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Dipolar Bent and Linear Acetylenes Substituted by Cationic Quinolinium and Anionic Benzoates. Formation of Mesomeric Betaines

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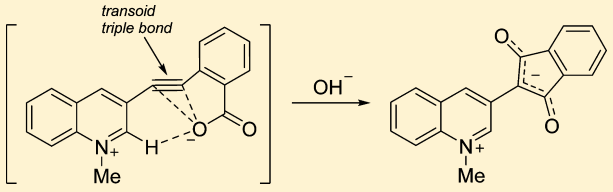
Supporting Information

ABSTRACT: 3-Ethynylquinoline was subjected to a Sonogashira−Hagihara reaction with methyl 2-, 3-, and 4-bromobenzoates, respectively, and then *N*-methylated to give 3-[((methoxycarbonyl)phenyl)ethynyl]-1-methylquinolinium salts (two X-ray analyses). On saponification of the 3- and 4-substituted benzoates, the mesomeric betaines 3- and 4-[(1-methylquinolinium-3-yl)ethynyl]benzoates were formed. By contrast, the 2-benzoate derivative gave either the corresponding (1-oxo-1*H*-isochromen-3-yl)quinolinium derivative or the mesomeric betaine 2-(1-methylquinolinium-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-inden-2-ide depending on the reaction conditions. A DFT calculation predicts a *transoid* conformation of the acetylene bond in the intermediate 2-[(1-methylquinolinium-3-yl)ethynyl]benzoate which is due to a strong hydrogen bond between the carboxylate group and 2*H* of the quinolinium ring, in addition to a 1,5-interaction between the carboxylate group and the CC triple bond. The bond angles of the *transoid* CC triple bond were calculated to be 211.6° and −175.1° in vacuo. The corresponding linear triple bond is 50.4 kJ/mol less stable in vacuo according to the calculation, and the N-heterocyclic carbene quinoline-2-ylidene is not formed as a tautomer.



INTRODUCTION

Heterocyclic mesomeric betaines (MB) are compounds which can exclusively be formulated by dipolar resonance forms. In these forms, the positive and negative charges are delocalized within a common π-electron system. Although sydnones[1] and münchnones[2] seemingly are among the most prominent examples, they represent only two variations of several hundred different structures of mesomeric betaines, among those 228 different types of mesoionic compounds.[3] In 1985, Ollis, Stanforth, and Ramsden proposed a comprehensive classification system for mesomeric betaines which was accepted until 2013.[4] They distinguished four major classes of heterocyclic mesomeric betaines possessing three types of conjugation, i.e., conjugated (CMB), cross-conjugated (CCMB), and pseudo-cross-conjugated mesomeric betaines (PCCMB) and ylides which are closely related to CMB. In 2013, Ramsden recognized two new classes employing a connectivity-matrix analysis[5] supported by DFT calculations.[6] The classification system is the basis to understanding the physical and chemical properties of mesomeric betaines, and this knowledge translates into interesting applications in materials chemistry,[7] synthetic organic chemistry,[8] and natural product chemistry.[9] The distinct classes of mesomeric betaines (MB) also open access to distinct types of N-heterocyclic carbenes (NHCs). Thus, normal NHCs (*n*NHCs) can be prepared under relatively mild conditions starting from pseudo-cross-conjugated mesomeric betaines.[10] By contrast, the formation of abnormal NHCs (*a*NHCs)[11] from mesomeric betaines requires harsh reaction conditions,[12] and the same is true for remote NHCs[12] that are available by other methods.[13] The relatively new class of anionic N-heterocyclic carbenes, however, can easily be formed starting from different types of MBs.[14] The interesting area of overlap between the classes of heterocyclic mesomeric betaines and N-heterocyclic carbenes was first summarized in review articles.[15]

Quinolinium-3-carboxylate (**1**) (benzotrigonelline, 3QB) is a typical example of a cross-conjugated mesomeric betaine (CCMB) (Scheme 1). It has been studied with respect to hydrogen-bond formation with mineral acids[16] and formation of hydrates.[17] It induces cellular arrest in G2 in *Pisum sativum*[18] and was studied as a chemical delivery system of metaiodobenzylguanidine (MIBG) to the central nervous system.[19] In the resonance forms of **1**, the charges are strictly delocalized in separate parts of the π-electron system (**I**), and this is characteristic of CCMBs. Additional features of this class of compounds are also fulfilled. Thus, the quinolinium ring is joined to the anion through union bonds ("*u*") to an unstarred position of the isoconjugated equivalent of the anionic fragment (**II**). This unstarred position is a nodal position of the highest

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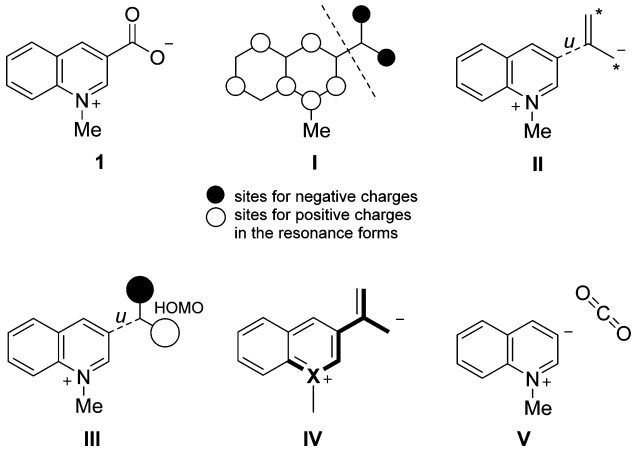
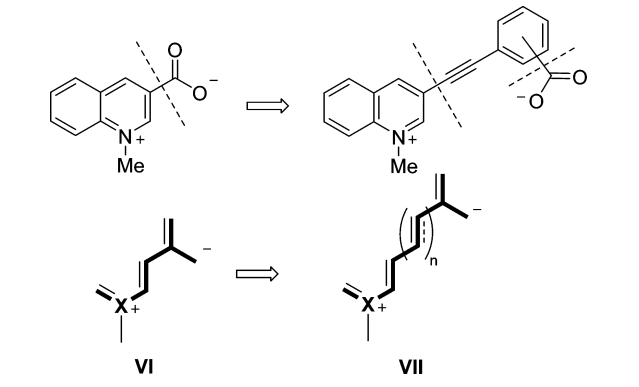
Scheme 1. Quinolinium-3-carboxylate as a Typical Representative of a CCMB



occupied molecular orbital (HOMO) (**III**) which causes a charge-separation in the ground state of the molecule.[20] The characteristic dipole type of this class of mesomeric betaines can be dissected from the resonance forms (**IV**). Formally, the CCMB quinolinium-3-carboxylate is the carbon dioxide adduct of the remote N-heterocyclic carbene quinolin-3-ylidene (**V**),[21] which seemingly is less examined than its benzoannelated derivative pyridin-3-ylidene.[22]

In continuation of our interest in mesomeric betaines and heteroaromatic cations in synthesis[23] and catalysis,[24] we present here π-electronically extended cross-conjugated heterocyclic mesomeric betaines (CCMB) possessing an acetylenic spacer between the charged moieties of the betaine (Scheme 2). The type of conjugation remains unchanged on insertion of conjugated spacers into the characteristic dipole type (**VI** → **VII**).

Scheme 2. Insertion of a Spacer Unit into the Union Bond of CCMB 1

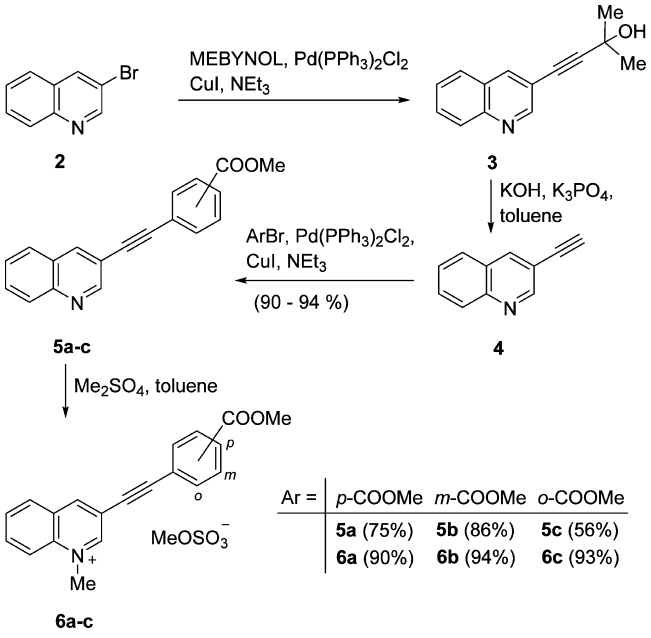


The role of triple bonds as spacers has been investigated intensively, e.g., with respect to conjugation,[25] electronic features of substituents,[26] and light-emitting efficiencies on substitution with donor and acceptor groups.[27] Due to the cross-conjugation, however, the triple bonds are thought to play the role of geometric spacers in the target molecules with respect to the frontier orbital profile. Nevertheless, some surprising results are presented here.

RESULTS AND DISCUSSION

Syntheses and X-ray Crystallographic Characterization. We started the synthesis of the target molecules from 3-bromoquinoline (**2**), which was subjected to a Sonogashira–Hagihara coupling under classical conditions to give 2-methyl-4-(quinolin-3-yl)but-3-yn-2-ol (**3**) (Scheme 3). Deprotection

Scheme 3. Synthesis of Methyl 2-(Quinolinium-3-ylethynyl)benzoates



Ar =	*p*-COOMe	*m*-COOMe	*o*-COOMe
	5a (75%)	**5b** (86%)	**5c** (56%)
	6a (90%)	**6b** (94%)	**6c** (93%)

without prior isolation gave 3-ethynylquinoline (**4**) in 91% yield by a method developed by us previously.[28] This method employs potassium hydroxide and potassium phosphate in toluene and results in clean and efficient deprotection reactions. 3-Ethynylquinoline (**4**) was then subjected to Sonogashira–Hagihara couplings with a slight excess (10–20%) of the acetylenes to give the esters **5a–c** in moderate to good yields. We then tested several methylation reactions of the esters **5a–c** to the corresponding salts **6a–c**. Methylation was best accomplished with dimethyl sulfate in toluene under reflux conditions. The salts **6a–c** precipitated as methylsulfates from the reaction mixtures and were then filtered off and dried in vacuo. The methylsulfate anion can be detected at 3.37 and 52.8 ppm in the NMR spectra. Methyl triflate in stoichiometric amounts at low temperatures (0–20 °C) in dichloromethane was found to give slightly lower yields of the quinolinium salts as the corresponding triflates. Methyl iodide in boiling acetone/methanol/acetonitrile gave only low yields of the corresponding iodide after long reaction times up to 72 h so that this approach was abandoned.

Single crystals of **6a** were obtained after an anion exchange to hexafluorophosphate by slow evaporation of a concentrated solution in MeCN (Figure 1), as the hexafluorophosphate crystallized better than the methyl sulfate. The salt crystallized monoclinic. The triple bond is slightly bent, and bond angles of 174.29(14)° (C3–C9–C10) and 176.92(14)° (C9–C10–C11) are found. The triple bond has a bond length of 119.56(18) pm, and the adjacent bonds are typical single bonds [142.92(16) pm/143.28(16) pm].

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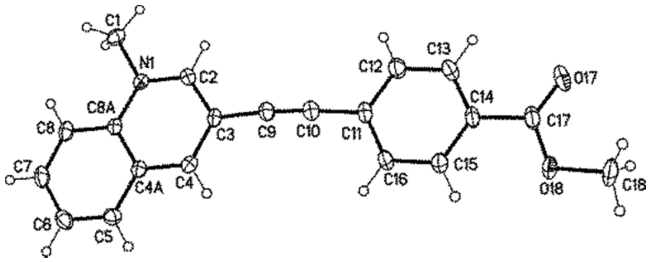


Figure 1. Molecular structure of quinolinium salt **6a** (PF_6 anion and solvent acetonitrile omitted for clarity; displacement parameters are drawn at 50% probability level).

Single crystals were also obtained of salt **6c** after anion exchange from a hot methanol solution. The compound also crystallized monoclinic (Figure 2). Bond angles are

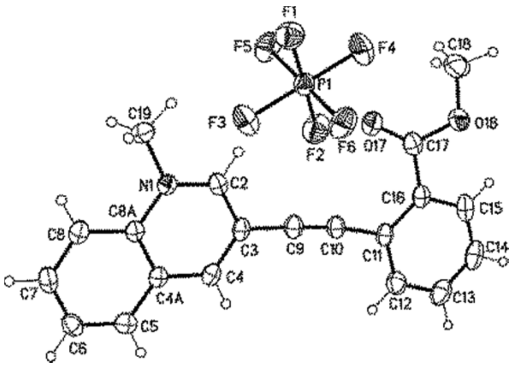
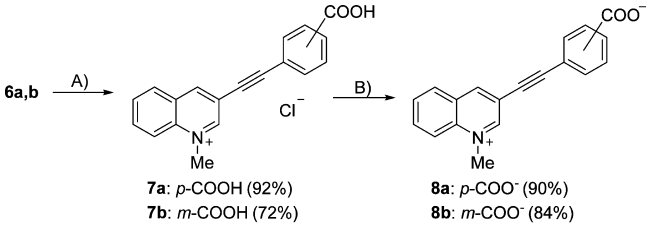


Figure 2. Molecular structure of **6c** (displacement parameters are drawn at 50% probability level).

176.66(18)° (C3−C9−C10) and 172.44(17)° (C9−C10−C11). The triple bond has a length of 119.1(2) pm; the single bonds were determined to be 143.0(2) pm and 143.5 (2) pm. Single crystals of the $COO-CD_3$ derivative of **6c** ("**6c_D**") were obtained after an anion exchange to hexafluorophosphate by slow evaporation of concentrated solution in deuterated MeCN. The salt also crystallized monoclinic. The triple bond of **6c_D** is slightly bent as well, and bond angles of 176.73(18)° (C3−C9−C10) and 172.35(17)° (C9−C10−C11) are found. The triple bond has a bond length of 119.8(2) pm, and the adjacent bonds are typical single bonds, which are 142.9(2) pm and 143.4(2) pm long.

In contrast to other betaine formations, the ester hydrolysis of the salts **6a−c** to the target betaines **8a−c** under acidic conditions (H_2SO_4, HCl, H_3PO_4, HBF_4) failed. On treatment of the salts **6a,b** with excess sodium hydroxide in a methanol−water mixture at elevated temperatures, decomposition to yet unidentified products occurred. On reaction at room temperature, followed by acidification to pH 3, the carboxylic acids **7a,b** precipitated (Scheme 4). The carboxylic acid proton of **7a** can be detected at δ = 13.31 ppm (DMSO-d_6). As expected, the ^{1}H NMR chemical shift differences of 2*H* and 4*H* of the quinolinium ring on formation of the carboxylic acids **7a,b** from the corresponding esters are small ($\Delta\delta$ = 0.07−0.15 ppm). Adjusting the pH value of solutions of the acids **7a,b** in methanol by triethylamine resulted in the formation of the target betaines **8a,b** in very good yields. In the IR spectra of **8a,b**, the triple bond stretching band is observable in medium intensity between 2211 and 2226 cm^{-1}. The calculated frontier orbitals of **8a** confirmed the classification as cross-conjugated

Scheme 4. Formation of the Mesomeric Betaines 8a,b

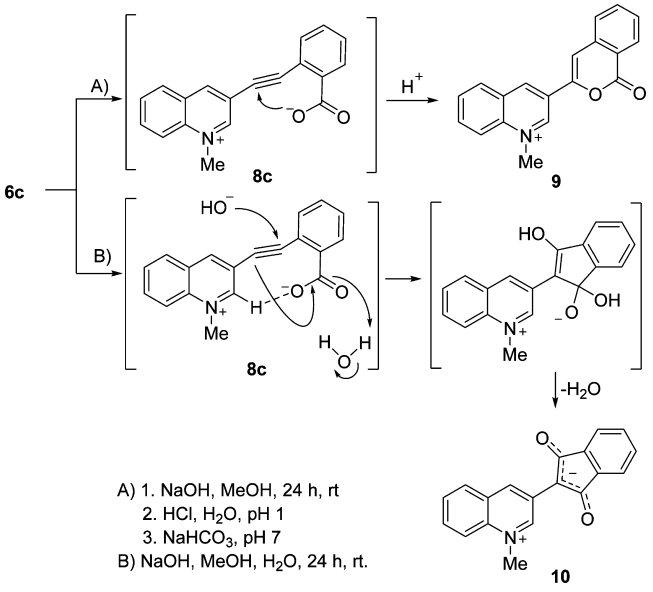


A) 1. NaOH, MeOH, H_2O; 2. HCl, H_2O, pH 3 - 5. B) NEt_3, MeOH, rt, 15 min.

heterocyclic mesomeric betaines (CCMB) as the highest occupied molecular orbitals (HOMOs) are indeed essentially located in the carboxylate group, whereas the LUMO is located in the quinolinium ring as well as in the carboxylate group. Some HOMO/LUMO profiles are shown in the Supporting Information.

On saponification, the ester **6c** showed a different behavior. The oxoisochromene **9** was obtained after addition of an excess of hydrochloric acid to the reaction mixture followed by neutralization with sodium bicarbonate (Scheme 5). Com-

Scheme 5. Reactions and Proposed Mechanisms of the Instable Mesomeric Betaine 8c



pound **9** proved to be unstable in NMR solution. 2-Ethynylbenzoic acid derivatives are known to form oxoisochromenes on treatment with $HgSO_4$ in aqueous sulfuric acid,[29] $PdCl_2(MeCN)_2$,[30] $AuCl/K_2CO_3$ in MeCN,[31] Rh(I) complexes,[32] LiOH in water,[33] iridium halides,[34] iron(III)-chloride/PhSeSePh,[35] and by other methods.

Saponification of the ester **6c** under slightly different reaction conditions in the presence of water gave a dark red solid in 87% yield, to which the structure of the conjugated mesomeric betaine **10** was assigned. The most characteristic chemical shift changes have been observed for the carbonyl carbon atom which differ considerably in **8a,b** (169.5/168.0 ppm) and **10** (189.4 ppm).

We then tried to intercept **8c** by a sequence of reactions beginning with the saponification of **5c** followed by *N*-methylation. On saponification of **5c** with excess of potassium

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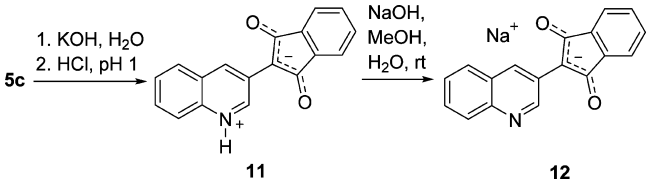
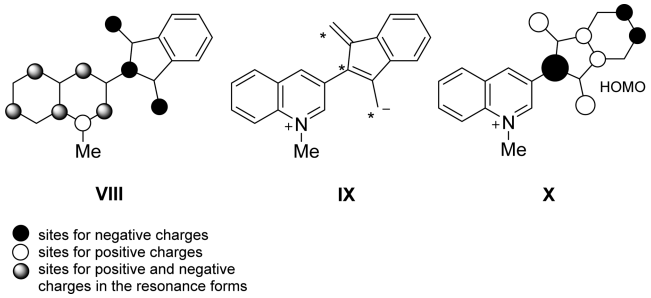
hydroxide followed by acidification of the reaction mixture, however, compound **11** precipitated which proved to be almost insoluble (Scheme 6). Treatment with base gave **12**, which could be characterized spectroscopically by NMR.

Scheme 6. Derivatives of the Mesomeric Betaine 10



Compounds **10** and **11** belong to the class of conjugated heterocyclic mesomeric betaines, as common sites for negative and positive charges exist in the resonance forms (**VIII**) (Scheme 7).[4,5,9,15a] The positive and negative partial structures

Scheme 7. Characteristics of CMB 10



are joined through a starred position (**IX**) which is an active position of the HOMO (**X**).[15a,20] The calculated HOMO/LUMO profile of **10** is shown in the Supporting Information.

Single crystals of 3-(3-hydroxy-1-oxo-1*H*-inden-2-yl)-1-methylquinolinium chloride, i.e., of the protonated form of **10**, were obtained from a saturated solution of **10** in a solvent mixture of methanol, water, and hydrochloric acid. A molecular drawing is shown in Figure 3.

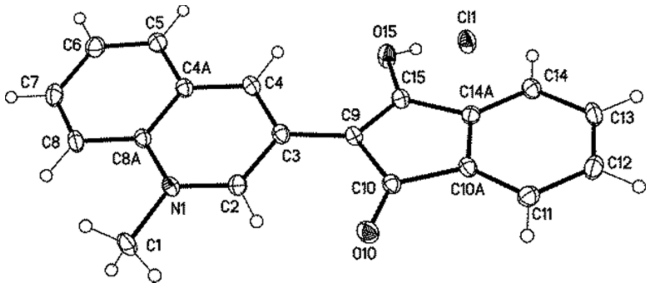
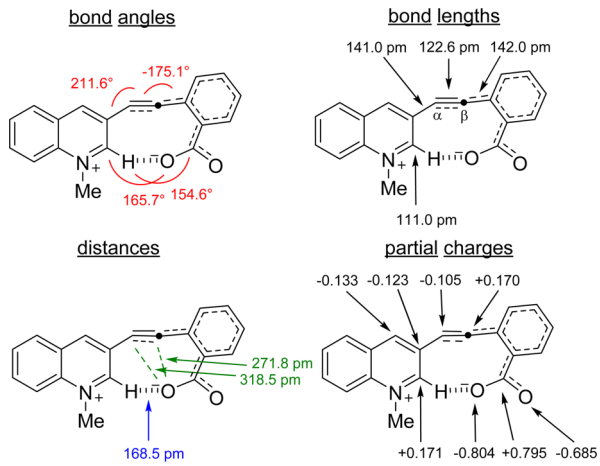


Figure 3. Molecular structure of **10** + H^+ (displacement parameters are drawn at 50% probability level).

The chemical behavior of the instable betaine **8c** can be understood in the light of results of DFT calculations which predict that its triple bond adopts a *transoid* conformation in the vacuum. The bond angle between C_α of the triple bond and C3 of the quinolinium ring was calculated to be +211.6° in vacuo, and the angle C_β to the benzoate ring was calculated to be −175.1° (Scheme 8). The angle is inter alia due to an intramolecular hydrogen bond between the carboxylate's oxygen atom and 2*H* of the quinolinium ring. The hydrogen

Scheme 8. Calculated Properties of the Instable Bent Betaine $8c_{bent}$



bond has a bond distance of 168.5 pm and can thus be characterized as strong[36] under these conditions. In addition, a 1,5 interaction between oxygen and C_β of the triple bond was calculated, as the distance (271.8 pm) is considerably shorter than the sum of the van der Waals radii (O, 152 pm; C, 170 pm). As a consequence, the bond length of the bent triple bond was calculated to be 122.6 pm, and this is longer than the triple bond of acetylene (118 pm).[37] The carbon atom C_α possesses a negative partial charge, whereas C_β is slightly positively charged. Bond lengths, distances, and partial charges of **8c** in the vacuum are shown in Scheme 8. The bent triple bond of **8c** influences the frontier orbital profile in such a way that the HOMO of **8c** possesses a small coefficient of the LUMO at C_β of the triple bond.

Nonlinear X−C≡C linkages are known, and *trans*-acetylene and *cis*-acetylene have been calculated.[38] Thus, diethynyl sulfide has an average bond angle of the S−C≡C linkage of 176.4(19)°, and a considerable elongation of the triple bond was ascribed to a decreased contribution from the dipolar resonance structure C≡C−S^+=C=C^-.[39] Deviations from linearity up to approximately 5° are also seen in $S(CN)_2$[40] and 1,2-bis[2-[2-(trimethylsilyl)ethynyl]phenyl] ethane-1,2-dione.[41] An angle of 170.5° at the primary carbon atom in addition to a very small bend of 0.7° in the *trans* mode at the secondary carbon was found in methyl 2-[(2,6-dimethoxyphenyl)ethynyl]-benzoate. In this case, the distance between the carbonyl oxygen atom and the primary carbon atom of the triple bond were determined to be 282.7(2) pm, indicative of weak 1,5-interactions.[42] According to a literature research concerning results of single-crystal analyses, the maximum angle of a bent acetylene was found to be 146.511°,[43] whereas the median is 177.082°.

The adoption of the linear conformer $8c_{linear}$, which is no energetic minimum according the calculation, requires ΔE = 50.4 kJ/mol in the vacuum (Scheme 9). We also calculated the hydrogen bond formation to 4-*H* of the quinolinium ($8c'_{bent}$), which required more than ΔE = 32.7 kJ/mol in vacuo. The formation of the pyridine-2-ylidene $8c_{NHC}$ required 51.2 kJ/mol. In solution, these values change considerably. Formation of the linear form starting from the bent betaine **8c** requires 19.7 kJ/mol in hexane, 18.7 kJ/mol in diethyl ether, 4.7 kJ/mol in methanol, 2.8 kJ/mol in THF, and 1.2 kJ/mol in water. The bent betaine $8c_{bent}$ has a calculated permanent dipole moment

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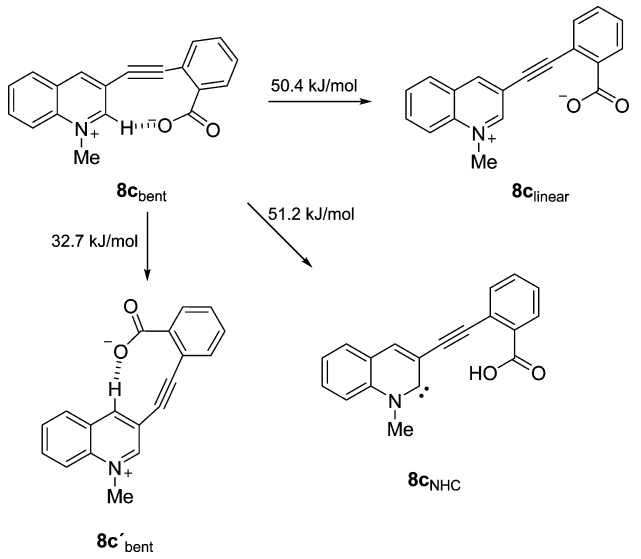
Scheme 9. Calculated Energy Differences between the $8c_{bent}$ and the Linear Conformer, Its Alternative $8c'_{bent}$, and the Carbene Tautomer $8c_{NHC}$



of 13.8 D, whereas its linear form has a dipole moment of 17.9 D.

CONCLUSIONS

Whereas the mesomeric betaines *m*- and *p*-[(1-methylquinolinium-3-yl)ethynyl]benzoates are stable and possess an almost linear triple bond separating the cationic and the anionic part of the molecule, the corresponding *o*-benzoate-derived betaine is unstable and reacts with hydroxide anions to give either an (1-oxo-1*H*-isochromen-3-yl)quinolinium derivative or the conjugated mesomeric betaine 2-(1-methylquinolinium-3-yl)-1,3-dioxo-2,3-dihydro-1*H*-inden-2-ide. A DFT calculation predicts an unusual *transoid* conformation of the acetylene bond in the instable betaine due to a strong hydrogen bond between the carboxylate group and 2*H* of the quinolinium ring in addition to a 1,5-interaction between the carboxylate group and the CC triple bond. This bent conformation makes the triple bond highly susceptible to a nucleophilic attack by hydroxide.

EXPERIMENTAL SECTION

General Considerations. Flash chromatography was performed with silica gel 60 (0.040−0.063 mm). ^{1}H NMR spectra were recorded at 400 or 600 MHz.^{13}C NMR spectra were recorded at 100 or 150 MHz, with the solvent peak or tetramethylsilane used as the internal reference. Multiplicities are described by using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Peak assignments were accomplished by analyzing the results of HMBC-, HSQC-NMR, and HH-NOESY measurements. Signal orientations in DEPT experiments were described as follows: o = no signal; + = up (CH, CH_3); − = down (CH_2). The NMR numbering is shown in the Supporting Information. MS (EI) were obtained with a MS/MS quadrupole mass spectrometer. ESIMS spectra were obtained at 4000 V capillary voltage and 30 V fragmentor voltage (unless otherwise noted) using a quadrupole MS spectrometer. Sample were sprayed from MeCN at 300 °C drying gas temperature. HRMS spectra were obtained with a Fourier transform-ion cyclotron resonance mass spectrometer. Melting points are uncorrected and were determined in an apparatus according to Dr. Tottoli. Yields are not optimized.

Crystal Structure Determinations. The single-crystal X-ray diffraction studies were carried out at 123(2) K using Mo Kα radiation (λ = 0.71073 Å) (**6a**, **6c_D**) or Cu Kα radiation (λ = 1.54178 Å) (**6c**, **10**). Direct methods (SHELXS-97)[44] or dual space methods (**10**) (SHELXD)[44] were used for structure solution, and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F2).[45] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(O) free). Semiempirical absorption corrections were applied. For **6a** and **6c_D**, extinction corrections were applied.

6a: colorless crystals, $C_{20}H_{16}NO_2{\cdot}PF_6{\cdot}C_2H_3N$, M = 488.36, crystal size 0.36 × 0.20 × 0.10 mm, monoclinic, space group $P2_1/c$ (No. 14), a = 15.5730(7) Å, b = 8.1725(3) Å, c = 17.7139(8) Å, β = 101.950(2)°, V = 2205.60(16) Å^3, Z = 4, ρ(calcd) = 1.471 Mg m^{-3}, F(000) = 1000, μ(Mo Kα) = 0.197 mm^{-1}, 67004 reflections ($2\theta_{max}$ = 55.2°), 5097 unique [R_{int} = 0.029], 302 parameters, R1 (for 4628 $I > 2\sigma(I)$) = 0.032, wR2 (all data) = 0.089, S = 1.05, largest diff peak and hole 0.381 and −0.296 e Å^{-3}.

6c: yellow crystals, $C_{20}H_{16}NO_2{\cdot}PF_6$, M = 447.31, crystal size 0.20 × 0.18 × 0.03 mm, monoclinic, space group $P2_1/n$ (No. 14), a = 13.8445(5) Å, b = 8.2667(3) Å, c = 17.2086(6) Å, β = 106.117(1)°, V = 1892.09(12) Å^3, Z = 4, ρ(calcd) = 1.570 Mg m^{-3}, F(000) = 912, μ(Cu Kα) = 1.999 mm^{-1}, 28286 reflections ($2\theta_{max}$ = 144.2°), 3717 unique [R_{int} = 0.029], 273 parameters, R1 (for 3370 $I > 2\sigma(I)$) = 0.033, wR2 (all data) = 0.089, S = 1.06, largest diff peak and hole 0.307 and −0.262 e Å^{-3}.

6c_D: colorless crystals, $C_{20}H_{13}D_3NO_2{\cdot}PF_6$, M = 450.33, crystal size 0.36 × 0.26 × 0.08 mm, monoclinic, space group $P2_1/n$ (No. 14), a = 13.8271(8) Å, b = 8.2406(5) Å, c = 17.2704(9) Å, β = 106.370(2)°, V = 1888.08(19) Å^3, Z = 4, ρ(calcd) = 1.584 Mg m^{-3}, F(000) = 912, μ(Mo Kα) = 0.221 mm^{-1}, 29589 reflections ($2\theta_{max}$ = 55.0°), 4338 unique [R_{int} = 0.040], 274 parameters, R1 (for 3479 $I > 2\sigma(I)$) = 0.038, wR2 (all data) = 0.088, S = 1.04, largest diff peak and hole 0.281 and −0.285 e Å^{-3}.

10: orange crystals, $C_{19}H_{14}NO_2{\cdot}Cl$, M = 323.76, crystal size 0.36 × 0.08 × 0.02 mm, monoclinic, space group $P2_1/c$ (No. 14), a = 10.2551(4) Å, b = 6.3701(2) Å, c = 22.6746(8) Å, β = 102.474(2)°, V = 1446.28(9) Å^3, Z = 4, ρ(calcd) = 1.487 Mg m^{-3}, F(000) = 912, μ(CuKα) = 2.417 mm^{-1}, 19704 reflections ($2\theta_{max}$ = 144.2°), 2814 unique [R_{int} = 0.044], 212 parameters, 1 restraint, R1 (for 2600 $I > 2\sigma(I)$) = 0.049, wR2 (all data) = 0.145, S = 1.09, largest diff peak and hole 0.603 and −0.501 e Å^{-3}.

CCDC 1455748 (**6a**), CCDC 1455749 (**6c**), CCDC 1455750 (**6c_D**), and 1455751 (**10** + H^+) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Calculations. All density-functional theory (DFT) calculations were carried out using the Jaguar 8.3.012 software[46] running on Linux 2.6.18-238.el5 SMP (x86_64) on five AMD Phenom II X6 1090T processor workstations (Beowulf-cluster) parallelized with OpenMPI. MM2-optimized structures were used as starting geometries. Complete geometry optimizations were carried out on the implemented LACVP* (Hay−Wadt effective core potential (ECP) basis on heavy atoms, N31G6* for all other atoms) basis set and with the B3LYP density functional. All calculated structures were proven to be true minima by the absence of imaginary frequencies (with the exception of **8c**, which is not a minimum). Plots were obtained using Maestro 9.7.012, the graphical interface of Jaguar. Solvent effects were estimated by help of the Poisson−Boltzmann Finite element method implemented in Jaguar. Partial charges were obtained with NBO 6.0[47] from the results of the DFT calculations.

General Procedure for the Preparation of the Methyl (Quinolin-3-ylethynyl)benzoates 5a−c. The reactions were carried out under nitrogen atmosphere. A mixture of 5 mmol of 3-bromoquinoline, 1 mol % of $Pd(PPh_3)_2Cl_2$, and 2 mol % of CuI was suspended in 7 mL of dry Et_3N with stirring. A sample of 3-ethynylquinoline (1.05 equiv) in dry Et_3N was added dropwise at ambient temperature. The resulting solutions were then stirred at reflux temperature until complete conversion was monitored by TLC. The mixtures were then allowed to cool to room temperature, treated

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with dichloromethane (50 mL), filtered through Celite, and washed with water. The organic phases were then dried over $MgSO_4$ and filtered, and the solvents were removed in vacuo. The resulting residues were finally purified by column chromatography (petroleum ether: ethyl acetate) to afford the products.

*Methyl 4-(Quinolin-3-ylethynyl)benzoate (**5a**).* Yield: 1078 mg of a brown solid, 75%. Mp: 138−139 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + TMS): δ = 9.00 (d, J = 2.2 Hz, 1H, 2-H), 8.33 (d, J = 2.2 Hz, 1H, 4-H), 8.11 (d, J = 8.6 Hz, 1H, 8-H), 8.06 (ddd, J = 1.4, 2.0, 8.3 Hz, 2H, 3′-H, 5′-H), 7.81 (d, J = 8.6 Hz, 1H, 5-H), 7.74 (ddd, J = 1.5, 6.8, 8.6 Hz, 1H, 7-H), 7.65 (ddd, J = 1.4, 2.0, 8.3 Hz, 2H, 2′-H, 4′-H), 7.58 (ddd, J = 1.5, 6.8, 8.6 Hz, 1H, 6-H), 3.94 (s, 3H, $COOCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + TMS): δ = 166.5 (o, COO), 152.0 (+, C2), 147.0 (o, C8a), 138.7 (+, C4), 131.7 (+, C2′, C4′), 130.4 (+, C8), 130.0 (o, C4′), 129.7 (+, C3′, C5′), 129.5 (+, C7), 127.7 (+, C5), 127.5 (+, C6), 127.3 (o, C4a), 127.2 (o, C1′), 116.9 (o, C3), 91.8 (o, Cα), 89.5 (o, Cβ), 52.3 (+, CH_3) ppm. IR (ATR): 3017, 1716, 1276, 1098, 953, 905, 855, 767, 742, 697, 480 cm^{-1}. MS (ESI): m/z = 287.3 [M$^+$]. HRMS (ESI): m/z calcd for $C_{19}H_{14}NO_2$ [M + H]$^+$ 288.1025, found 288.1022.

*Methyl 3-(Quinolin-3-ylethynyl)benzoate (**5b**).* Yield: 1170 mg of a colorless solid, 86%. Mp: 116−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + TMS): δ = 9.01 (d, J = 2.0 Hz, 1H, 2-H), 8.32 (d, J = 2.0 Hz, 1H, 4-H), 8.26 (td, J = 0.5, 2.6 Hz, 1H, 2′-H), 8.11 (d, J = 8.6 Hz, 8-H), 8.04 (dt, J = 1.4, 7.8 Hz, 1H, 4′-H), 7.81 (d, J = 8.6 Hz, 1H, 5-H), 7.78−7.71 (m, 2H, 6′-H, 7-H), 7.58 (ddd, J = 1.3, 6.9, 8.6 Hz, 1H, 6-H), 7.46 (td, J = 0.5, 7.8 Hz, 1H, 5′-H), 3.95 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + TMS): δ = 166.3 (o, COO), 152.0 (+, C2), 147.0 (o, C8a), 138.5 (+, C4), 135.8 (+, C6′), 132.9 (+, C2′), 130.6 (o, C3′), 130.3 (+, C4′), 129.8 (+, C8), 129.5 (+, C7), 128.7 (+, C5′), 127.7 (+, C5), 127.4 (+, C6), 127.2 (o, C4a), 123.1 (o, C1′), 117.1 (o, C8a), 91.5 (o, Cα), 87.5 (o, Cβ), 52.4 (+, CH_3) ppm. IR (ATR): 2949, 1719, 1485, 1439, 1269, 1262, 1237, 1127, 994, 902, 782, 744, 677, 487, 474, 454 cm^{-1}. MS (ESI): m/z = 287.2 [M]$^+$. HRMS (ESI): m/z calcd for $C_{19}H_{13}NO_2$ [M]$^+$ 287.0946, found 287.0948.

*Methyl 2-(Quinolin-3-ylethynyl)benzoate (**5c**).* Yield: 807 mg of a light brownish solid, 56%. Mp: 64−65 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + TMS): δ = 9.05 (d, J = 2.0 Hz, 1H, 2-H), 8.36 (d, J = 2.0 Hz, 1H, 4-H), 8.11 (d, J = 8.6 Hz, 1H, 8-H), 8.02 (dd, J = 1.5, 7.8 Hz, 1H, 6′-H), 7.81 (d, J = 8.6 Hz, 1H, 5-H), 7.76−7.69 (m, 2H, 3′-H, 7-H), 7.60−7.50 (m, 2H, 4′-H, 6-H), 7.42 (td, J = 1.3, 7.8 Hz, 1H, 5′-H), 3.99 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + TMS): δ = 166.5 (o, COO), 152.2 (+, C2), 147.0 (o, C8a), 138.5 (+, C4), 134.2 (+, C5′), 131.9 (o, C2′), 131.8 (+, C3′), 130.7 (+, C4′), 130.2(+, C8), 129.5 (+, C6′), 128.5 (+, C7), 127.7 (+, C5), 127.4 (+, C6), 127.3 (C4a), 123.1 (o, C1′), 117.5 (o, C3), 91.5 (o, Cα), 91.4 (o, Cβ), 52.3 (+, CH_3) ppm. IR (ATR): 2952, 1731, 1565, 1485, 1435, 1270, 1250, 1111, 1076, 899, 746, 6923, 471 cm-1. MS (ESI): m/z = 287.3 [M]$^+$. HRMS (ESI): m/z calcd for $C_{19}H_{14}NO_2$ [M + H]$^+$ 288.1025, found 288.1030.

General Procedure for the Preparation of Salts 6a−c. Samples of 0.5 mmol of the esters **5a−c** were dissolved in toluene containing 1 drop of nitrobenzene. Then 0.75 mmol of dimethyl sulfate was added with stirring. Thereafter, the resulting mixture was stirred at reflux temperature. After completion of the reaction (controlled by TLC), the solution was cooled, and the crude product was filtered off, washed with ethyl acetate (3 × 10 mL), and dried to afford the product.

*3-((4-(Methoxycarbonyl)phenyl)ethynyl)-1-methylquinolinium Methylsulfate (**6a**).* Yield: 186 mg of a brownish solid, 90%. Mp: 219−220 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.91 (d, J = 1.2 Hz, 1H, 2-H), 9.54 (s, 1H, 4-H), 8.55 (d, J = 9.0 Hz, 1H, 8-H), 8.46 (d, J = 9.0 Hz, 1H, 5-H), 8.33 (ddd, J = 1.3, 7.0, 9.0 Hz, 1H, 6-H), 8.14−8.07 (m, 3H, 4′-H, 2′-H, 6′-H), 7.83 (ddd, J = 1.5, 1.9, 8.2 Hz, 2H, 3′-H, 5′-H), 4.66 (s, 3H, NCH_3), 3.90 (s, 3H, $COOCH_3$), 3.37 (s, 3H, $CH_3SO_4^-$) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.5 (o, COO), 152.2 (+, C2), 148.3 (+, C4), 137.5 (o, C8a), 136.3 (+, C7), 132.1 (+, C2′, C6′), 130.7 (+, C6), 130.5 (o, C4a), 130.4 (+, C5), 129.7 (+, C3′, C5′), 128.7 (o, C4′), 125.2 (C1′), 119.3 (+, C8), 116.2 (o, C3), 93.5 (o, Cβ), 85.9 (o, Cα), 52.8 (+, CH_3SO_4), 52.5 (+, $COOCH_3$), 45.5 (+, NCH_3) ppm. IR (ATR): 1721, 1278, 1240, 1215, 1170, 1097, 1057, 1005, 866, 766, 729, 696, 607, 574 cm^{-1}. MS (ESI): m/z = 302.1 [M]$^+$. HRMS (ESI): m/z calcd for $C_{20}H_{16}NO_2$ [M]$^+$ 302.1181, found 302.1183.

*3-((3-(Methoxycarbonyl)phenyl)ethynyl)-1-methylquinolinium Methylsulfate (**6b**).* Yield: 195 mg of a colorless solid, 90%. Mp: 221−222 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.91 (s, 1H, 2-H), 9.54 (s, 1H, 4-H), 8.55 (d, J = 8.9 Hz, 1H, 8-H), 8.45 (d, J = 8.9 Hz, 1H, 5-H), 8.33 (ddd, J = 1.3, 7.0, 8.9 Hz, 1H, 7-H), 8.22 (s, 1H, 2′-H), 8.15−8.07 (m, 6-H, 4′-H), 7.95 (dt, J = 1.5, 7.7 Hz, 1H, 6′-H), 7.71 (t, J = 7.7 Hz, 1H, 5′-H), 4.66 (s, 3H, NCH_3), 3.91 (s, 3H, $COOCH_3$), 3.38 (s, 3H, $CH_3SO_4^-$) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.2 (o, COO), 152.2 (+, C2), 148.1 (+, C4), 137.4 (o, C8a), 136.2 (+, C6′), 135.9 (+, C7), 132.2 (+, C2′), 130.6 (+, C4′), 130.5 (+, C6), 130.4 (o, C4a), 130.3 (+, C5), 129.9 (+, C5′), 128.7 (o, C3′), 121.2 (o, C1′), 119.3 (+, C8), 116.4 (o, C3), 93.4 (o, Cβ), 84.2 (o, Cα), 52.7 (+, $CH_3SO_4^-$), 52.5 (+, $COOCH_3$), 45.5 (+, NCH_3) ppm. IR (ATR): 3048, 1718, 1440, 1289, 1230, 1139, 1013, 1000, 772, 757, 732, 609, 578, 551, 431 cm^{-1}. MS (ESI): m/z = 302.1 [M]$^+$. HRMS (ESI): m/z calcd for $C_{20}H_{16}NO_2$ [M]$^+$ 302.1181, found 302.1180.

*3-((2-(Methoxycarbonyl)phenyl)ethynyl)-1-methylquinolinium Methylsulfate (**6c**).* The compound was synthesized according to the general procedure. Yield: 194 mg of a yellow solid, 93%. Mp: 216−217 °C. The deuterated form **6c_D** was prepared as follows: 3-((2-(methoxycarbonyl)phenyl)ethynyl)-1-methylquinolinium methylsulfate (413 mg, 1 mmol) was dissolved in methanol-d_4 (5 mL), and then 40% D_2O solution of sodium hydroxide (200 mg) was added with stirring. The resulting mixture was stirred for 1 h. Then the solution was precipitated with water solution of NH_4PF_6 (1 equiv), filtered, washed with water and ether, and dried in vacuo. Data for **6c**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.80 (d, J = 1.0 Hz, 1H, 2-H), 9.47 (s, 1H, 4-H), 8.54 (d, J = 9.1 Hz, 1H, 8-H), 8.50 (d, J = 9.1 Hz, 1H, 5-H), 8.32 (ddd, J = 1.5, 7.1, 9.1 Hz, 1H, 6-H), 8.11 (ddd, J = 1.5, 7.1, 9.1 Hz, 1H, 7-H), 8.04 (dd, J = 1.0, 8.0 Hz, 1H, 6′-H), 7.85 (dd, J = 1.0, 8.0 Hz, 1H, 3′-H), 7.76 (td, J = 1.5, 7.6 Hz, 1H, 4′-H), 7.66 (td, J = 1.5, 7.6 Hz, 1H, 5′-H), 4.66 (s, 3H, NCH_3), 3.96 (s, 3H, $COOCH_3$), 3.36 (s, $CH_3SO_4^-$) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.5 (o, COO), 151.9 (+, C2), 148.0 (+, C4), 137.4 (o, C8a), 136.1 (+, C7), 134.3 (+, C5′), 132.7 (+, C6′), 131.8 (o, C2′), 130.6 (+, C6), 130.5 (+, C4′), 130.4 (+, C5), 130.2 (+, C3′), 128.8 (o, C4a), 120.7 (o, C1′), 119.2 (+, C8), 116.8 (o, C3), 93.4 (o, Cβ), 87.4 (o, Cα), 52.8 (+, CH_3SO_4), 52.5 (+, $COOCH_3$), 45.5 (+, NCH_3) ppm. IR (ATR): 2923, 2219, 1737, 1272, 1258, 1133, 1082, 832, 765, 761, 698, 556, 434 cm^{-1}. MS (ESI): m/z = 302.1 [M]$^+$. HRMS (ESI): m/z calcd for $C_{20}H_{16}NO_2$ [M]$^+$ 302.1188, found 302.1181.

General Procedure for the Ester Hydrolysis. The corresponding salt (1 mmol) was dissolved in methanol (5 mL), and then sodium hydroxide (1 N in water, 10 equiv) was added with stirring. The resulting mixture was stirred overnight. The solution was acidified (pH = 3) and then concentrated in vacuo, and the crude product was purified by column chromatography with $CHCl_3$−MeOH as eluent.

*3-[(4-Carboxyphenyl)ethynyl]-1-methylquinolinium Chloride (**7a**).* Yield: 64 mg of a brownish solid, 92%. Mp: 97−98 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.97 (d, J = 1.2 Hz, 1H, 2-H), 9.55 (s, 1H, 4-H), 8.55 (d, J = 9.0 Hz, 1H, 8-H), 8.47 (d, J = 9.0 Hz, 1H, 5-H), 8.32 (ddd, J = 1.3, 6.9, 9.0 Hz, 1H, 7-H), 8.10 (t, J = 9.0 Hz, 1H, 6-H), 8.06 (ddd, J = 1.5, 1.9, 8.3 Hz, 2H, 3′-H, 5′-H), 7.79 (ddd, J = 1.5, 1.9, 8.3 Hz, 2H, 2′-H, 6′-H), 4.67 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.5 (o, COO), 152.2 (+, C2), 148.2 (+, C4), 137.4 (o, C9), 136.2 (+, C7), 131.9 (+, C2′, C6′), 131.8 (o, C4′), 130.6 (+, C6), 130.4 (+, C5), 129.8 (+, C3′, C5′), 128.7 (o, C4a), 124.7 (o, C1′), 119.2 (+, C8), 116.3 (o, C3), 93.7 (o, Cβ), 85.6 (o, Cα), 45.4 (+, CH_3) ppm. IR (ATR): 3031, 2211, 1695, 1596, 1543, 1520, 1353, 1273, 1253, 1158, 1012, 770, 748, 694, 626, 478, 434 cm^{-1}. MS (ESI): m/z = 288.0 [M]$^+$. HRMS (ESI): m/z calcd for $C_{19}H_{14}NO_2$ [M]$^+$ 288.1025, found 288.1022.

*3-[(3-Carboxyphenyl)ethynyl]-1-methylquinolinium Chloride (**7b**).* Yield: 209 mg of a brownish solid, 72%. Mp: 247−248 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.99 (s, 1H, 2-H), 9.56 (s, 1H, 4-H), 8.56 (d, J = 8.9 Hz, 1H, 8-H), 8.48 (d, J = 8.9 Hz, 1H, 5-H), 8.32

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J. Org. Chem. 2016, 81, 4202−4209

(ddd, J = 1.5, 7.0, 8.9 Hz, 1H, 7-H), 8.22 (s, 1H, 2′-H), 8.11 (t, J = 8.9 Hz, 1H, 6-H), 8.08 (dt, J = 1.3, 7.9 Hz, 1H, 4′-H), 7.88 (dt, J = 1.3, 7.9 Hz, 1H, 6′-H), 7.65 (t, J = 7.9 Hz, 1H, 5′-H), 4.67 (s, 3H, CH_3) ppm. ^{13}C NMR (150 MHz, DMSO-d_6): δ = 166.8 (o, COO), 152.3 (+, C2), 148.1 (+, C4), 137.4 (o, C9), 136.1 (+, C7), 135.1 (+, C6′), 133.0 (o, C3′), 132.5 (+, C2′), 130.7 (+, C4′), 130.6 (+, C6), 130.4 (+, C5), 129.5 (+, C5′), 128.8 (o, C4a), 120.8 (o, C1′), 119.3 (+, C8), 116.6 (o, C3), 93.7 (o, Cβ), 83.9 (o, Cα), 45.5 (+, CH_3) ppm. IR (ATR): 2225, 1705, 1520, 1379, 1213, 1172, 1141, 1057, 1002, 747, 684, 609, 578, 550, 430 cm^{-1}. MS (ESI): m/z = 288.0 [M]$^+$. HRMS (ESI): m/z calcd for $C_{19}H_{14}NO_2$ [M]$^+$ 288.1025, found 288.1024.

*4-((1-Methylquinolinium-3-yl)ethynyl)benzoate (**8a**).* To a solution of 0.25 mmol (80 mg) of 3-((4-carboxyphenyl)ethynyl)-1-methylquinolinium in methanol (4 mL) was added 0.3 mmol (0.042 mL) of triethylamine. The resulting mixture was stirred for 15 min and then dried in vacuo. The residue was chromatographed on silica gel (MeOH/$CHCl_3$). Yield: 64 mg of a light green solid, 90%, mp 196−197 °C. ^{1}H NMR (400 MHz, MeOH-d_4): δ = 9.67 (s, 1H, 2-H), 9.32 (s, 1H, 4-H), 8.51 (d, J = 8.8 Hz, 1H, 8-H), 8.41 (d, J = 8.8 Hz, 1H, 5-H), 8.30 (ddd, J = 1.3, 7.0, 8.8 Hz, 1H, 7-H), 8.09 (t, J = 8.8 Hz, 1H, 6-H), 7.98 (d, J = 8.6 Hz, 2H, 3′-H, 5′-H), 7.61 (d, J = 8.6 Hz, 2H, 2′-H, 6′-H), 4.73 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, methanol-d_4): δ = 169.5 (o, COO), 153.2 (+, C2), 149.5 (o, C4), 140.3 (o, C9), 139.1 (o, C4′), 137.5 (+, C7), 132.5 (+, C2′, C6′), 132.0 (+, C7), 131.7 (+, C5), 130.8 (o, C4a), 130.6 (+, C3′, C5′), 124.0 (o, C1′), 119.9 (+, C8), 119.5 (o, C3), 96.7 (o, Cβ), 84.6 (o, Cα), 46.4 (+, CH_3) ppm. IR (ATR): 2183, 1584, 1541, 1415, 1385, 1283, 848, 779, 745, 695 cm^{-1}. MS (ESI): m/z = 288.0 [M + H]$^+$. HRMS (ESI): m/z calcd for $C_{19}H_{14}NO_2$ [M + H]$^+$ 288.1025, found 288.1022.

*3-((1-Methylquinolinium-3-yl)ethynyl)benzoate (**8b**).* To a solution of 0.5 mmol (162 mg) of 3-((3-carboxyphenyl)ethynyl)-1-methylquinolinium in methanol (4 mL) was added 0.5 mmol (0.07 mL) of triethylamine. The resulting mixture was stirred for 15 min and then dried in vacuo. The residue was chromatographed on silica gel (MeOH/$CHCl_3$). Yield: 120 mg of a light green solid, 84%. Mp: 213-214 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.91 (s, 1H, 2-H), 9.51 (s, 1H, 4-H), 8.53 (d, J = 7.6 Hz, 1H, 8-H), 8.44 (d, J = 7.6 Hz, 1H, 5-H), 8.31 (t, J = 7.6 Hz, 1H, 7-H), 8.22 (s, 1H, 2′-H), 8.10 (t, J = 7.6 Hz, 1H, 6-H), 8.06 (d, J = 7.4 Hz, 1H, 4′-H), 7.77 (d, J = 7.4 Hz, 1H, 6′-H), 7.58 (t, J = 7.4, 1H, 5′-H), 4.65 (s, 3H, CH_3) ppm. ^{13}C NMR (150 MHz, DMSO-d_6): δ = 168.0 (o, COO), 152.7 (+, C2), 148.4 (+, C4), 137.4 (o, C9), 136.1 (+, C7), 135.8 (o, C3′), 133.4 (+, C6′), 132.6 (+, C2′), 130.8 (+, C4′), 130.6 (+, C6), 130.3 (+, C5), 129.0 (+, C5′), 128.8 (o, C4a), 120.3 (o, C1′), 119.3 (+, C8), 116.7 (o, C3), 94.6 (o, Cβ), 83.5 (o, Cα), 45.5 (+, CH_3) ppm. IR (ATR): 2225, 1695, 1558, 1379, 1256, 1223, 1156, 1142, 1029, 760, 636, 516 cm^{-1}. MS (ESI): m/z = 288.0 [M + H]$^+$. HRMS (ESI): m/z calcd for $C_{19}H_{14}NO_2$ [M + H]$^+$ 288.1025, found 288.1025.

*1-Methyl-3-(1-oxo-1H-isochromen-3-yl)quinolinium Chloride (**9**).* 3-((2-(Methoxycarbonyl)phenyl)ethynyl)-1-methylquinolinium methylsulfate (256 mg, 0.6 mmol) was dissolved in methanol (5 mL), and then sodium hydroxide (10 equiv) was added with stirring. The resulting mixture was stirred over a period of 24 h. The solution was then acidified (pH = 1), followed by neutralization with sodium bicarbonate, and concentrated in vacuo. The crude product was purified by column chromatography with $CHCl_3$/MeOH as eluent. Yield: 139.6 mg of a yellow solid, 70%. Mp: >275 °C. ^{1}H NMR (400 MHz, methanol-d_4): δ = 9.99 (d, J = 1.3 Hz, 1H, 2-H), 9.67 (s, 1H, 4-H), 8.56−8.52 (m, 2H, 5-H, 8-H), 8.35−8.30 (m, 2H, 7-H, 8′-H), 8.13−8.08 (m, 1H, 6-H), 7.95−7.90 (m, 1H, 6′-H), 7.81−7.79 (m, 2H, 4′-H, 5′-H), 7.73−7.68 (m, 1H, 7′-H), 4.56 (s, 3H, CH_3) ppm. ^{13}C NMR (150 MHz, methanol-d_4): δ = 162.5 (o, C1′), 149.7 (o, C8a′), 148.8 (+, C2), 148.59 (o, C3′) 143.1 (+, C4), 139,9 (o, C8a), 137.8 (+, C7), 137.0 (o, C6′), 135.6 (o), 133.6 (o), 132.2 (+, C6), 131.3 (+, C7′), 130.68 (+, C8′), 128.5 (+, C4′), 120.1 (+, C8), 107.4 (+, C4′), 46.7 (+, CH_3). IR (ATR): 3098, 2836, 1638, 1587, 1565, 1486, 1455, 1363, 1345, 1330, 1320, 1250, 1210, 1172, 1124, 1109, 1074, 1044, 983, 921, 897, 807, 790, 778, 752, 726, 684, 665, 631, 553 cm^{-1}. MS (ESI): m/z = 288.1 [M]$^+$. HRMS (ESI): m/z calcd for $C_{19}H_{14}NO_2$ [M]$^+$ 288.1025, found 288.1022.

*2-(1-Methylquinolinium-3-yl)-1,3-dioxo-2,3-dihydro-1H-inden-2-ide (**10**).* 3-((2-(Methoxycarbonyl)phenyl)ethynyl)-1-methylquinolinium methylsulfate (413 mg; 1 mmol) was dissolved in methanol (5 mL), and then sodium hydroxide (1 N in water, 10 equiv) was added with stirring. The resulting mixture was stirred overnight. The solution was then acidified (pH = 3) and concentrated in vacuo, and the crude product was purified by column chromatography with $CHCl_3$/MeOH as eluent. Yield: 249 mg of a red solid, 87%. Mp: >300 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.44 (d, J = 1.5 Hz, 1H, 2-H), 9.74 (s, 1H, 4-H), 8.25 (d, J = 8.8 Hz, 1H, 8-H), 8.19 (d, J = 8.8 Hz, 1H, 5-H), 7.86 (ddd, J = 1.5, 6.7, 8.8 Hz, 1H, 7-H), 7.79 (t, J = 8.8 Hz, 1H, 6-H), 7.44−7.38 (m, 2H, 5′-H, 8′-H), 7.37−7.33 (m, 2H, 5′-H, 6′-H), 4.56 (s, 3H, CH_3) ppm. ^{13}C NMR (150 MHz, DMSO-d_6): δ = 189.4 (o,C1′, C3′), 145.7 (+, C2), 139.7 (o, C3a′, C18), 133.7 (o, C8a), 132.9 (o, C3), 131.3 (+, C4), 130.8 (+, C5′, C8′), 130.7 (+, C7), 130.1 (o, C4a), 129.1 (+, C6), 129.0 (+, C5), 118.6 (+, C8), 118.4 (+, C6′, C7′), 97.2 (o, C2′), 45.8 (+, CH_3) ppm. IR (ATR): 1599, 1227, 1203, 1160, 1436, 1407, 1373, 1348, 1338, 890, 758, 719, 510 cm^{-1}. MS (ESI): m/z = 288.0 [M + H]$^+$. HRMS (ESI): m/z calcd for $C_{19}H_{14}NO_2$ [M + H]$^+$ 288.1025, found 288.1024.

*1,3-Dioxo-2-(quinolinium-3-yl)-2,3-dihydro-1H-inden-2-ide (**11**)/Sodium 1,3-Dioxo-2-(quinolin-3-yl)-2,3-dihydro-1H-inden-2-ide (**12**).* Methyl 2-(quinolin-3-ylethynyl)benzoate (19 mmol) was dissolved in methanol (7 mL), and then potassium hydroxide (1N in water, 10 equiv) was added with stirring. The resulting mixture was stirred for 48 h. The solution was then acidified (pH = 1), and compound **11** precipitated. The product was filtered off, subsequently washed with water and with ethyl acetate, and finally dried in vacuo. Yield: 363 mg of an orange solid (70%), mp >300 °C. IR (ATR): 3060, 2440, 2051, 1977, 1929, 1677, 1609, 1559, 1432, 1355, 907, 867, 758, 717, 612, 548, 516, 468, 415 cm^{-1}. MS (ESI): m/z = 272.0 [M − H]$^-$. HRMS (ESI): m/z calcd for $C_{18}H_{10}NO_2$ [M − H]$^-$ 272.0712; found 272.0711. To obtain a soluble species for NMR experiment, the salt was neutralized with NaOH in a water−methanol mixture and dried in vacuo. ^{1}H NMR (600 MHz, methanol-d_4): δ = 9.89 (s, 1H, H-2), 9.04 (s, 1H, H-4), 7.90−7.88 (d, 1H, J = 8.1 Hz, H-8), 7.81−7.80 (d, 1H, J = 8.1 Hz, H-5), 7.55−7.52 (m, 1H, H-7), 7.48−7.46 (m, 1H, H-6), 7.36−7.32 (m, 4H, H-4′/H-5′/H-6′/H-7′) ppm. ^{13}C NMR (150 MHz, methanol-d_4): δ = 193.9 (o, C1′/C3′), 150.9 (+, C2), 144.9 (o,C8a), 141.1 (o, C3a′/C7a′), 132.1 (o, C3), 130.5 (o, C4a), 130.2 (+, C4), 128.7 (+, C5), 128.3 (+, C8), 128.2 (+, C7), 127.3 (+, C6), 119.2 (+, C5′/C6′), 103.3 (o, C2′) ppm.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00561.

X-ray data for **6a**, **6c_D**, **6c**, and **10** (CIF)

HOMO/LUMO profiles of the ester **5a** and of the mesomeric betaines **8a**, **8c$_{bent}$**, and **10**; NMR spectra; details of the DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Browne, D. L.; Harrity, J. P. *Tetrahedron* **2010**, *66*, 553−568. (b) Gilchrist, T. L. *Science of Synthesis*; George Thieme, 2004; Vol. *13*, pp 109−126.

DOI: 10.1021/acs.joc.6b00561
J. Org. Chem. 2016, 81, 4202−4209

(2) Huisgen, R.; Gotthardt, H.; Bayer, H. O. *Angew. Chem.* **1964**, *76*, 185; *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 136.
(3) (a) Ollis, W. D.; Ramsden, C. A. *Adv. Heterocycl. Chem.* **1976**, *19*, 1−122. (b) Ramsden, C. A. *Comprehensive Organic Chemistry*; Sammes, P. G., Ed.; Pergamon Press: Oxford, 1979; Vol. 4, pp 1171−1228.
(4) Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239−2329.
(5) Ramsden, C. A. *Tetrahedron* **2013**, *69*, 4146−4159.
(6) (a) Ramsden, C. A.; Oziminski, W. P. *Tetrahedron* **2014**, *70*, 7158−7165. (b) Oziminski, W. P.; Ramsden, C. A. *Tetrahedron* **2015**, *71*, 7191−7198.
(7) (a) Gonsior, N.; Mohr, F.; Ritter, H. *Beilstein J. Org. Chem.* **2012**, *8*, 390−397. (b) Koch, A.; Jonas, U.; Ritter, H.; Spiess, H. W. *Tetrahedron* **2004**, *60*, 10011−10018. (c) Theis, A.; Menges, B.; Mittler, S.; Mierzwa, M.; Pakula, T.; Ritter, H. *Macromolecules* **2003**, *36*, 7520−7526. (d) Tonami, H.; Uyama, H.; Kobayashi, S.; Menges, B.; Mittler, S.; Theis, A.; Ritter, H. *Macromol. Chem. Phys.* **2003**, *204*, 1079−1084.
(8) (a) Zhang, J.; Franz, M.; Hübner, E.; Schmidt, A. *Tetrahedron* **2016**, *72*, 525−531. (b) Guan, Z.; Nieger, M.; Schmidt, A. *Eur. J. Org. Chem.* **2015**, *2015*, 4710−4719. (c) Guan, Z.; Hillrichs, K.; Ünlü, C.; Rissanen, K.; Nieger, M.; Schmidt, A. *Tetrahedron* **2015**, *71*, 276−282.
(9) Schmidt, A. *Adv. Heterocycl. Chem.* **2003**, *85*, 67−171.
(10) (a) Sauvage, X.; Zaragoza, G.; Demonceau, A.; Delaude, L. *Adv. Synth. Catal.* **2010**, *352*, 1934−1948. (b) Voutchkova, A. M.; Feliz, M.; Clot, E.; Eisenstein, O.; Crabtree, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 12834−12846. (c) Voutchkova, A. M.; Appelhans, L. N.; Chianese, A. R.; Crabtree, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17624−17625. (d) Thomazeau, C.; Olivier-Bourbigou, H.; Magna, L.; Luts, S.; Gilbert, B. *J. Am. Chem. Soc.* **2003**, *125*, 5264−5265. (e) Sauvage, X.; Demonceau, A.; Delaude, L. *Adv. Synth. Catal.* **2009**, *351*, 2031−2038. (f) Fèvre, M.; Pinaud, J.; Leteneur, A.; Gnanou, Y.; Vignolle, J.; Taton, D.; Miqueu, K.; Sotiropoulos, J.-M. *J. Am. Chem. Soc.* **2012**, *134*, 6776−6784. (g) Bissinger, P.; Braunschweig, H.; Kupfer, T.; Radacki, K. *Organometallics* **2010**, *29*, 3987−3990.
(11) (a) Gründemann, S.; Kovacevic, A.; Albrecht, M.; Faller Robert, J. W.; Crabtree, R. H. *Chem. Commun.* **2001**, 2274−2275. (b) Schuster, O.; Yang, L.; Raubenheimer, H. G.; Albrecht, M. *Chem. Rev.* **2009**, *109*, 3445−3478.
(12) Dreger, A.; Nieger, M.; Drafz, M. H. H.; Schmidt, A. *Z. Naturforsch., B: J. Chem. Sci.* **2012**, *67*, 359−366.
(13) (a) Lavallo, V.; Dyker, C. A.; Donnadieu, B.; Bertrand, G. *Angew. Chem.* **2008**, *120*, 5491−5494; *Angew. Chem., Int. Ed.* **2008**, *47*, 5411−5414. (b) Christl, M.; Engels, B. *Angew. Chem.* **2009**, *121*, 1566−1567; *Angew. Chem., Int. Ed.* **2009**, *48*, 1538−1539. (c) Hänninen, M. H. H.; Peuronen, A.; Tuononen, H. M. *Chem. - Eur. J.* **2009**, *15*, 7287−7291. (d) Han, Y.; Huynh, H. V. *Dalton Trans.* **2011**, *40*, 2141−2147.
(14) (a) Benhamou, L.; Vujkovic, N.; César, V.; Gornitzka, H.; Lugan, N.; Lavigne, G. *Organometallics* **2010**, *29*, 2616−2630. (b) Danopoulos, A. A.; Monakhov, K. Yu. *Chem. - Eur. J.* **2013**, *19*, 450−455. (c) Liu, M.; Nieger, M.; Schmidt, A. *Chem. Commun.* **2015**, *51*, 477−479. (d) Pidlypnyi, N.; Wolf, S.; Liu, M.; Rissanen, K.; Nieger, M.; Schmidt, A. *Tetrahedron* **2014**, *70*, 8672−8680. (e) Pidlypnyi, N.; Namyslo, J. C.; Drafz, M. H. H.; Nieger, M.; Schmidt, A. *J. Org. Chem.* **2013**, *78*, 1070−1078.
(15) (a) Schmidt, A.; Wiechmann, S.; Freese, T. *ARKIVOC* **2013**, *i*, 424−469. (b) Schmidt, A.; Dreger, A. *Curr. Org. Chem.* **2011**, *15*, 2897−2970.
(16) (a) Barczynski, P.; Szafran, M. *Polym. J. Chem.* **2009**, *83*, 1061−1074. (b) Barczynski, P.; Katrusiak, A.; Koput, J.; Dega-Szafran, Z.; Szafran, M. *J. Mol. Struct.* **2009**, *918*, 39−54.
(17) Barczynski, P.; Katrusiak, A.; Koput, J.; Szafran, M. *J. Mol. Struct.* **2008**, *889*, 394−407.
(18) Lynn, D. G.; Lewis, D. H.; Tramontano, W. A.; Evans, L. S. *Phytochemistry* **1984**, *23*, 1225−1228.
(19) Gourand, F.; Mercey, G.; Ibazizène, M.; Tirel, O.; Henry, J.; Levacher, V.; Perrio; Barré, C. L. *J. Med. Chem.* **2010**, *53*, 1281−1287.
(20) (a) Potts, K. T.; Murphy, P. M.; Kuehnling, W. R. *J. Org. Chem.* **1988**, *53*, 2889−2898. (b) Potts, K. T.; Murphy, P. M.; DeLuca, M. R.; Kuehnling, W. R. *J. Org. Chem.* **1988**, *53*, 2898−2910.
(21) Musavi, S. M.; Amani, J.; Noruzi, P. *Int. J. Quantum Chem.* **2015**, *115*, 224−230.
(22) (a) Lavorato, D. J.; Terlouw, J. K.; McGibbon, G. A.; Dargel, T. K.; Koch, W.; Schwarz, H. *Int. J. Mass Spectrom.* **1998**, *179−180*, 7−14. (b) Stander-Grobler, E.; Schuster, O.; Heydenrych, G.; Cronje, S.; Tosh, E.; Albrecht, M.; Frenking, G.; Raubenheimer, H. G. *Organometallics* **2010**, *29*, 5821−5833.
(23) Schmidt, A.; Rahimi, A.; Gjikaj, M. *Synthesis* **2009**, *2009*, 2371−2378.
(24) Rahimi, A.; Namyslo, J. C.; Drafz, M.; Halm, J.; Hübner, E.; Nieger, M.; Rautzenberg, N.; Schmidt, A. *J. Org. Chem.* **2011**, *76*, 7316−7325.
(25) Thomas, R.; Lakshmi, S.; Pati, S. K.; Kulkarni, G. U. *J. Phys. Chem. B* **2006**, *110*, 24674−24677.
(26) Katsuyama, I.; Chouthaiwale, P. V.; Cui, H.-L.; Ito, Y.; Sando, A.; Tokiwa, H.; Tanaka, F. *Tetrahedron* **2013**, *69*, 4098−4104.
(27) Yamaguchi, Y.; Tanaka, T.; Kobayashi, S.; Wakamiya, T.; Matsubara, Y.; Yoshida, Z. *J. Am. Chem. Soc.* **2005**, *127*, 9332−9333.
(28) Smeyanov, A.; Schmidt, A. *Synth. Commun.* **2013**, *43*, 2809−2816.
(29) Sakamoto, T.; An-naka, M.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2754−2759.
(30) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, *1999*, 1145−1148.
(31) Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979−9990.
(32) Man, B. Y.-W.; Knuhtsen, A.; Page, M. J.; Messerle, B. A. *Polyhedron* **2013**, *61*, 248−252.
(33) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533−2545.
(34) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437−5440.
(35) Sperança, A.; Godoi, B.; Pinton, S.; Back, D. F.; Menezes, P. H.; Zeni, G. *J. Org. Chem.* **2011**, *76*, 6789−6797.
(36) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press, 1997; ISBN 978-0195095494.
(37) Simonetta, M.; Gavezzotti, A.; Patai, S. In *The Chemistry of the Carbon−Carbon Triple Bond*; Wiley: New York, 1978; pp 1−56.
(38) (a) Hougen, J. T.; Merer, A. J. *J. Mol. Spectrosc.* **2011**, *267*, 200−221. (b) Hougen, J. T. *J. Mol. Spectrosc.* **2012**, *278*, 41−51.
(39) Matzger, A. J.; Lewis, K. D.; Nathan, C. E.; Peebles, S. A.; Peebles, R. A.; Kuczkowski, R. L. *J. Phys. Chem. A* **2002**, *106*, 12110−12116.
(40) Demaison, J.; Wlodarczak, G.; Rück, H.; Wiedenmann, K. H.; Rudolph, H. D. *J. Mol. Struct.* **1996**, *376*, 399−411.
(41) Sparrow, C. R.; Fronczek, F. R.; Watkins, S. F. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2012**, *68*, o2809.
(42) Smith, G. T.; Howard, A. A. K.; Wallis, J. D. *Phys. Chem. Chem. Phys.* **2001**, *3*, 4501−4507.
(43) Li, Q.; Sue, C.-H.; Basu, S.; Shveyd, A. K.; Zhang, W.; Barin, G.; Fang, L.; Sarjeant, A. A.; Stoddart, J. F.; Yaghi, O. M. *Angew. Chem.* **2010**, *122*, 6903−6907; *Angew. Chem., Int. Ed.* **2010**, *49*, 6751−6755.
(44) Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112−122.
(45) Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3−8.
(46) *Jaguar, version 8.3*; Schrodinger, Inc.: New York, 2014.
(47) Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Landis, C. R.; Weinhold, F. *NBO 6.0*; Theoretical Chemistry Institute, University of Wisconsin: Madison, WI, 2013.

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J. Org. Chem. 2016, 81, 4202−4209