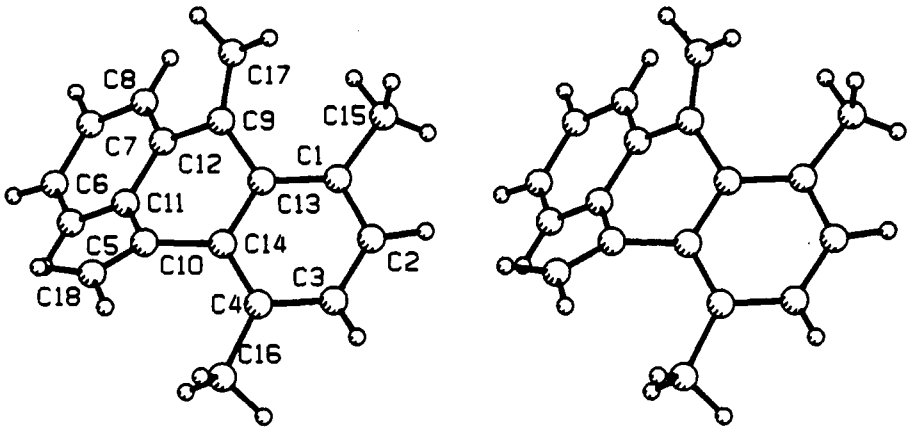

Figure 2. Stereo PLUTO[18] plot showing the molecular geometry and numbering scheme for 1,4-dimethyl-9,10-anthraquinodimethane (2).

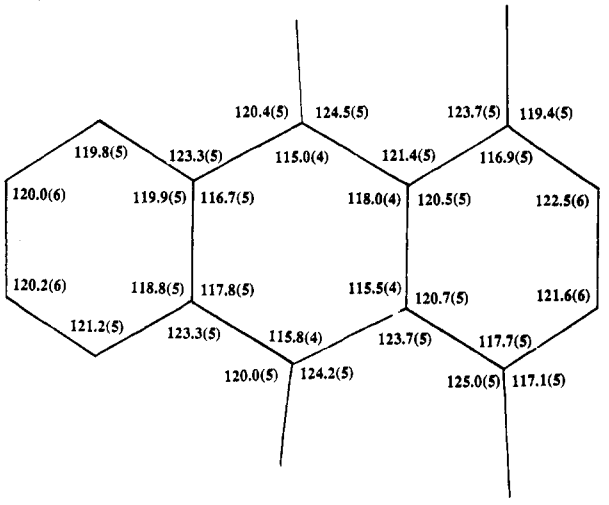

Figure 3. Carbon bond angles (deg) for 1,4-dimethyl-9,10-anthraquinodimethane (2) established by X-ray crystallography. Estimated standard deviations in the least significant figure are given in parentheses.

find boat (ΔH_f = 79.3 kcal/mol), planar (ΔH_f = 87.2 kcal/mol), and chair (ΔH_f = 84.1 kcal/mol) minima for that compound using molecular mechanics.

Experimental Section

The title compound was prepared from 1,4-dimethylanthraquinone as previously described.[8,9] Melting point, infrared spectra, and ^{1}H NMR spectra were as reported.[9] Crystallization of **2** from wet acetone yielded clear prism crystals of X-ray quality. Data collection for the X-ray structure analysis was done at ambient temperature on a crystal of approximate dimensions 0.4 × 0.2 × 0.7 mm. All measurements were made on a Rigaku AFC6S diffractometer with graphite-monochromated molybdenum Kα radiation.[13] Twenty reflections were used for the unit cell determination (2θ range 20.1–26.9°, ω scan peak width at half-height 0.28), corresponding to a monoclinic cell in the space group $P2_1/a$ with the following lattice parameters: a = 6.760 (1) Å, b = 23.044 (5) Å, c = 8.454 (2) Å, β = 97.29 (1)°, V = 1306.2 (8) Å^3. For Z = 4 and formula weight 232.32, the calculated density was 1.181 g/cm^3. Of the 2574 reflections collected, 2371 were unique. The structure was solved by direct methods.[14,15] Neutral atom scattering factors were taken from Cromer and Waber.[16] Anomalous dispersion effects were included in F_{calc};[17] the values for $\Delta f'$ and $\Delta f''$ were those of Cromer.[16]

All molecular mechanics calculations were done by using the MMX88 force field in the computer program PCMODEL, available from Serena Software, Bloomington, IN. MMX is a derivative of Allinger's MM2 with π VESCF subroutines. Structure comparisons were done by using the companion program PCDISPLAY, available from the same company.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research and to the National Science Foundation Research in Undergraduate Institutions Instrumentation Program (grant no. 8818307) for creation of The New England Molecular Structure Center at Keene State College.

Supplementary Material Available: Additional tables of crystallographic data including torsion angles, bond angles involving the hydrogen atoms, and anisotropic thermal parameters for **2** (4 pages); table of observed and calculated structure factors for **2** (16 pages). Ordering information is given on any current masthead page.

(13) Mo Kα (λ = 0.71069 Å), 6.0° take-off angle, ω-2θ scan, scan rate 8°/min, scan width (1.37 + 0.30 tan θ)°, 2θ_{max} (50.5°), Lorentz-polarization and absorption corrections, secondary extinction (0.23589 × 10^{-5}).

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(15) All calculations were performed by using the TEXSAN, TEXRAY Structure Analysis Package, version 2.1, of Molecular Structure Corporation, The Woodlands, TX. Full-matrix least-squares refinement, $\sum w(|F_o| - |F_c|)^2$, $4F_o^2/\sigma^2(F_o^2)$, p factor (0.03), 997 observations ($I > 3.00\sigma(I)$), 228 variables, reflection/parameter ratio (4.37), R = 0.058, R_w = 0.076, goodness of fit 2.47, maximum shift/error in final cycle (0.08), maximum peak in final difference map (0.20 e$^-$/Å^3), minimum peak in final difference map (−0.17 e$^-$/Å^3).

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Diels–Alder Reactions of *N*-Sulfonyl-1-aza-1,3-butadienes: Development of a Synthetic Approach to the Streptonigrone C Ring

Dale L. Boger* and Shinsuke Nakahara

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

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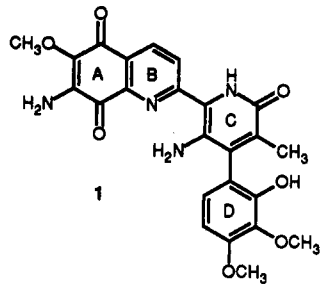
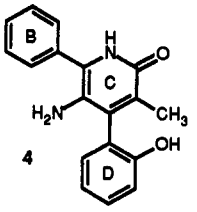
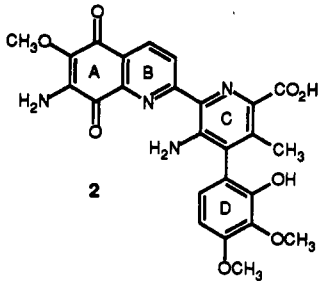
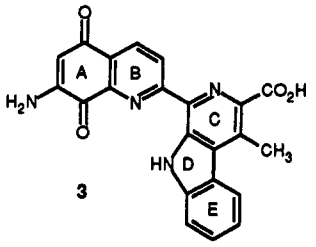
Streptonigrone (1), isolated from an unidentified *Streptomyces* species and identified through extensive

spectroscopic studies,[1] represents the newest member of the naturally occurring agents related to the quinone antitumor antibiotics streptonigrin (2) and lavendamycin (3).[2] In the continuation of the development of methodology suited to the preparation of members of this class of agents,[3-6] herein we detail the preparation of 4 constituting the fully functionalized C ring of 1 based on the application of our recently introduced Diels–Alder reactions of *N*-sulfonyl-1-aza-1,3-butadienes[6-9] and a unique set of transformations leading to aromatization of the product *N*-sulfonyltetrahydropyridines.



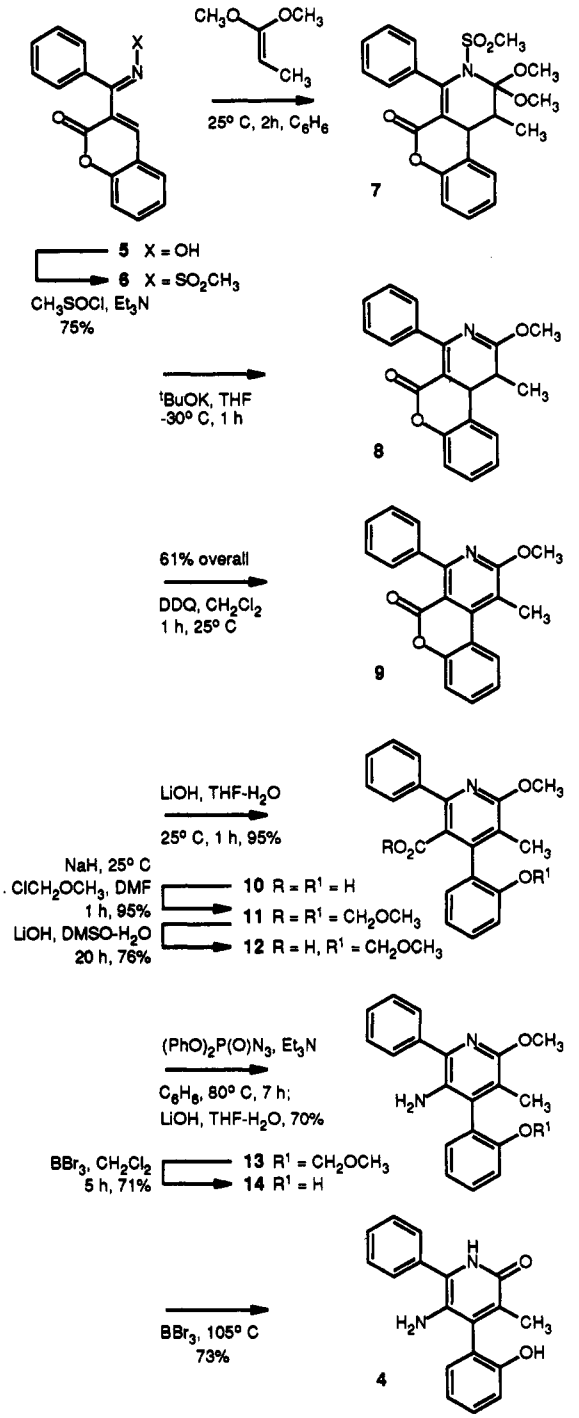






Treatment of the oxime 5[6] with methylsulfinyl chloride in the presence of triethylamine (0 °C, 15 min) and subsequent in situ homolytic rearrangement of the *O*-methylsulfinyl oxime (25 °C, 1 h) provided the *N*-(methylsulfonyl)-1-aza-1,3-butadiene 6 in excellent yield (75%).[6,7,10] Treatment of 6 with 1,1-dimethoxy-1-propene[11] *at room temperature* (2 h, 25 °C, C_6H_6) led to formation of the sensitive [4 + 2] cycloadduct 7 in a reaction that by design is facilitated by the complementary substitution of the 1-aza diene with a C-3 electron-withdrawing substituent.[6] Thus, the C-3 carboxylate of 6 serves to accelerate the rate of inverse electron demand Diels–Alder reaction, offers a convenient manner to protect the

Scheme I



D-ring phenol, and ultimately serves as the necessary functionality for introduction of the pyridone C-ring amine. Efforts to purify and characterize the sensitive adduct 7 generally led to hydrolysis and consequently was most expediently taken on without purification. In the course of subsequent efforts to promote the aromatization[12] of 7 to provide 9, treatment of 7 with potassium *tert*-butoxide was found to cleanly provide 8 as a stable, isolable material. Presumably 8 arises from deprotonation of the methanesulfonamide, loss of sulfene facilitated by the vinylogous amide activation of the departing amine, and finally loss of methoxide. Aromatization of 8 through treatment with

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(11) Mueller, F. J.; Eichen, K. Ger. Patent 2331675; *Chem. Abstr.* **1974**, *81*, 63153v.

(12) Comparable efforts with the phenylsulfonyl amide were not successful (*t*BuOK, -30 °C, THF, 1 h), and direct treatment of 7 with DDQ occasionally led to direct formation of 9 albeit in much lower conversions.

DDQ cleanly provided **9**. In initial studies, the intermediate isolation and characterization of **7**–**8** was carried out, but the conversion of **6** to **9** proved more convenient to conduct without purification of the intermediates and provided **9** in 60% overall yield for the three steps (Scheme I).

Hydrolysis of the lactone **9** (4 N LiOH, THF–H_2O) followed by protection of the free phenol as its methoxymethyl ether under conditions that led to carboxylic acid esterification (NaH, DMF, $ClCH_2OCH_3$, 25 °C) and subsequent ester hydrolysis (4 N LiOH, 76%) provided **12** in excellent overall yield and proved superior to efforts to selectively protect the phenol in the presence of the free carboxylic acid. Modified Curtius rearrangement on the free carboxylic acid employing the Shioiri–Yamada reagent ($(PhO)_2P(O)N_3$, benzene–H_2O)[13,14] provided **13** and permitted the introduction of the pyridone C-5 amine. Surprisingly, the intermediate isocyanate derived from Curtius rearrangement of the acyl azide proved unusually stable and isolable[15] and the complete conversion of **12** to **13** required the deliberate addition of hydroxide (4 N LiOH, THF–H_2O) to the reaction mixture to complete the isocyanate hydrolysis. In addition, attempts to trap the isocyanate in situ with *tert*-butyl alcohol to provide the amine (*tert*-butyloxy)carbonyl derivative proved unsuccessful and led to isolation of the isocyanate and/or the corresponding acyl azide derivative.[15,16] Sequential or concurrent deprotection of the methoxymethyl and methyl ethers (BBr_3, CH_2Cl_2) provided pyridone **4** and completed the preparation of the fully functionalized C-ring pyridone found in streptonigrone. The application of the observations in the total synthesis of streptonigrone are in progress and will be reported in due course.

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(14) Attempted Curtius rearrangement on **10** directly ($(PhO)_2P(O)N_3$, Et_3N, *t*-BuOH, reflux, 3.5 h) provided predominantly **9** (50%).

(15) For the isocyanate of **13**: viscous oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.95–7.90 (m, 2 H), 7.47–7.19 (m, 5 H), 7.15–7.11 (m, 2 H), 5.15 (d, 1 H, J = 6.8 Hz, OC*H*HOCH$_3$), 5.08 (d, 1 H, J = 6.8 Hz, OCH*H*OCH$_3$), 4.02 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_2OCH_3), 1.95 (s, 3 H, CH_3); CIMS (isobutane) m/e (relative intensity) 377 (M^+ + H, base); CIHRMS m/e 377.1505 ($C_{22}H_{20}N_2O_4$ requires 377.1501). For the acyl azide derivative of the isocyanate of **13**: mp 154–155 °C ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.73–7.68 (m, 2 H), 7.47–7.32 (m, 4 H), 7.21 (d, 1 H, J = 8.4 Hz), 7.15–7.09 (m, 2 H), 6.38 (s, 1 H, NH), 5.07 (s, 2 H, OCH_2OCH_3), 4.04 (s, 3 H, OCH_3), 3.28 (s, 3 H, OCH_2OCH_3), 1.96 (s, 3 H, CH_3): IR (KBr) ν_{max} 3268, 2140, 1678, 1524, 1494, 1360, 1236, 1200, 1152, 1000 cm^{-1}; EIMS m/e (relative intensity) 419 (M^+, 20), 376 (44), 331 (20), 317 (21), 45 (base); CIMS (isobutane) m/e (relative intensity) 420 (M^+ + H, 17), 377 (base); EIHRMS m/e 419.1602 ($C_{22}H_{21}N_5O_4$ requires 419.1594).

(16) Similar observations albeit in lower conversions were made with intermediates bearing a *tert*-butyldimethylsilyl versus methoxymethyl protecting group. For **12** (R^1 = $SiMe_2tBu$): 64% from **10**, mp 168–169 °C ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.65–7.61 (m, 2 H), 7.39–7.36 (m, 3 H), 7.25 (dt, 1 H, J = 7.7, 2.1 Hz), 7.04 (dd, 1 H, J = 7.5, 2 Hz), 6.94 (dt, 1 H, J = 7.4, 1 Hz), 6.83 (dd, 1 H, J = 8.1, 0.9 Hz), 4.03 (s, 3 H, OCH_3), 1.95 (s, 3 H, CH_3), 0.69 (s, 9 H, $C(CH_3)_3$), 0.10 (s, 3 H, $Si(CH_3)_2$), –0.02 (s, 3 H, $Si(CH_3)_2$); IR (KBr) ν_{max} 2932, 2858, 1696, 1566, 1494, 1452, 1360, 1282, 1254, 1168, 912 cm^{-1}; EIMS m/e (relative intensity) 392 (base), 374 (4), 75 (15); CIMS (isobutane) m/e (relative intensity) 450 (M^+ + H, base); CIHRMS m/e 450.2097 ($C_{26}H_{31}NO_4Si$ requires 450.2101). For isocyanate of **13** (R^1 = $SiMe_2tBu$): viscous oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.87–7.83 (m, 2 H), 7.49–7.31 (m, 4 H), 7.13–7.04 (m, 2 H), 6.95 (d, 1 H, J = 8.3 Hz), 4.00 (s, 3 H, OCH_3), 1.96 (s, 3 H, CH_3), 0.68 (s, 9 H, $C(CH_3)_3$), 0.09 (s, 3 H, $Si(CH_3)_2$), 0.08 (s, 3 H, $Si(CH_3)_2$); CIMS (isobutane) m/e (relative intensity) 447 (M^+ + H, base). In addition to the expected products derived from Curtius rearrangement of the acyl azide (ca. 58% **14** with hydrolysis of silyl ether), the cyclic carbamate derived from (*tert*-butyldimethylsilyl)oxy (or liberated phenol) trap of the isocyanate were observed. For the cyclic carbamate: mp 210–212 °C ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.67–7.60 (m, 2 H), 7.56–7.19 (m, 7 H), 6.53 (s, 1 H, NH), 4.01 (s, 3 H, OCH_3), 2.35 (s, 3 H, CH_3); IR (KBr) ν_{max} 3266, 1746, 1490, 1474, 1446, 1388, 1360, 1186, 1168, 1156, 966 cm^{-1}; EIMS m/e (relative intensity) 332 (M^+, base), 317 (11), 315 (15), 77 (20); CIMS (isobutane) m/e (relative intensity) 333 (M^+ + H, base); EIHRMS m/e 332.1165 ($C_{20}H_{16}N_2O_3$ requires 332.1161).

Experimental Section

1-Phenyl-1-[(methylsulfonyl)imino]-1-(2-oxo-2*H*-1-benzopyran-3-yl)methane (6). A solution of **5**[6,17] (265 mg, 1.0 mmol) in 40 mL of carbon tetrachloride cooled to 2 °C under nitrogen was treated with triethylamine (307 μL, 2.2 mmol, 2.2 equiv) and methyl sulfinyl chloride (135 μL, 2.0 mmol, 2 equiv). The resulting reaction mixture was stirred at 2 °C for 15 min and then at 25 °C for 1 h under nitrogen. The solvent was evaporated, and the residue was purified by flash chromatography (3 × 15 cm of SiO_2, 20% EtOAc–hexane eluant) to afford **6** (245 mg, 327 mg theoretical, 75%) as a white, crystalline solid: mp 193–194 °C ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.91 (dd, 2 H, J = 7.3, 1.4 Hz, ArH), 7.84 (s, 1 H, ArH), 7.67–7.30 (m, 7 H, ArH), 3.25 (s, 3 H, SO_2CH_3); IR (KBr) ν_{max} 1717, 1626, 1610, 1590, 1564, 1313, 1180, 1143, 808, 780, 758, 694, 506 cm^{-1}; EIMS m/e (relative intensity) 327 (M^+, 39), 248 (base), 89 (18), 77 (19); CIMS (isobutane), m/e (relative intensity) 328 (M^+ + H, base); EIHRMS m/e 327.0565 ($C_{17}H_{13}NO_4S$ requires 327.0565).

Anal. Calcd for $C_{17}H_{13}NO_4S$: C, 62.37; H, 4.00; N, 4.29. Found: C, 62.54; H, 4.10; N, 4.34.

2-Methoxy-1-methyl-4-phenyl-1,10b-dihydro-5*H*-1-benzopyrano[3,4-*c*]pyridin-5-one (8). A solution of **6** (164 mg, 0.50 mmol) and 1,1-dimethoxy-1-propene[11] (590 μL, 5.0 mmol, 10 equiv) in 1 mL of benzene was stirred at 25 °C for 2 h under nitrogen. The reaction mixture was concentrated in vacuo. For **7**: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.30–6.84 (m, 9 H, ArH), 3.34 (s, 3 H, OCH_3), 3.23 (s, 3 H, OCH_3), 2.73 (s, 3 H, SO_2CH_3), 1.15 (d, 3 H, J = 6.1 Hz, CH_3); CIMS (isobutane) m/e (relative intensity) 430 (M^+ + H, 6), 328 (base).[18] The residue was dissolved in 5 mL of tetrahydrofuran, and the solution was treated with potassium *tert*-butoxide (281 mg, 2.5 mmol, 5 equiv). The reaction mixture was stirred at –30 °C for 1 h. The reaction mixture was poured onto 40 mL of water and extracted with EtOAc (50 mL). The organic extract was washed with saturated aqueous NaCl (30 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification of the residue by flash chromatography (2 × 5 cm SiO_2, 10% EtOAc–hexane eluant) afforded **8** (83 mg, 160 mg theoretical, 52%) as EIHRMS light yellow, crystalline solid: mp 161–162 °C ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.68–7.63 (m, 2 H, ArH), 7.38–7.09 (m, 7 H, ArH), 3.94 (s, 3 H, OCH_3), 3.78 (d, 1 H, J = 8.7 Hz, =C*H*CHCH$_3$), 3.18 (qd, 1 H, J = 8.7, 7 Hz, =CHC*H*CH$_3$), 1.54 (d, 3 H, J = 7 Hz, CH_3); IR (KBr) ν_{max} 1736, 1622, 1592, 1560, 1488, 1274, 1222, 1198, 1158, 1136, 1016, 760 cm^{-1}; EIMS, m/e (relative intensity) 319 (M^+, 31), 305 (7), 304 (base), 201 (15), 173 (61); CIMS (isobutane) m/e (relative intensity) 320 (M^+ + H, base); EIHRMS, m/e 319.1208 ($C_{20}H_{17}NO_3$ requires 319.1208).

Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.35; H, 5.46; N, 4.41.

2-Methoxy-1-methyl-4-phenyl-5*H*-1-benzopyrano[3,4-*c*]-pyridin-5-one (9). From 8. A solution of **8** (15 mg, 0.047 mmol) in 0.47 mL of methylene chloride was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 12.8 mg, 0.056 mmol, 1.2 equiv), and the reaction mixture was stirred at 25 °C for 1 h. A separated precipitate (hydroquinone) was removed by filtration and the filtrate was concentrated in vacuo. Flash chromatography (1 × 5 cm SiO_2, 10% EtOAc–hexane eluant) afforded **9** (13.5 mg, 14.9 mg theoretical, 91%) as a white, crystalline solid: mp 151–152 °C ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 8.22 (dd, 2 H, J = 8.3, 1.4 Hz, ArH), 7.61–7.28 (m, 7H, ArH), 4.10 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3); IR (KBr) ν_{max} 1742, 1550, 1448, 1416, 1354, 1252, 1214, 1202, 1154, 1080, 966, 760, 712 cm^{-1}; EIMS m/e (relative intensity) 317 (M^+, base), 316 (85), 302 (52), 115 (21), 77 (24); CIMS (isobutane) m/e (relative intensity) 318 (M^+ + H, base); EIHRMS m/e 317.1052 ($C_{20}H_{15}NO_3$ requires 317.1052). Mp

(17) Oxime **5** was prepared in two steps through condensation of ethyl benzoylacetate with *o*-hydroxybenzaldehyde (0.06 equiv of piperidine, 0.16 equiv of AcOH, C_6H_6, 80 °C, 3 h, 60–80%) followed by oxime formation ($HONH_2$·HCl, pyridine, EtOH).

(18) Attempted purification by chromatography on silica gel led to isolation of the methyl ester derived from orthoester hydrolysis: ^1H NMR ($CDCl_3$, 200 MHz) δ 11.03 (s, 1 H, NH), 7.60–6.90 (m, 9 H, ArH), 3.85 (d, 1 H, J = 6.6 Hz), 3.54 (s, 3 H, OCH_3), 2.75 (s, 3 H, SO_2CH_3), 2.47 (p, 1 H, J = 7 Hz), 0.85 (d, 3 H, J = 7.0 Hz, CH_3); CIMS (isobutane) m/e (relative intensity) 416 (M^+ + H, base).

151–152 °C ($CHCl_3$-hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 8.22 (dd, 2 H, J = 8.3, 1.4 Hz, ArH), 7.61–7.28 (m, 7H, ArH), 4.10 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3); IR (KBr) ν_{max} 1742, 1550, 1448, 1416, 1354, 1252, 1214, 1202, 1154, 1080, 966, 760, 712 cm^{-1}; EIMS, *m/e* (relative intensity) 317 (M^+, base), 316 (85), 302 (52), 115 (21), 77 (24); CIMS (isobutane), *m/e* (relative intensity) 318 (M^+ + H, base); EIHRMS, *m/e* 317.1052 ($C_{20}H_{15}NO_3$ requires 317.1052).

Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Found: C, 76.01; H, 4.61; N, 4.13.

2-Methoxy-1-methyl-4-phenyl-5*H*-1-benzopyrano[3,4-*c*]-pyridin-5-one (9). Directly from 6. A solution of **6** (491 mg, 1.5 mmol) and 1,1-dimethoxy-1-propene[11] (1.77 mL, 15 mmol, 10 equiv) in 3 mL of benzene was stirred at 25 °C for 2 h under nitrogen. The reaction mixture was concentrated in vacuo. The residue was dissolved in 15 mL of tetrahydrofuran, and the solution was treated with potassium *tert*-butoxide (842 mg, 7.5 mmol, 5 equiv). The reaction mixture was stirred at −30 °C for 1 h. The reaction mixture was poured onto 120 mL of water and extracted with EtOAc (120 mL). The organic extract was washed with saturated aqueous NaCl (60 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in 14 mL of methylene chloride and was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 352 mg, 1.55 mmol, 1.1 equiv). The reaction mixture was stirred at 24 °C for 1 h. The separated precipitate (hydroquinone) was removed by filtration, and the filtrate was concentrated in vacuo. Flash chromatography (2 × 7 cm of SiO_2, 10% EtOAc–hexane eluant) afforded **9** (291 mg, 476 mg theoretical, 61%) as a white crystalline solid.

4-(2-Hydroxyphenyl)-6-methoxy-5-methyl-2-phenylpyridine-3-carboxylic Acid (10). A solution of **9** (67.5 mg, 0.21 mmol) in 630 μL of tetrahydrofuran was treated with 4 N aqueous lithium hydroxide (210 μL, 0.84 mmol, 4 equiv), and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with water (40 mL), made acidic with the addition of saturated aqueous NH_4Cl, and extracted with EtOAc (80 mL). The organic extract was washed with saturated aqueous NaCl (30 mL), dried ($NaSO_4$), and concentrated in vacuo. Recrystallization from chloroform–hexane afforded **10** (68 mg, 71.3 mg theoretical, 95%) as a white crystalline solid: mp 159–160 °C ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.63–7.60 (m, 2 H, ArH), 7.34–7.15 (m, 4 H, ArH), 6.96–6.85 (m, 2 H, ArH), 6.77 (d, 1 H, *J* = 8.3 Hz, ArH), 5.45 (br s, OH), 4.04 (s, 3 H, OCH_3), 1.92 (s, 3 H, CH_3); IR (KBr) ν_{max} 3420, 1730, 1700, 1560, 1490, 1450, 1406, 1358, 1204, 1168, 756 cm^{-1}; EIMS *m/e* (relative intensity) 335 (M^+, 12), 317 (88), 316 (base), 302 (76), 115 (20); CIMS (isobutane) *m/e* (relative intensity) 336 (M^+ + H, 48), 318 (base), 292 (47); EIHRMS *m/e* 335.1158 ($C_{20}H_{17}NO_4$ requires 335.1158).

Anal. Calcd for $C_{20}H_{17}NO_4 \cdot {}^1/_5H_2O$: C, 70.87; H, 5.17; N, 4.13. Found: C, 70.62; H, 5.18; N, 4.09.

Methoxymethyl 6-Methoxy-4-[2-[(methoxymethyl)oxy]-phenyl]-5-methyl-2-phenylpyridine-3-carboxylate (11). A solution of **10** (168 mg, 0.50 mmol) in 1.5 mL of *N,N*-dimethylformamide was cooled to 0 °C under nitrogen and treated with sodium hydride (60 mg, 1.5 mmol, 3 equiv). The reaction mixture was stirred for 3 min (0 °C) before methoxymethyl chloride (115 μL, 1.5 mmol, 3 equiv) was added. The reaction mixture was allowed to warm to 25 °C (10 min), and stirring was continued for an additional 45 min. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (9 mL). The organic extract was washed with saturated aqueous NaCl (4 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification of the residue by flash chromatography (2 × 7 cm of SiO_2, 10% EtOAc–hexane eluant) afforded **11** (202 mg, 212 mg theoretical, 95%) as a viscous oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.71–7.66 (m, 2 H, ArH), 7.42–7.18 (m, 5 H, ArH), 7.08–6.97 (m, 2 H, ArH), 5.12 (d, 1 H, *J* = 7.1 Hz, OC*H*HOPh), 5.08 (d, 1 H, *J* = 7.1 Hz, OCH*H*OPh), 4.87 (d, 1 H, *J* = 5.9 Hz, OC*H*HOCOpy), 4.81 (d, 1 H, *J* = 5.9 Hz, OCH*H*OCOpy), 4.05 (s, 3 H, OCH_3), 3.39 (s, 3 H, CH_3OCH_2OPh), 2.88 (s, 3 H, CH_3OCH_2OCOpy), 1.95 (s, 3 H, CH_3); IR (neat) ν_{max} 1736, 1562, 1494, 1452, 1414, 1360, 1204, 1156, 1126, 1114, 1084, 1018, 758 cm^{-1}; EIMS *m/e* (relative intensity) 423 (M^+, 1), 316 (16), 302 (8), 288 (1), 45 (base); CIMS (isobutane) *m/e* (relative intensity) 424 (M^+ + H, 67), 362 (base), 318 (46); EIHRMS *m/e* 424.1743 ($C_{24}H_{25}NO_6$ requires 424.1760).

6-Methoxy-4-[2-[(methoxymethyl)oxy]phenyl]-5-methyl-2-phenylpyridine-3-carboxylic Acid (12). A solution of **11** (23 mg, 0.054 mmol) in 0.1 mL of dimethyl sulfoxide was treated with a solution of lithium hydroxide (39 mg, 0.92 mmol, 17 equiv) in 0.33 mL of water at 25 °C under nitrogen. The resulting reaction mixture was warmed at reflux for 20 h. The reaction mixture was cooled, diluted with water (5 mL), made acidic with the addition of saturated aqueous NH_4Cl, and extracted with EtOAc (9 mL). The organic extract was washed with saturated aqueous NaCl (4 mL), dried (Na_2SO_4), and concentrated in vacuo. Recrystallization from ethyl acetate afforded **12** (15.6 mg, 20.5 mg theoretical, 76%) as a white crystalline solid: mp 190–191 °C (EtOAc); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.67–7.63 (m, 2 H, ArH), 7.34–7.21 (m, 4 H, ArH), 7.05 (d, 1 H, *J* = 8.4 Hz, ArH), 6.95–6.93 (m, 2 H, ArH), 4.89 (s, 2 H, OCH_2OCH_3), 4.03 (s, 3 H, OCH_3), 3.17 (s, 3 H, OCH_2OCH_3), 1.92 (s, 3 H, CH_3); IR (KBr) ν_{max} 2950, 1688, 1560, 1492, 1456, 1420, 1362, 1270, 1200, 1168, 1156, 1116, 1078, 1006, 758, 704 cm^{-1}; EIMS *m/e* (relative intensity) 379 (M^+, 25), 317 (80), 316 (base), 302 (43); CIMS (isobutane) *m/e* (relative intensity) 380 (M^+ + H, base), 318 (95); EIHRMS *m/e* 379.1418 ($C_{22}H_{21}NO_5$ requires 379.1420).

Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.65; H, 5.58; N, 3.69. Found: C, 69.35; H, 5.54; N, 4.01.

3-Amino-6-methoxy-4-[2-[(methoxymethyl)oxy]phenyl]-5-methyl-2-phenylpyridine (13). A solution of **12** (11.4 mg, 0.03 mmol) in 3 mL of benzene was treated with diphenyl phosphorazidate (97 μL, 0.45 mmol, 15 equiv) and triethylamine (63 μL, 0.45 mmol, 15 equiv) at 25 °C. The resulting reaction mixture was stirred at 25 °C for 15 min and at reflux for 7 h. The solvent was removed, and the residue in 0.5 mL of tetrahydrofuran was treated with 4 N aqueous lithium hydroxide (200 μL, 0.8 mmol, 27 equiv to **12**). The resulting reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with water (12 mL) and extracted with EtOAc (15 mL). The organic extract was washed with saturated aqueous NaCl (5 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification of the residue by flash chromatography (2 × 8 cm SiO_2, 10% EtOAc–$CHCl_3$ eluant) afforded **13** (7.4 mg, 10.5 mg theoretical, 70%) as a viscous oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.83–7.78 (m, 2 H, ArH), 7.49–7.24 (m, 5 H, ArH), 7.15–7.13 (m, 2 H, ArH), 5.10 (s, 2 H, OCH_2OCH_3), 3.96 (s, 3 H, OCH_3), 3.35 (s, 3 H, OCH_2OCH_3), 3.33 (s, 2 H, NH_2), 1.91 (s, 3 H, CH_3); IR (neat) ν_{max} 3442, 3358, 1492, 1456, 1396, 1358, 1190, 1158, 1080, 1022, 994 cm^{-1}; EIMS *m/e* (relative intensity) 350 (M^+, base), 317 (30), 289 (17), 77 (16), 45 (94); CIMS (isobutane) *m/e* (relative intensity) 351 (M^+ + H, base); EIHRMS *m/e* 350.1623 ($C_{21}H_{22}N_2O_3$ requires 350.1630).

3-Amino-4-(2-hydroxyphenyl)-6-methoxy-5-methyl-2-phenylpyridine (14). A solution of **13** (10 mg, 0.028 mmol) in 0.4 mL of methylene chloride cooled to −72 °C under nitrogen was treated with boron tribromide (114 μL, 1 M solution in CH_2Cl_2, 0.11 mmol, 4 equiv). The resulting reaction mixture was stirred at −72 °C for 15 min and allowed to warm to 25 °C (1.5 h), and stirring was continued for an additional 4 h under nitrogen. Methanol (1 mL) was added to quench the excess boron tribromide, and then water (5 mL) was added. The resulting reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with EtOAc (8 mL). The organic extract was washed with saturated aqueous NaCl (4 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification of the residue by flash chromatography (1 × 7 cm of SiO_2, 10% EtOAc–hexane eluant) afforded **14** (6.2 mg, 8.7 mg theoretical, 71%) as a light yellow solid: mp 173–175 °C ($CHCl_3$–hexane); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.76–7.70 (m, 2 H, ArH), 7.51–7.30 (m, 4 H, ArH), 7.15–7.00 (m, 3 H, ArH), 3.95 (s, 3 H, OCH_3), 1.97 (s, 3H, CH_3); IR (KBr) ν_{max} 3422, 3382, 1490, 1448, 1398, 1352, 1188, 1176, 1148, 1008, 766, 704 cm^{-1}; EIMS *m/e* (relative intensity) 306 (M^+, base), 289 (4); CIMS (isobutane) *m/e* (relative intensity) 307 (M^+ + H, base); EIHRMS *m/e* 306.1371 ($C_{19}H_{18}N_2O_2$ requires 306.1368).

5-Amino-4-(2-hydroxyphenyl)-3-methyl-6-phenyl-2-pyridone (4). Boron tribromide (1.0 mL, 1 M solution in CH_2Cl_2, 1.0 mmol, 30 equiv) was added to **14** (10 mg, 0.033 mmol) at 25 °C under nitrogen, and the resulting solution was stirred at 105 °C for 1 h in a resealable Kontes vial. MeOH (1 mL) and water (5 mL) were added. The resulting mixture was neutralized with saturated aqueous $NaHCO_3$ and was extracted with EtOAc (8 mL). The organic extract was washed with saturated aqueous NaCl (4 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification of the residue by flash chromatography (1 × 5 cm

of SiO_2, EtOAc eluant) afforded 4 (7 mg, 9.6 mg theoretical, 73%) as a light yellow solid: mp 215–217 °C ($CHCl_3$–MeOH); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.52–7.29 (m, 6 H, ArH), 7.11–6.98 (m, 3 H, ArH), 3.18 (br s, 2 H, NH_2), 1.92 (s, 3 H, CH_3); ^{13}C NMR (CD_3OD, 600 MHz) δ 161.9, 154.5, 144.5, 133.5, 130.5, 130.2, 129.7, 129.5, 129.4, 127.1, 126.5, 126.0, 123.0, 120.5, 116.5, 13.5; IR (KBr) ν_{max} 3060, 1612, 1528, 1496, 1450, 1372, 1342, 1288, 1238, 752, 700 cm^{-1}; UV (MeOH) λ_{max} 282 (4800), 360 nm (6200); EIMS *m/e* (relative intensity) 292 (M^+, base), 275 (16), 104 (38), 77 (56); EIHRMS *m/e* 292.1205 ($C_{18}H_{16}N_2O_2$ requires 292.1212).

Similarly the aminophenol 14 (1 mg, 0.0033 mmol) was treated with 47.5% aqueous hydrogen bromide (0.1 mL), and the resulting reaction mixture was warmed at 105 °C for 1 h in a resealable Kontes vial. After being cooled to 25 °C, the reaction mixture was diluted with water (5 mL), neutralized with saturated aqueous $NaHCO_3$, and extracted with EtOAc (8 mL). The organic extract was washed with saturated aqueous NaCl (4 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo and purification of the residue by flash chromatography (1 × 5 cm SiO_2, EtOAc eluant) afforded 4 (0.4 mg, 0.96 mg theoretical, 42%).

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Supplementary Material Available: ^1H NMR spectra of 4, 11, 13–14 (4 pages). Ordering information is given on any current masthead page.

Improved Radical Stabilization Energies

Michael Lehd and Frank Jensen*

Department of Chemistry, Odense University, DK-5230 Odense M., Denmark

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Considerable effort has been expended in the studies of how various functional groups interact with a radical center and to determine quantitatively the stabilization by a substituent.[1] As accurate experimental stabilization energies are difficult to obtain, theoretical values have been widely used. Previous calculations of radical stabilization energies (RSE) of monosubstituted methyl radicals have used unrestricted (UHF) or restricted open-shell Hartree–Fock (ROHF) methods.[2,3] The UHF method produces wave functions that are not eigenfunctions of the S^2 operator and all UHF wave functions show some degree of spin contamination from higher multiplets. In many cases the spin contamination is negligible, but in systems where the odd electron can be delocalized, the problem can be severe (see, e.g., Table I). By using an ROHF wave function, the spin contamination can be eliminated entirely; however, ROHF wave functions are not readily amenable to subsequent introduction of electron correlation via a perturbation expansion. In any case it is desirable to determine what level of theory is necessary for obtaining accurate results.

Recently a new method for decreasing spin contamination in UHF wave functions has been introduced where the first spin contaminant is annihilated self-consistently during the SCF procedure.[4] The procedure has been labeled AUHF, and the corresponding wave function can be used as a reference for a Møller–Plesset (MP) perturbation expansion,[5] giving rise to the acronym AUMP.[6] A series of calculations have recently been presented by Baker, from which it appears that the AUMP method is operationally equivalent to performing MP calculations using an ROHF reference wave function.[6] We here present improved estimates of RSE's for a number of substituents attached to methyl and allyl radicals using the AUMP method.

Table I. $\langle S^2 \rangle$ Values for the Radicals in Reactions 1–3

	$\dot{C}H_2X$		$\dot{X}CHCHCH_2$		$\dot{C}H_2CXCH_2$	
X	UHF[a]	AUHF[b]	UHF[a]	AUHF[b]	UHF[a]	AUHF[b]
H	0.761	0.754	0.975	0.782	0.975	0.782
F	0.759	0.753	0.967	0.781	0.963	0.781
OH	0.759	0.754	0.955	0.778	0.960	0.777
CH	0.972	0.759	1.156	0.779	1.125	0.787
NH_2	0.759	0.754	0.945	0.777	0.960	0.781
BH_2	0.756	0.753	0.962	0.775	1.000	0.788
CHO	1.005	0.758	1.271	0.778	1.250	0.778
CH_3	0.762	0.754	0.971	0.781	0.978	0.782

[a] 3-21G basis set. [b] 6-31G* basis set.

The RSE's are defined by the following isodesmic reactions,[3,7] positive values indicate a stabilizing interaction:

$$\dot{C}H_2X + CH_4 \rightarrow CH_3X + \dot{C}H_3 \quad (1)$$

$$\dot{C}H_2CHCHX + CH_4 \rightarrow CH_3X + \dot{C}H_2CHCH_2 \quad (2)$$

$$\dot{C}H_2CXCH_2 + CH_4 \rightarrow CH_3X + \dot{C}H_2CHCH_2 \quad (3)$$

All geometries have been fully optimized at the ROHF/3-21G level for methyl radicals, at the UHF/3-21G level for allyl radicals, and at the RHF/3-21G level for all closed shell molecules.[8] The UHF method was used for allyl radicals due to the symmetry breaking problems associated with ROHF methods.[9] Only the trans isomers in reaction 2 have been considered; the differences between cis and trans isomers are on the order of a few kcal/mol.

Previous calculations of RSE's for reaction 1 at the ROHF/4-31G level[2] give almost the same results as our AUHF/6-31G* calculations (Table II), indicating little basis set effect. Calculations at the UHF/3-21G level[3] show similar results for the systems with X = F, OH, NH_2, BH_2, and CH_3. For the CN, CHO, and $CHCH_2$ substituents, however, quite large differences appear, and Table I shows that this is due to spin contamination. Including electron correlation increases all RSE's by 1–3 kcal/mol, and the AUMP4 results are almost identical with those at the AUMP2 level. Experimental data are scarce, but kinetic studies show RSE values for cyano of 5–7 kcal/mol,[10] for vinyl of 9–14 kcal/mol,[11] for hydroxy of 8–11

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