1.21 (t, ^3J(H,H) = 7.1, 3 H, CH$_3$ of OEt); 2.52 (q, ^4J(H,H) = 0.6, 6 H, 2 Me-Py); 4.12 (q, ^3J(H,H) = 7.1, 2 H, OCH$_2$); 4.13 (q, ^3J(H,H) = 7.1, 2 H, OCH$_2$); 8.34–8.36 (m, 1 H-Py); 8.36–8.38 (m, 2 H-Py). ^{13}C-NMR (99 MHz, [D$_3$]-MeCN): 14.2 (CH$_3$), 14.9 (CH$_3$); 18.6 (CH$_3$); 60.8 (CH$_2$); 64.0 (CH$_2$); 111.3 (C); 132.1 (C); 140.1 (C); 143.3 (br., CH); 146.6 (C); 151.2 (CH); 162.2 (C); 168.5 (C); 170.9 (C); 171.2 (C); 183.2 (C). Anal. calc. for $C_{19}H_{19}NO_7$ (373.36): C 61.12, H 5.13, N 3.75; found C 60.98, H 4.99, 3.56.

2,5-Bis-ethoxycarbonyl-3,6-dioxo-4-((4-dimethylamino)-1-pyridinium-1-yl)-cyclohexa-1,4-dienolate (4f): To a solution of **2b** (172 mg, 0.536 mmol) in acetone (15 mL; with 1 drop of water), a solution of DMAP (230 mg, 1.88 mmol) in acetone (10 mL) was added quickly (an orange precipitate forms initially) and the reaction mixture stirred 1 h at r.t. The resulting precipitate was isolated by filtration and washed with a little acetone to remove strongly coloring matters. The solid was redissolved in MeCN (5 mL) and acetone (10 mL). Silver oxide (120 mg, 0.5 mmol) was added and the suspension vigorously stirred for 5 minutes. Filtration through Celite and evaporation of the filtrate gave a crude solid, which was recrystallized from MeCN (2 mL) and Et_2O (6 mL; overlayering) at 0 °C. Filtration and washing of the solid with a little Et_2O gave dark brown-violet solid (159.2 mg, 76%). The material is soluble in CH_2Cl_2 and acetone with dark-violet color, or in water with brown-red color. Crystals suitable for X-ray diffraction were obtained from dark-violet solutions of **4f** in CH_2Cl_2–hexane. M.p. 187–189 °C dec. IR (KBr): 2982w, 1738w, 1684m, 1659s, 1558s, 1309m, 1229m, 1194m. ^{1}H-NMR (395 MHz, [D$_3$]-MeCN): 1.13 (t, ^3J(H,H) = 7.1, 3 H, CH$_3$ of OEt); 1.23 (t, ^3J(H,H) = 7.1, 3 H, CH$_3$ of OEt); 3.23 (s, 6 H, NMe$_2$); 4.14 (q, ^3J(H,H) = 7.1, 2 H, OCH$_2$); 4.18 (q, ^3J(H,H) = 7.1, 2 H, OCH$_2$); 6.91 (A of AB, ψ-d, ^3J(H,H) = 8.0, 2 H-Py); 7.85 (B of AB, ψ-d, ^3J(H,H) = 8.0, 2 H-Py). ^{13}C-NMR (99 MHz, [D$_3$]-MeCN): 14.4 (CH$_3$); 14.9

(CH_3); 41.3 (CH_3); 60.7 (CH_2); 63.8 (CH_2); 108.2 (CH); 111.4 (C); 132.5 (C); 143.3 (CH); 145.8 (C); 158.7 (C); 163.6 (C); 169.0 (C); 170.8 (C); 172.6 (C); 184.1 (C). Anal. calc. for $C_{19}H_{20}N_2O_7$ (388.37): C 58.76, H 5.19, N 7.21; found C 58.48, 5.05, 7.26.

Reaction of Liebermann's betaines with oxygen nucleophiles

Diethyl 2,5-dihydroxy-3,6-dioxo-cyclohexa-1,4-diene-1,4-dicarboxylate (11):[16] Chloroquinone **2b** (322 mg, 1 mmol) was added with stirring to a solution of NaOH (880 mg, ca. 20 mmol) in H_2O (50 mL) to give a homogeneous, dark-yellow solution. After stirring for 1 h at r.t., the solution was quickly neutralized and slightly acidified (pH 3) with aq 2.4 M HCl, followed by evaporation to dryness. The residue was dissolved in hot EtOH (20 mL) and CH_2Cl_2 (20 mL). After standing at 4 °C, the mixture was filtered over Celite and the filtrate evaporated to dryness. The solid residue was dissolved in CH_2Cl_2 (10 mL), the solution filtered over Celite (removes huminous material) and evaporated to a volume of ca 3 mL. On overlayering with hexane (5 mL) and standing overnight at 4°C, yellow needles separated (228 mg, 80%). Crystals for X-ray were obtained by placing a vial with a $CHCl_3$ solution of the substance into a diffusion chamber filled with heptane. M.p. 153–154.5 °C (lit. 152 °C).[16a] IR (KBr): 3440m br., 3006m, 1681s, 1637s, 1566s, 1479m, 1409m, 1380m, 1322s, 1210s, 1025m, 921m. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.44 (t, ^3J(H,H) = 7.1, 6 H, 2 CH_3 of OEt); 4.48 (q, ^3J(H,H) = 7.1, 4 H, 2 OCH_2); 13.73 (br. s, 2 OH, 92.5% abundance); 15.00 (br s, 2 OH, 7.5% abundance). ^{1}H-NMR (400 MHz, (D_6)-DMSO): 1.23 (t, ^3J(H,H) = 7.1, 6 H, 2 CH_3 of OEt); 4.20 (q, ^3J(H,H) = 7.1, 4 H, 2 OCH_2); 9.53 (br s, 2 OH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 14.0 (CH_3); 63.4 (CH_2); 106.6 (C); 169.5 (C); 1 signal not visible due to broadening by dynamic exchange. ^{13}C-NMR (101 MHz, (D_6)-DMSO): 14.10 (C); 60.62 (C); 110.23 (C); 163.31 (C); 168.51 (C). ESI-MS (neg. mode): 283 ([M–H]$^-$), fragmentation pathway 237, 209, 137, 92. Anal. calc. for $C_{12}H_{12}O_8$ (284.22): C 50.71, H 4.26; found C 50.29, H 4.20.

Diethyl 2,3,5,6-tetrahydroxyterephthalate (12): To a suspension of chloroquinone **2b** (698.4 mg, 2.175 mmol) in H_2O (50 mL), aq 1 M NaOH (20 mL, 20 mmol) was added in portions of 5 mL. After stirring for 1 h at r.t., the resulting, homogeneous, dark-yellow-brown solution was treated with a solution of $Na_2S_2O_4$ (85%; 1.73 g, 8.5 mmol) in water (10 mL). After stirring for 10 min at r.t., the solution was neutralized and slightly acidified with dilute aq 2 M HCl (ca 15 mL), inducing precipitation. The suspension was stirred in an ice bath for 30 min and the product isolated by filtration and washing with ice water, followed by a mixture of ice-water/acetone. The resulting gold-yellow needles were dissolved in sufficient CH_2Cl_2 and the solution filtered. The filtrate was evaporated to a small volume (3–4 mL), over-layered with pentane (ca 10 mL) and set aside for crystallization. After 1 d, the mother liquors were removed with a pipette and the crystalline solid was washed 3 times with pentane, each time removing the washing phases with a pipette. After drying in vacuum, yellow-orange crystals remained (527.3 mg, 85%), which were moderately soluble in CH_2Cl_2, $CDCl_3$ or EtOAc, but well soluble in DMSO. A crystal for X-ray structural analysis was obtained by slow evaporation of a $CDCl_3$ solution from an NMR tube (Figure S-1). M.p. 181–182 °C dec. (lit. 178 °C).[6][17] ^{1}H-NMR (400 MHz, $CDCl_3$): 1.51 (t, ^3J(H,H) = 7.1, 6 H, 2 CH_3 of OEt); 4.61 (q, ^3J(H,H) = 7.1, 4 H, 2 OCH_2); 9.03 (s, 4 H, 2 OH). ^{1}H-NMR (400 MHz, [D_6]-DMSO): 1.29 (t, ^3J(H,H) = 7.1, 6 H, 2 CH_3 of OEt); 4.31 (q, ^3J(H,H) = 7.1, 4 H, 2 OCH_2); 8.82 (br s, 4 H, 4 OH). ^{13}C-NMR (101 MHz, $CDCl_3$; ref. = 77.16 ppm): 14.30 (CH_3); 63.58 (CH_2); 105.50 (C); 139.92 (C); 169.23 (C). ^{13}C-NMR (101 MHz, [D_6]-DMSO): 14.02 (CH_3); 61.20 (CH_2); 112.06 (C); 136.67 (C); 166.97 (C).

Zinc(II) salt of 11 (13): To a dark-red solution of betain **4b** (207.6 mg, 0.784 mmol) in water (15 mL), $ZnCl_2$ (570 mg, 4.18 mmol) was added and the mixture stirred at r.t. A turbid yellow-red suspension (yellow precipitate, red solution) was quickly formed. After stirring overnight, the suspension was filtered and the solids washed with water. The solid was dried in high vacuum and placed in an oven at 100 °C for 2 h to give yellow-brown, fine powder (285.7 mg, 95%) analyzing approximately as [$Zn(C_{12}H_{10}O_8)(H_2O)_2$]. Anal. calc. for $C_{12}H_{14}O_{10}Zn$ (383.61): C 37.57, H 3.68, Zn 17.04, found C 37.89, 38.04, H 4.11, 3.91, Zn 16.8 (EDTA titration); calc. for $Zn(C_{12}H_{10}O_8)(H_2O)_{1.8}$: C 37.93, H 3.61, Zn 17.21.

Dimethyl 5-hydroxy-2-(3,4-methylenedioxyphenyloxy)-3,6-dioxo-cyclohexa-1,4-diene-1,4-dicarboxylate, pyridinium salt (14): To a suspension of **6a** (310 mg, 0.812 mmol) in acetone (10 mL) and 5 drops of water, a solution of pyridine (0.38 mL, 4.7 mmol) in acetone (6 mL) was added dropwise. After standing for 1 h at r.t., a solution of sesamol (benzo[*d*][1,3]dioxol-5-ol; 330 mg, 2.39 mmol) in acetone (6 mL) was added to the violet suspension, and the reaction mixture stirred for 20 h at r.t. The resulting orange suspension was filtered and the solids washed with a little acetone. After drying in high vacuum, 302 mg of a brown powder remained. A batch of the crude product (177 mg) was stirred with warm MeCN (5 mL), filtered, and set aside in a closed vessel at 4 °C. After 1 week, a mixture of red-brown and yellow crystals was isolated by decantation and washed with a little MeCN/*t*BuOMe. Another recrystallization of this material from

MeCN/*t*BuOMe again provided a mixture of two kinds of crystals (yellow and red-brown). A few of the red-brown crystals of **14** were separated manually and submitted to X-ray diffraction structure determination. ^{1}H-NMR (395 MHz, $CDCl_3$): 3.70 (s, 3 H, OMe); 3.87 (s, 3 H, OMe); 5.98 (s, 2 H, OCH_2O); 6.49 (dd, ^3J(H,H) = 8.4, ^4J(H,H) = 2.5, 1 H-Ar); 6.64 (d, ^4J(H,H) = 2.5, 1 H-Ar); 6.70 (d, ^3J(H,H) = 8.4, 1 H-Ar); 7.68–7.73 (m, 2 H-Py); 8.15 (tt, ^3J(H,H) = 7.9, ^4J(H,H) = 1.7, 1 H-Py); 8.81–8.84 (m, 2 H-Py); 12.99 (br s, 1 N^+H). ^{13}C-NMR (99 MHz, $CDCl_3$): 52.2 (CH_3); 52.5 (CH_3); 101.6 (CH); 101.8 (CH_2); 108.0 (CH); 111.1 (CH); 121.7 (C); 125.7 (CH); 127.7 (C); 141.5 (CH); 145.0 (C); 145.8 (CH); 148.5 (C); 148.8 (C); 151.0 (C); 155.6 (C); 162.9 (C); 168.0 (C); 169.0 (C); 175.8 (C).

Supplementary Material

Supporting information (figures, ^{1}H and ^{13}C NMR spectra) for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

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Author Contribution Statement

Project design by LH and KS. Experiments, data analysis and writing of the manuscript by LH, with contributions to data analysis and writing by PN. X-ray crystallography by PA and PN.

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