A New Class of Photolabile Chelators for the Rapid Release of Divalent Cations: Generation of Caged Ca and Caged Mg

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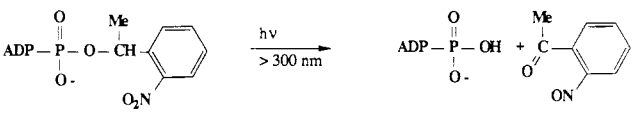
The synthesis of 2-nitro-4,5-dimethoxyphenyl derivatives of EGTA and EDTA is reported. These tetracarboxylate chelators are designed for the rapid photochemically initiated release of divalent cations in intact physiological systems. The key step in the synthesis is the use of high-pressure synthetic technology for the construction of the tertiary amine moiety of both types of chelator.

Calcium plays an important role as a "second messenger" in a variety of physiological processes and the regulation of cellular Ca^{2+} is central to the control of excitation–contraction coupling in muscle and excitation–secretion coupling in many systems.[1] Magnesium is a necessary cofactor in ATP-dependent enzymatic processes including ion pumps, the myosin ATPase in muscle, and a variety of kinases; it is also necessary in most processes where organophosphates are enzymatic substrates.[2] Therefore the ability to regulate rapidly the concentration of these divalent cations for the quantitative study of the kinetics of such processes with minimal perturbation to the system is clearly a very desirable goal.[3] One general approach to the rapid release of physiologically significant organic molecules and cations is the "caging" of their active functionality by using the photoremovable *o*-nitrobenzyl group.[4] This approach was first utilized by us with caged ATP,[5] where a *o*-nitrobenzyl ester of ATP releases ATP upon illumination.



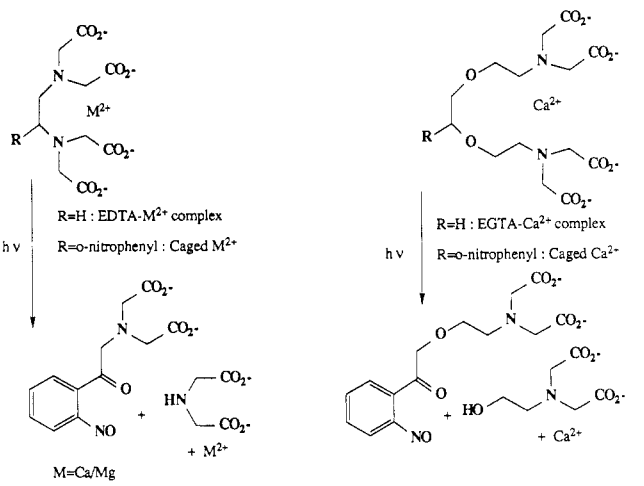
Photorelease of Caged ATP

We have recently applied this general photochemical regulatory protocol to produce a step increase in the concentration of calcium and magnesium ions.[6] In this paper we describe the synthesis of molecules designed to be novel divalent cation chelators which on exposure to ultraviolet light are photocleaved. The photolysis products bind divalent cations much less tightly than do the intact chelators. It was envisioned that *o*-nitrophenyl-substituted derivatives of EDTA and EGTA would serve initially as chelators having high affinities for the divalent cations, which would, upon specific chemical transformation (i.e., photochemical irradiation), allow the rapid release of the bound species (Scheme I). The basis for the increase in, for example, the free calcium ion concentration is based on the great difference in affinities for calcium ion between the tetracarboxylate chelators (K_d ca. 10^{-8} M at neutral pH) and the diacetic acid products (K_d ca. 10^{-3} M at neutral pH).

Results and Discussion

Our initial priority was the synthesis of a caged calcium species, and we hoped that substitution of an aromatic moiety for a proton on the ethylenic subunit between the ethereal oxygens would not disturb the chelator's affinity too much; however, we envisioned that the construction of the vicinal ether linkages would prove less than straightforward. Therefore, we chose as our first synthetic target an analogue of EGTA in which the ethylenic subunit between the ethereal oxygens was replaced by a methylenic moiety bearing the aromatic chromophore. This change in the structure of EGTA allowed us rapid and facile synthetic access to a molecule, **2**, which we hoped would have similar chelation properties to EGTA itself.

Scheme I



The diiodide **1** could be synthesized (see Scheme II) in large quantities by acetalization of 6-nitroveraldehyde with 2-bromoethanol, followed by halogen exchange. However, the amination of **1** with iminodiacetic acid, diethyl ester proved to be surprisingly troublesome. The use of a wide variety of solvents and organic or inorganic bases led, only at best, to the *mono*aminated product. Diamination could not be achieved by using standard thermal methods; only diminished yields of unidentified side products were isolated. The desired transformation was finally accomplished with recourse to high-pressure synthetic technology. Thus, diiodide **1** was dissolved in excess secondary amine, and the solution was subjected to 5000 psi for 8 days to yield compound **2**, as the sole product, in 65% yield. This is, as far as we know, the first example of the use of high-pressure chemistry to effect the alkylation of

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(3) Lester, H. A.; Nerbonne, J. M. *Annu. Rev. Biophys. Bioeng.* **1982**, *11*, 151. For an alternative approach to this problem, see: Tsien, R. Y.; Zucker, R. S. *Biophys. J.* **1986**, *50*, 843.
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(5) Kaplan, J. H.; Forbush, B.; Hoffman, J. F. *Biochemistry* **1978**, *17*, 1929.
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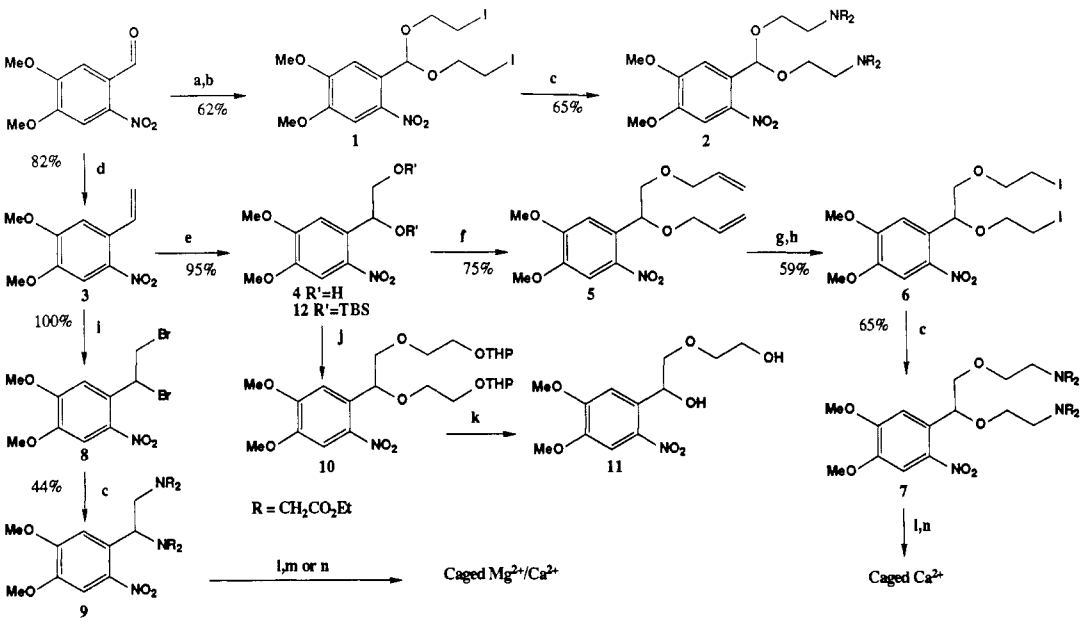
Scheme II[a]



[a] Reagents: (a) 2-bromoethanol, TsOH, benzene, reflux, 8 h; (b) NaI, acetone, reflux, 1 h; (c) iminodiacetic acid diethyl ester, 5000 psi, 8 or 21 days; (d) Ph_3PCH_2, THF, 0 °C, 1 h, then room temperature, 18 h; (e) OsO_4, MNO, *t*-BuOH/H_2O, room temperature, 45 h; (f) (i) *n*-Bu_2SnO, MeOH, reflux, 1 h; (ii) allyl iodide, *n*-Bu_4NI, PhMe, reflux, 24 h; (iii) NaH, allyl bromide, DME, room temperature, 1 h; (g) (i) O_3, CH_2Cl_2; (ii) $NaBH_4$, MeOH; (h) Ph_3P, imidazole, I_2, PhMe, 0.5 h; (i) Br_2, CH_2Cl_2, 0 °C, 1 h; (j) base, $BrCH_2CH_2OP'$, base = KH, P' = THP, 4 → **10**; base = TlOEt, P' = TBS, or base = KH, P' = TBDPS, no reaction; base = KH, P' = TBS, 4 → **12**; base = Na or NaH, 4 → **3**; (k) H^+; (l) 1 M NaOH/EtOH; (m) $MgCl_2$; (n) $CaCl_2$.

a secondary amine. Unfortunately, compound **2** had a disappointingly low affinity for Ca^{2+} compared with EGTA. Therefore, we turned to the synthesis of the 2-nitro-4,5-dimethoxyphenyl derivative of EGTA, **7**.

The construction of diol **4** from *o*-nitroveratraaldehyde via styrene **3** was straightforward (see Scheme II, 80% overall yield). Thus, with good quantities of **4** in hand, we had to achieve bis two-carbon homologation of this diol, with subsequent functional group interconversion, to diiodide **6**. The use of standard or modified Williamson ether formation conditions with the THP (tetrahydropyranyl) ether of iodo or bromoethanol, led to the smooth and rapid reformation of styrene **3** in quantitative yield. Changing the base to KH gave the desired product, **10**, in 46% yield. However, THP removal using weak acid or Lewis acid yielded only diol **11**. Recourse to other hyroxyl-protecting groups or alternative bases resulted either in protecting group transfer (with TBS, *tert*-butyldimethylsilyl) or no reaction (TlOEt and DPBS, diphenyl-*tert*-butylsilyl).

The high-yielding and clean transformation of **3** to **6** was finally accomplished in the following manner. Regiospecific alkylation of **3** at the primary hyroxyl position with allyl iodide via the tin ketal[7] of **4**, with subsequent alkylation of the benzylic hyroxyl using classical Williamson ether synthesis techniques, gave the diallyl ether **5** in 75% overall yield. On a large scale, it was found that high yields were best achieved when the monoallyl ether was isolated and purified. Transformation of **5** to **6** was accomplished by ozonolysis of **5** and in situ reduction of the ozonide to the corresponding diol, which was iodinated[8] in excellent yield to give the diiodide **6**. This was aminated at high pressure to afford the desired EGTA analogue **7**.

The phenyl EDTA analogue **9** was synthesized by bromination of **3** to yield dibromide **8**, which was subjected to high pressure amination to give the desired tetraester (Scheme II). It must be emphasized again that the transformation of **8** to **9** could not be accomplished under a wide variety of thermal conditions. Nor could **9** be synthesized from the ditosylate of **4** under these same thermal conditions. Equilibrium dissociation constants for the binding of Ca^{2+} and Mg^{2+} to the tetrasodium salt of **9** have been determined. This was carried out by titrating the chelator with excess $CaCl_2$ and measuring the free [Ca^{2+}] with a Ca^{2+}-selective electrode, similar measurements were then performed in the presence of $MgCl_2$. Values were obtained for **9** of about 5.0×10^{-9} M (pH 7, 20 °C, 130 mM KCl) for the equilibrium dissociation content for Ca^{2+} and about 2×10^{-6} M for Mg^{2+}. Compound **7** bound Ca^{2+} much more weakly, $K_d \sim 25 \times 10^{-6}$ M. The detailed experimental procedures and applications of these photolabile chelators in physiological systems is described elsewhere.[6] In addition, we are studying in detail the photochemistry of these systems in order to quantitate the rate of cation release.

Experimental Section

***o*-Nitroveratraldehyde Bis(2-bromoethyl) Acetal.** A solution of *o*-nitroveratraldehyde (10.0 g, 47.4 mmol) and 2-bromoethanol (33.0 mL, 465 mmol) in toluene with tosic acid catalyst was heated at reflux for 8 h, and water was removed from the reaction mixture by azeotropic distillation. The solution was concentrated in vacuo and purified by flash chromatography on silica gel (elution with 30% ethyl acetate in hexanes) to give 13.0 g (62%) of the dibromide as a yellow solid, mp 84–85 °C: ^1H NMR (200 MHz, $CDCl_3$) δ 7.57 (s, 1 H), 7.42 (s, 1 H), 6.32 (s, 1 H), 4.07–3.85 (m, 4 H), 4.02 (s, 3 H), 3.96 (s, 3 H), 3.56–3.47 (6 lines, 4 H); IR ($CHCl_3$, cm^{-1}) 3010, 1525, 1280; HRMS, $C_{13}H_{17}Br_2NO_6$ requires 440.9417, observed 440.9415.

***o*-Nitroveratraldehyde Bis(2-iodoethyl) Acetal (1).** A solution of dibromide (5.0 g, 11.8 mmol) and sodium iodide (10.7 g, 71.1 mmol) was heated at reflux in dry acetone for 1 h. The solution was filtered and concentrated in vacuo. The resulting solid was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were dried and

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(8) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 2* **1980**, 2866.

concentrated to give 6.34 g (100%) of diiodide **1** as a yellow solid, mp 102–103 °C: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57 (s, 1 H), 7.43 (s, 1 H), 6.33 (s, 1 H), 4.04 (s, 3 H), 3.96 (s, 3 H), 3.91–3.79 (m, 4 H), 3.31 (t, J = 7.0 Hz, 4 H); IR ($CHCl_3$, cm^{-1}) 3010, 1530, 1280; HRMS, $C_{13}H_{17}NO_6I_2$ required 536.9146, observed 536.9197.

***o*-Nitroveratraldehyde Bis[2-(bis((ethoxycarbonyl)-methyl)amino)ethyl] Acetal (2).** A solution of diiodide 1 (1.15 g, 2.13 mmol) in iminodiacetic acid diethyl ester (2.39 g, 12.6 mmol) was subjected to a pressure of 5000 psi for 8 days. Flash chromatographic purification (elution with 15% hexanes in ethyl acetate) gave 0.698 g (65%) of tetraester **2** as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48 (s, 1 H), 7.28 (s, 1 H), 6.09 (s, 1 H), 4.07 (q, J = 6.1 Hz, 8 H), 3.95 (s, 3 H), 3.89 (s, 3 H), 3.75–3.56 (m, 4 H), 3.54 (s, 8 H), 2.95 (t, J = 5.7 Hz, 4 H), 1.18 (t, J = 6.1 Hz, 12 H); IR ($CHCl_3$, cm^{-1}) 3010, 1740, 1530, 1280; HRMS, $C_{29}H_{45}N_3O_{14}$ requires 659.2903, M + 1 observed 660.2980.

2-Nitro-4,5-dimethoxystyrene (3). To a magnetically stirred suspension of methyl triphenylphosphonium bromide (22.02 g, 61.6 mmol) in dry THF at 0 °C under N_2 was added a 1 M solution of sodium hexamethyldisilazide in the same solvent (61.6 mL, 61.6 mmol). The resulting mixture was stirred at 0 °C for 1 h, a solution of *o*-nitroveratraldehyde (10.0 g, 47.4 mmol) in dry THF (100 mL) was added by canulation, and stirring was continued for an additional 18 h at room temperature. A solution of saturated NH_4Cl (200 mL) was added and the product extracted with CH_2Cl_2 (3 × 150 mL), dried, and concentrated. Flash chromatographic purification of the residue on silica gel (elution with 25% ethyl acetate in hexanes) furnished 8.13 g (82%) of styrene **3** as a yellow solid, mp 58–60 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.59 (s, 1 H, 7.31 (dd, J = 10.9, 0.7 Hz, 1 H), 6.97 (s, 1 H), 5.64 (dd, J = 17.3, 0.7 Hz, 1 H), 5.34 (dd, J = 10.9, 0.7 Hz, 1 H), 4.00 (s, 1 H), 3.95 (s, 1 H); IR ($CHCl_3$, cm^{-1}) 3010, 1515, 1330, 1275, 1210, 770, 725; HRMS, $C_{10}H_{11}NO_4$ requires 209.0688, M + 1 observed 210.0761.

1-(2-Nitro-4,5-dimethoxyphenyl)ethane-1,2-diol (4). To a magnetically stirred solution of **3** (3.8 g 18.2 mmol) was added osmium tetraoxide (0.0457 mg 0.18 mmol) in *tert*-butyl alcohol (2.34 mL) and 4-methylmoroholine *N*-oxide (2.35 g, 20.0 mmol) as an 80% solution in H_2O. The reaction mixture was stirred at room temperature for 45 h, concentrated in vacuo, and purified by flash chromatography on silica gel (elution with ethyl acetate) to give 4.00 g (90%) of diol **4** as a yellow solid, mp 118–120 °C (0.175 g, 0.837 mmol of starting material was recovered, the yield was thus 95% based on consumed starting material): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.53 (s, 1 H), 7.11 (s, 1 H), 6.22 (dd, J = 5.7, 9.6 Hz, 1 H), 4.07–4.00 (m, 2 H), 4.02 (s, 1 H), 3.97 (s, 1 H); IR ($CHCl_3$, cm^{-1}) 3600, 3400, 3010, 1535, 1280; HRMS, $C_{10}H_{13}NO_6$ requires 243.0739, observed 243.0748.

1-(2-Nitro-4,5-dimethoxyphenyl)-1,2-bis(allyloxy)ethane (5). Residual water was removed from a mixture of diol **4** (1.0 g, 4.11 mmol) and di-*n*-butyltin oxide (1.075 g, 4.32 mmol) by azeotropic distillation with toluene. The suspension was concentrated in vacuo, dry methanol (30 mL) was added, and the solution was refluxed under N_2 for 2 h. The solution was concentrated, and tetra-*n*-butylammonium iodide (3.04 g, 4.11 mmol), dry allyl iodide (1.38 g, 16.2 mmol), and dry toluene were added. The reaction mixture was refluxed for 22 h, diluted with H_2O (50 mL), and extracted with ethyl acetate (3 × 75 mL). The combined organic layers were dried and concentrated, and the residue was subjected to flash chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to give 0.200 g (20%) of recovered starting material and 0.889 g (80%) monoallyl ether (100% based on recovered starting material). To a stirred suspension of NaH (0.10 g, 4.17 mmol) in dry DME (10 mL) under N_2 was added a solution of the monoallyl ether (0.889 g, 3.29 mmol) and dry allyl bromide (1.40 g, 11.6 mmol) in dry DME (10 mL) at 0 °C. The reaction mixture was stirred for 1 h at room temperature, H_2O (50 mL) was added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried, concentrated, and subjected to flash chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to give 0.796 g (75%) of diallyl ether **5** as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.76 (s, 1 H), 7.16 (s, 1 H), 6.00–5.83 (m, 2 H), 5.40 (dd, J = 3.1, 6.6 Hz, 1 H), 5.32–5.13 (m, 4 H), 4.16–4.02 (m, 4 H), 4.00 (s, 3 H), 3.97 (s, 3 H), 3.73 (dd, J = 3.1, 8.8 Hz, 1 H), 3.64 (dd, J = 6.6, 8.8 Hz, 1 H); IR ($CHCl_3$, cm^{-1}) 1515, 1270; HRMS, $C_{16}H_{21}NO_6$ requires 323.1367, observed 323.1368.

1-(2-Nitro-4,5-dimethoxyphenyl)-1,2-(2-hydroxyethoxy)-ethane. Ozone was bubbled through a cold (−78 °C) magnetically stirred solution of diallyl ether **5** (0.783 g, 2.43 mmol) in CH_2Cl_2 (30 mL) until the solution was blue. Solvent evaporation left a residue, which was taken up in methanol (40 mL) and $NaBH_4$ (0.55 g, 12.2 mmol) was added to a magnetically stirred, cold (0 °C) solution. The reaction mixture was stirred for a further 18 h at room temperature, dilute HCl solution (20 mL) was added, and the product was extracted with $CHCl_3$ (3 × 100 mL). The combined organic were dried, concentrated in vacuo, and purified by flash chromatography on silica gel (elution with 10% methanol in ethyl acetate) to give 0.523 g (65%) of the diol as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.64 (s, 1 H), 7.29 (s, 1 H), 5.43 (dd, J = 2.6, 7.8 Hz, 1 H), 3.99 (s, 3 H), 3.96 (s, 3 H), 3.89–3.60 (m, 10 H), 3.51 (dd, J = 3.1, 5.8 Hz, 1 H), 3.47 (dd, J = 7.8, 5.8 Hz, 1 H); IR ($CHCl_3$, cm^{-1}) 3440, 3000, 2915, 1520, 1335, 1275, 1055.

1-(2-Nitro-4,5-dimethoxyphenyl)-1,2-bis(2-iodoethoxy)-ethane (6). To a magnetically stirred solution in toluene (20 mL) of the diol (0.110 g, 0.332 mmol) were added triphenylphosphine (0.700 g, 2.66 mmol), imidazole (0.180 g, 2.66 mmol) and iodine (0.500 g, 1.99 mmol). The reaction mixture was stirred at room temperature for 0.5 h, saturated $NaHCO_3$ (20 mL) was added, the reaction mixture was stirred for a further 5 min, then enough I_2 was added to color the organic phase, and the reaction mixture was stirred for a further 10 min. The reaction mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were dried, concentrated in vacuo, and purified by flash chromatography on silica gel (elution with 10% ethyl acetate in hexanes) to give 0.155 g (91%) of the diiodide as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.64 (s, 1 H), 7.36 (s, 1 H), 5.39 (dd, J = 2.8, 6.7 Hz, 1 H), 4.05 (s, 3 H), 3.96 (s, 3 H), 3.89–3.64 (m, 6 H), 3.36–3.25 (m, 4 H); IR ($CHCl_3$, cm^{-1}) 1515, 1330, 1270. HRMS, $C_{14}H_{17}I_2NO_6$ requires 548.9148, observed 548.9145.

7-(2-Nitro-4,5-dimethoxyphenyl)-3,12-bis[(ethoxy-carbonyl)methyl]-6,9-dioxa-3,12-diazatetradecanedioic Acid Diethyl Ester (7). A solution of diiodide **6** (0.166 g, 0.301 mmol) in iminodiacetic acid diethyl ester (0.285 g, 1.505 mmol) was subjected to a pressure of 5000 psi for 8 days. Flash chromatographic purification (elution with 15% hexanes in ethyl acetate) gave 0.136 g (65%) of **7** as a yellow oil (and unreacted secondary amine): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.52 (s, 1 H), 7.16 (s, 1 H), 5.21 (dd, J = 3.3, 6.4 Hz, 1 H), 4.16–4.01 (m, 8 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.66–3.43 (m, 6 H), 3.52 (s, 4 H), 3.51 (s, 4 H), 2.89 (m, 4 H), 1.27 (m, 12 H); IR ($CHCl_3$, cm^{-1}) 3010, 1735, 1540, 1280; HRMS, $C_{30}H_{47}N_3O_{14}$ requires 696.2970, observed 696.2950.

1-(2-Nitro-4,5-dimethoxyphenyl)ethane-1,2-diyl 1,2-Dibromide (8). To a cold (0 °C) magnetically stirred solution of styrene **3** (8.13 g, 38.9 mmol) in CH_2Cl_2 (150 mL) was added bromine (6.39 g, 0.040 mmol). The reaction mixture was extracted with a saturated $Na_2S_2O_3$ solution (100 mL), and the organic phase was dried and concentrated in vacuo to give 14.35 g (100%) dibromide **8** as a yellow solid, mp 47–52 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.53 (s, 1 H), 7.11 (s, 1 H), 6.20 (dd, J = 5.7, 9.7 Hz, 1 H), 4.07–3.99 (m, 2 H), 4.02 (s, 3 H), 3.97 (s, 3 H); IR ($CHCl_3$, cm^{-1}) 3005, 1535, 1280. HRMS, $C_{10}H_{11}Br_2NO_4$ requires 368.9035, observed 368.9034.

1-(2-Nitro-4,5-dimethoxyphenyl)-*N*,*N*,*N*′,*N*′-tetrakis-[(ethoxycarbonyl)methyl]-1,2-ethanediamine (9). A solution of dibromide **8** (1.37 g, 3.72 mmol) in iminodiacetic acid diethyl ester (3.52 g, 18.6 mmol) was subjected to 5000 psi for 21 days. Flash chromatographic purification on silica gel (elution with 30% ethyl acetate in hexanes) gave 0.980 g (44%) tetraester **9** as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.69 (s, 1 H), 7.43 (s, 1 H), 5.13 (dd, J = 7.1, 8.9 Hz, 1 H), 4.13–4.03 (8 lines, 8 H), 3.95 (s, 3 H), 3.88 (s, 3 H), 3.78–3.42 (m, 8 H), 3.14 (dd, J = 7.1, 13.8 Hz, 1 H), 2.89 (dd, J = 8.9, 13.8 Hz, 1 H), 1.24–1.16 (6 lines, 12 H); IR ($CHCl_3$, cm^{-1}) 3010, 1735, 1540, 1280; HRMS, $C_{26}H_{39}N_3O_{12}$ requires 585.2535, M + 1 observed 586.2612.

Iminodiacetic Acid Diethyl Ester. To a magnetically stirred suspension of iminodiacetic acid (50 g, 0.376 mol) in absolute ethanol (1000 mL) under N_2 was added boron trifluoride etherate (100 g, 1.127 mmol). The reaction mixture was refluxed for 3 days and concentrated in vacuo to a volume of 150 mL, saturated $NaHCO_3$ solution (500 mL) was added, and the reaction mixture

was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic layers were dried and concentrated in vacuo. The crude product was distilled at 10 mmHg to give 65.2 g (92%) of iminodiacetic acid diethyl ester as a colorless liquid: ^1H NMR (250 MHz, $CDCl_3$) δ 4.18 (q, J = 7.1 Hz, 4 H), 3.45 (s, 4 H), 1.92 (s, 1 H), 1.27 (t, J = 7.1 Hz, 6 H); IR ($CHCl_3$, cm^{-1}) 3320, 3010, 2990, 1740, 1230, 1190, 1090; HRMS, $C_8H_{15}NO_4$ requires 189.1002, observed 189.1001.

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Registry No. 1, 113430-84-5; 1 (dibromide), 113430-93-6; 2, 113430-85-6; 3, 65907-71-3; 4, 113430-86-7; 5, 113430-87-8; 6, 113430-88-9; 6 (diol), 113430-92-5; 7, 113430-89-0; 8, 113430-90-3; 9, 113430-91-4; Ca^{2+}, 14127-61-8; Mg^{2+}, 22537-22-0; $Br(CH_2)_2OH$, 540-51-2; $HN(CH_2CO_2Et)_2$, 6290-05-7; $HN(CH_2CO_2H)_2$, 142-73-4; o-nitroveratraldehyde, 20357-25-9.

Synthesis and Chiroptical Properties of (1*S*)-[2,5-$^2H_2$]Bicyclo[2.2.2]octa-2,5,7-triene (2,5-Dideuteriobarrelene)

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(1*S*)-[2,5-$^2H_2$]Bicyclo[2.2.2]octa-2,5,7-triene (1) (2,5-dideuteriobarrelene) was prepared from (1*R*)-bicyclo-[2.2.2]oct-7-ene-2,5-dione by $LiAlD_4$ reduction followed by pyrolysis of the bis[*O*-*p*-tolyl thionocarbonate] ester of the resulting dideuterio diol. The circular dichroism of 1 ($\Delta\epsilon_{max}^{246} = +0.008$, $\Delta\epsilon_{max}^{215} \simeq -0.07$) is the first example obtained from a deuteriated longicyclically conjugated triene, whose chirality is due only to isotopic substitution.

Introduction

Barrelene[2] (**2**, bicyclo[2.2.2]octa-2,5,7-triene), with its D_{3h} symmetry and longicyclically homoconjugated system of three carbon–carbon double bonds, has long interested chemists, especially from the standpoint of its chemical reactivity and its molecular and electronic structure. Strong nonbonded repulsions of the π centers lead to stretching of the C–C single bonds[3], and hence considerable intramolecular strain, as detected (i) by the largest (−37.57 kcal/mol) heat of hydrogenation[4] ever observed for saturation of a C=C bond, (ii) by a low barrier for thermal decomposition into acetylene and benzene, and (iii) by facile photochemical rearrangement to semibullvalene.[6] Dominant *through-space* interaction among the π orbitals leads to splitting of the three π levels into a totally antibonding π HOMO (α_2') and two lower energy, more bonding e' (π) combinations, as detected by photoelectron spectroscopy: IP = 8.23, 9.65, and 10.02 eV.[7] Here again, intramolecular strain is evident by the comparatively low IP value (8.23 eV) vs that of, e.g., bicyclo[2.2.2]octa-2,5-diene (8.87 eV). Further evidence for unusual π-orbital interaction may be found in the near-UV spectrum of barrelene, for which two transitions have been detected [ϵ_{max}^{239} 320, ϵ_{max}^{208} 1120 (ethanol[2])]; cf. norbornadiene [ϵ_{sh}^{230} 200, ϵ_{sh}^{220} 870, ϵ_{sh}^{213} cp 1550, ϵ_{sh}^{202} 2400].[8] Attempts to explain the electronic structure and spectrum from theory include the initial π-electron PPP study in 1960[9] to more recent[10] SCF–CI MO treatments.

In view of our previously reported success in detecting hidden electronic transitions in norbornadiene by circular dichroism (CD) spectroscopy[8], we initiated a similar study of transannular orbital interactions in barrelene. Our chiral, target molecule was dideuteriobarrelene (1), whose synthesis and CD spectrum we describe in this work.

Synthesis and Stereochemistry

Previous synthetic work on the synthesis of barrelene (**2**) provided two short, independent methods for the preparation of dideuteriobarrelene (**1**).[11,12] For both methods, the key chiral intermediate was bicyclo[2.2.2]-oct-7-ene-2,5-dione (**3a** + **3b**), which was available in three steps from hydroquinone and maleic anhydride: (1) Diels–Alder cycloaddition to afford (±)-5,7-dioxobicyclo[2,2,2]octane-2,3-dicarboxylic anhydride in low yield (15%), (2) hydrolysis to the corresponding dicarboxylic acid, and (3) lead tetraacetate or electrolytic double decarboxylation. The low yield in step 1 is not a major disadvantage because the starting materials are relatively

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