°C; NMR ($CDCl_3$) δ 2.96 (m, 2 H), 3.22 (s, 3 H), 3.68 (m, 2 H), 3.88 (s, 3 H), 7.10 (d, 1 H, J = 2.0 Hz), 7.15 (dd, 1 H, J = 10 Hz, J = 2.0 Hz), 7.86 (d, 1 H, J = 10.0 Hz); IR ($CDCl_3$) 1630, 1680 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.94; N, 6.39. Found: C, 65.74; H, 6.09; N, 6.49.

Photolysis of 4-Carbomethoxy-*N*-methylphthalimide (21d) and 1-Hexene. Photolysis by the general procedure gave a pair of products characterized as **23d** and **24d** in a 27:73 ratio in 46% yield. Pure compound **24d**: mp 118–119 °C NMR ($CDCl_3$) δ 3.01 (m, 2 H), 3.25 (s, 3 H), 3.71 (m, 2 H), 3.96 (s, 3 H), 7.70 (d, 1 H, J = 8.0 Hz), 8.21 (dd, 1 H, J = 8.0 Hz, J = 2.0 Hz), 8.55 (d, 1 H, J = 2.0 Hz); IR ($CDCl_3$) 1635, 1690, 1720 cm^{-1}.

Compound **23d**: mp 86–87 °C; NMR ($CDCl_3$) δ 3.00 (m, 2 H), 3.25 (s, 3 H), 3.71 (m, 2 H), 3.96 (s, 3 H), 8.27 (dd, 1 H, J = 8.0 Hz, J = 2.0 Hz), 8.31 (d, 1 H, J = 2.0 Hz), 8.47 (d, 1 H, J = 8.0 Hz). For the mixture: Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.16; H, 5.26; N, 5.67. Found: C, 62.75; H, 5.29; N, 5.57.

Quantum Yield Determinations. Quantum yields were determined by using a blackbox apparatus and a 200-W superpressure Hg lamp in a Bausch and Lomb high-intensity grating monochromator. Light was monitored by a digital electronic actinometer which was calibrated by ferrioxalate actinometry between runs. Samples were submitted to three freeze–pump–thaw cycles before irradiation at 297 nm. Analysis was by HPLC and results are presented in Table I.

Acknowledgment. We thank the National Science Foundation for their generous support.

Registry No. **9**, 69656-56-0; **10**, 69656-55-9; **13**, 64837-64-5; **21a**, 63196-45-2; **21b**, 29103-90-0; **21c**, 63197-17-1; **21d**, 79431-06-4; **23a**, 79431-11-1; **23b**, 79431-12-2; **23c**, 79431-07-5; **23d**, 79431-09-7; **24b**, 79431-13-3; **24c**, 79431-08-6; **24d**, 79431-10-0; **25a**, 86611-64-5; **25b**, 86611-65-6; **25c**, 86611-66-7; **25d**, 86611-67-8; **26a**, 86611-68-9; **26b**, 86611-69-0; **26c**, 86611-70-3; **26d**, 86611-71-4; **27a**, 86611-72-5; **27b**, 86611-73-6; **27c**, 86611-74-7; **27d**, 86611-75-8; **28**, 86632-09-9; **29a**, 826-73-3; **29b**, 6729-50-6; **38b**, 86611-76-9; **39b**, 86611-77-0; **40a**, 86611-78-1; **40b**, 86611-79-2; *N*-methylphthalimide, 550-44-7; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; 4-(2,2-dimethylpropyl)-3,4-dihydro-2-methyl-2-benzapine-1,5-dione, 86611-80-5; 4,4-dimethylpentene, 762-62-9; 4,5-dichloro-*N*-methylphthalimide, 86611-81-6; 4,5-dichlorophthalic acid, 56962-08-4; 4,5-dichlorophthalic anhydride, 942-06-3; methylamine, 74-89-5; 4,5-dichlorophthalic acid monomethylamide, 86611-82-7; 1-hexene, 592-41-6; methyltriphenylphosphonium bromide, 1779-49-3; ethyl levulinate, 539-88-8; ethyl 4-methyl-4-pentenoate, 4911-54-0; 4-methyl-4-penten-1-ol, 22508-64-1; 4-methyl-4-penten-1-ol tosylate, 25163-50-2; 5-bromo-2-methyl-1-pentene, 41182-50-7; potassium phthalimide, 1074-82-4; 4-methylphthalic acid, 4316-23-8; 4-methylphthalimide, 40314-06-5; 5-bromo-1-pentene, 1119-51-3; 4-hydroxyphthalic acid, 610-35-5; dimethyl 4-hydroyphthalate, 22479-95-4; dimetyl 4-methoxyphthalate, 22895-19-8; 4-methoxyphthalic acid, 1885-13-8; 4-carbomethoxyphthalic anhydride, 28281-76-7.

Substituent Effects on the Formation of Aminocarboxy-Type Capto-Dative Free Radicals

Richard J. Himmelsbach, Anthony D. Barone, Don L. Kleyer, and Tad H. Koch*

Department of Chemistry, University of Colorado, Boulder, Colorado 80309

Received March 22, 1983

The interplay of steric effects and inductive, electronic effects on the formation of aminocarboxy-type, capto-dative free radicals from their dimers is described. Irradiation of 5,5-bis(acetoxymethyl)-5,6-dihydro-3-methyl-1,4-oxazin-2-one (**7**), 5,5-bis[(caproyloxy)methyl]-5,6-dihydro-3-methyl-1,4-oxazin-2-one (**8**), 5,5-bis(acetoxymethyl)-5,6-dihydro-3-ethyl-1,4-oxazin-2-one (**9**), and 3-(acetoxymethyl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (**10**) in 2-propanol solvent yielded photoreductive dimers bi[5,5-bis(acetoxymethyl)-3-methyl-2-oxomorpholin-3-yl] (**3**), bi[5,5-bis[(caproyloxy)methyl]-3-methyl-2-oxomorpholin-3-yl] (**4**), bi[5,5-bis(acetoxymethyl)-3-ethyl-2-oxomorpholin-3-yl] (**5**), and bi[3-(acetoxymethyl)-5,5-dimethyl-2-oxomorpholin-3-yl] (**6**). Upon dissolution in chloroform solvent **3**, **5**, and **6** underwent bond homolysis at the 3–3′ bond to give the respective oxomorpholin-3-yl radicals characterized by EPR spectroscopy. The rate constants and activation parameters for bond homolysis were determined by using *N*-methylisatin and diphenylpicrylhydrazyl as radical trapping agents and ranged from 21 to 30 kcal/mol. The variation in $\Delta H^{\ddagger}$ was assigned to inductive, electronic effects and steric effects based upon EPR hyperfine splitting constants.

Radicals stabilized by the synergistic effect of electron-donating and -withdrawing groups have been named capto-dative by Viehe and co-workers[1] and merostabilized by Katritzky and co-workers[2] and have been discussed in terms of a push–pull effect by Balaban and co-workers.[3] Important examples in carbon chemistry include the aminocarboxy-,[4] aminocyano-,[5] and thiocyano-substituted[6,7] methyl radicals as well as cyano-[8,9] and carboxy-substituted pyridinyls.[10,11]

As emphasized in general by Griller and Ingold, radical persistence is a function of steric interactions and electronic delocalization.[12] For capto-dative radicals electronic

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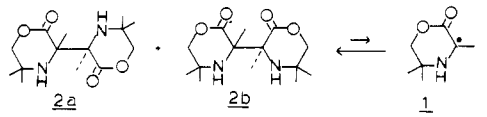
delocalization is best represented by valence bond structures with odd electron density on the electron-donating substituent. The corresponding Linnett structures have a double/quartet of electrons for each atom with favorable polarization.[13] Schleyer and co-workers have calculated the electronic stabilization attributed solely to the captodative effect to be 3 kcal/mol for the aminocyano-substituted carbon radical and 10 kcal/mol for the aminoboron-substituted radical.[14]

We have reported the formation of 3,5,5-trimethyl-2-oxomorpholin-3-yl (1), an aminocarboxy capto-dative radical, upon dissolution of *meso*- and *dl*-bi(3,5,5-trimethyl-2-oxomorpholin-3-yl) (**2a** and **2b**).[4] In chloroform



2a 2b 1

solvent $\Delta H°$ and $\Delta H^{\ddagger}$ are 22 and 27 kcal/mol, respectively.[15] We describe here the interplay of steric effects and inductive, electronic effects on the ease of formation of radicals of this type. We are concerned about these effects because radical formation in part controls the kinetics of radical dimer redox chemistry.[16] This redox chemistry shows promise for the detoxification of the anthracycline antitumor drugs.[17]

Results and Discussion

Synthesis of Radical Dimers. Radical dimers **3–6** were prepared by photoreduction of the corresponding 5,6-dihydro-3,5-5-trisubstituted-1,4-oxazin-2-ones **7–10** in isopropyl alcohol solvent in the range of −40 °C. The irradiations were performed in a water-cooled, Pyrex immersion well containing a 450-W mercury lamp, and the irradiation solutions were externally cooled by a refrigerated bath. The isolated yields of the dimers as a mixture of diastereomers ranged from 30% to 99%. Separation of the diastereomers was generally possible by low temperature, silica gel, column chromatography. The tetrakis(caproyloxy)-substituted dimer **4** was prepared to demonstrate the feasability of preparation of a lipophylic radical dimer.

The photoreaction results from excitation of the n–π^* transition of the oxazinones in the region of 320 nm. The n,π^* excited state reacts with solvent to give ultimately[18] oxomorpholinyl radicals **11–14**, respectively, which then efficiently dimerize at the reduced temperature.

Oxazinones **7** and **8** were prepared by bisacylation of 5,5-bis(hydroxymethyl)-5,6-dihydro-3-methyl-1,4-oxazin-2-one (**15**) by using the appropriate anhydride plus pyridine, and oxazinone **9** was prepared by similar bisacylation of 5,5-bis(hydroxymethyl)-5,6-dihydro-3-ethyl-1,4-oxazin-2-one (**16**). Condensation of tris(hydroxymethyl)aminomethane with ethyl pyruvate and ethyl α-oxobutyrate in butanol afforded the bis(hydroxymethyl)oxazinones **15** and **16**. Overall yields for the syntheses of **7–9** were in the range of 25% based upon the α-oxo ester. Oxazinone **10** was prepared in 48% yield by chlorination of 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**17**) at the 3-methyl substituent with *tert*-butyl hypochlorite in the dark followed by substitution of the chlorine with sodium acetate in dimethylformamide. All of the new materials were adequately characterized by their relatively simple spectroscopic properties as reported in the Experimental Section. The syntheses are summarized in Scheme I.

Table I. EPR Data for Oxomorpholinyls 1, 11, 13, and 14[a]

radical	g	a_{CH_3}, G	a_{CH_2},[b] G	a_N, G	a_{NH}, G	a_{CH_2},[c] G
1	2.0035	10.9		6.4	4.2	0.3
11	2.0035	11.9		5.7	3.7	0.4
13	2.0035		8.3	5.5	3.6	0.3
14	2.0037		5.2	7.5	5.2	0.4

[a] Spectra were observed in the absence of oxygen at 60 °C in chloroform solvent. [b] CH_2 substituent at the 3-position. [c] CH_2 at the 6-position of the ring.

Table II. Rate Constants for Bond Homolysis in Chloroform Solvent

dimer	temp, K	rate constant, s^{-1}
3	311.5	$(9.10 \pm 0.02) \times 10^{-7}$
	311.5	$(9.01 \pm 0.01) \times 10^{-7}$
	321.4	$(4.37 \pm 0.01) \times 10^{-6}$
	321.8	$(4.42 \pm 0.01) \times 10^{-6}$
	332.6	$(2.23 \pm 0.02) \times 10^{-5}$
	332.7	$(2.13 \pm 0.02) \times 10^{-5}$
5	290.1	$(7.22 \pm 0.02) \times 10^{-5}$
	290.1	$(7.93 \pm 0.02) \times 10^{-5}$
	301.8	$(4.35 \pm 0.01) \times 10^{-4}$
	301.8	$(4.34 \pm 0.02) \times 10^{-4}$
	305.3	$(7.12 \pm 0.03) \times 10^{-4}$
	310.9	$(1.43 \pm 0.01) \times 10^{-3}$
	310.9	$(1.45 \pm 0.01) \times 10^{-3}$
6	287.4	$(7.17 \pm 0.10) \times 10^{-5}$
	288.4	$(9.73 \pm 0.05) \times 10^{-5}$
	301.5	$(4.20 \pm 0.06) \times 10^{-4}$
	301.5	$(4.24 \pm 0.03) \times 10^{-4}$
	310.2	$(1.23 \pm 0.01) \times 10^{-3}$
	312.3	$(1.48 \pm 0.01) \times 10^{-3}$

Table III. Activation Parameters for Radical Formation in Chloroform and Methanol Solvents

dimer	solvent	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal deg^{-1} mol^{-1}	ref
2b	$CHCl_3$	27.3 ± 0.2	6.7 ± 0.5	15
2b	MeOH	22.6 ± 0.4	6.6 ± 0.5	17
3	$CHCl_3$	30.4 ± 0.1	11.3 ± 0.6	
5	$CHCl_3$	24.8 ± 0.3	8.2 ± 1.0	
6	$CHCl_3$	21.1 ± 0.3	−5.8 ± 1.7	

Formation and Characterization of Oxomorpholinyls. Anerobic chloroform solutions of the radical dimers **3**, **5**, and **6** gave EPR signals upon being warmed. The signals were assigned to radicals **11**, **13**, and **14**, consistent with the g values and splitting constants compared in Table I with those of radical **1**. In the presence of oxygen **3**, **5**, and **6** were oxidized to the respective oxazinones **7**, **9**, and **10**.

The rates of bond homolysis as a function of temperature were measured in chloroform solvent with *N*-methylisatin[15] or 2,2-diphenyl-1-picrylhydrazyl (DPPH) as radical trapping agents.[15] Radical trapping resulted in quantitative reduction of *N*-methylisatin to *N*,*N*′-dimethylisatide or quantitative reduction of DPPH to 2,2-diphenyl-1-picrylhydrazine and oxidation of the oxomorpholinyl radicals to their respective oxazinones. The reactions followed good first-order kinetics, and the rate of bond homolysis of **2a** determined by using DPPH as radical scavenger compared favorably with the rate previously determined by using *N*-methylisatin as a radical scavenger.[15] DPPH rather than

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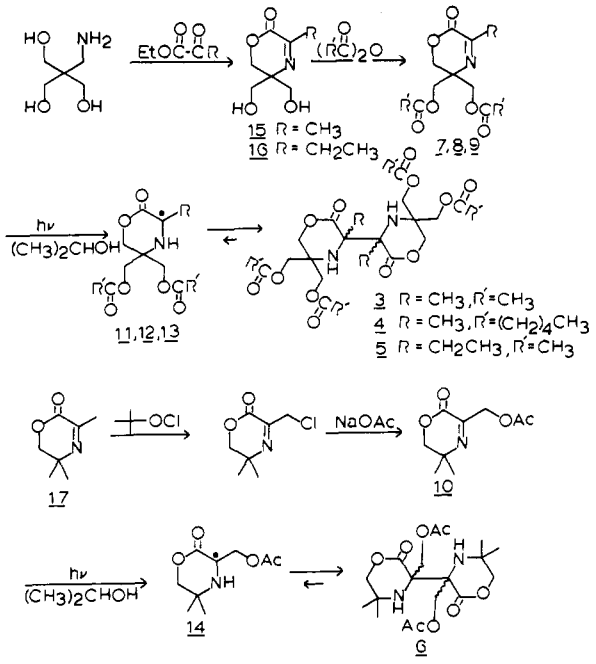
Scheme I



N-methylisatin was used to trap **11** because during the time of reaction, *N*-methylisatin appeared to react with **7**.[19] The other dimers reacted sufficiently rapidly that this side reaction did not interfere with the kinetic measurements. The first-order rate constants are reported in Table II, and the activation parameters are compared with those of **2a** in Table III. Dimer stereochemistry was not established, and mixtures of stereoisomers were sometimes used in these measurements because previous studies of homolysis of **2a,b** and their lactam analogues[19] indicated that the activation parameters for bond homolysis of stereoisomers are within experimental error of each other.

The data in Table III reveal a 9 kcal/mol variation in the activation enthalpy with nonconjugating structural variations. We interpret the effect on $\Delta H^{\ddagger}$ in terms of steric effects in the dimers and inductive, electronic effects in the radicals. Viehe and co-workers have demonstrated that capto-dative radicals are planer;[20] consequently, spin density at the radical center is directly proportional to a_{CH_3} (Fischer's theory[21]). On the assumption that delocalization leads to electronic stabilization, the a_{CH_3}'s indicate that radical **1** is more stable than radical **11**. A similar interpretation of the relative magnitude of the a_{CH_2}'s for radicals **13** and **14** is clouded by an unknown conformational factor with respect to the C–CH_2R bond. Direct correlation of relative spin density at nitrogen with a_{NH} should also be possible since the radicals compared here are structurally quite similar. In this correlation the larger a_{NH} is the larger the spin density on nitrogen and the more delocalized the radical. The a_{NH} values in Table I then indicate the following order of electronic stabilization of the radicals: **14** > **1** > **11**, **13**. In the literature, correlation of nitrogen spin density[22] and both nitrogen and carbon spin densities[23] with N–H hyperfine splitting constants for less structurally related amino-substituted carbon radicals have achieved moderate success.

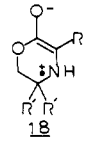
Table IV. EPR Data for Radical 1 as a Function of Solvent at 60 °C

solvent	a_{CH_3}, G	a_N, G	a_{NH}, G	a_{CH_2}, G
chloroform	10.9	6.4	4.2	0.3
Me_2SO	10.5	6.4	4.4	0.3
ethanol	10.1	6.5	5.2	0.3
methanol	9.9	6.5	5.3	0.2

Table V. EPR Data for Radical 1 as a Function of Temperature in Chloroform Solvent

temp, °C	g	a_{CH_3}, G	a_N, G	a_{NH}, G	a_{CH_2}, G
50		10.9	6.4	4.3	0.3
60	2.0035	11.0	6.4	4.2	0.3
70		11.0	6.4	4.0	0.3
80	2.0034	11.1	6.4	3.9	0.3
90		11.1	6.4	3.8	0.3

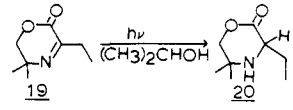
A similar electronic effect is evident in a_{CH_3} and a_{NH} for **1** as a function of solvent as shown in Table IV.[24] The more polar solvents facilitate electron delocalization by radical solvation because electron delocalization, as evident from structure **18**, leads to a more polar radical. Polar solvents similarly lower $\Delta H^{\ddagger}$ as shown in Table III.



18

Note that the a_{NH} values in Table I were compared at a single temperature because a_{NH} is temperature dependent, as shown for radical **1** in Table V. A similar temperature dependence for a_{NH} has been reported for α radicals of glycine and alanine.[23]

The electronic stabilization suggested by the EPR data parallels the enthalpy of activation for bond homolysis of all the dimers except dimer **5** (Table III). The EPR data indicate similar electronic stabilization for radicals **11** and **13**, but the enthalpies of activation for homolysis of **3** and **5** differ by 6 kcal/mol. Hence, the steric effect of replacing methyl with ethyl in the dimers is important. Steric interaction between the methyls of **2b** was also evident in X-ray diffraction data.[25] Additional evidence for the importance of steric effects is the lack of photoreductive dimerization of 5,6-dihydro-5,5-dimethyl-3-ethyl-1,4-oxazin-2-one (**19**) in 2-propanol solvent. The only product observed from irradiation of **19** was 5,5-dimethyl-3-ethyl-2-oxomorpholine (**20**).[26] Furthermore, the radical



19 **20**

dimer without the *gem*-dimethyl substituents at the 5- and 5′-positions, bi(3-methyl-2-oxomorpholin-3-yl), underwent bond homolysis with reluctance.[27] Steric interactions are also important in the bond homolysis of **6**, but it is unlikely that they account for the entire effect observed, especially since CPK models suggest less steric interaction from

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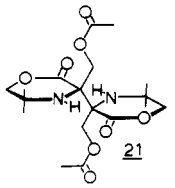
acetoxymethyl than from ethyl.

As shown in Table III, there is a substantial difference in the entropy of activation for bond homolysis of **6** relative to $\Delta S^{\ddagger}$ for the other dimers. The negative $\Delta S^{\ddagger}$ is consistent with orientation of the acetoxy substituents prior to homolysis, probably with their C–O bonds coplaner with the 3–3′ bond of the dimer. This orientation, shown in conformation **21**, would facilitate the acetoxy substituent's



21

serving as an electron-withdrawing group for the incipient radicals. In essence the entropy factor protects dimer **6** from bond homolysis. Huyser and co-workers have observed a similar entropy of activation for homolysis of the pyridinyl dimer 1,1′,2,2′,6,6′-hexamethyl-3,3′,5,5′-tetracarboethoxy-1,1′,2,4′-tetrahydro-2,4′-bipyridine (**22**).[28] Orientation of the carboethoxy substituents of **22** would lead to capto-dative stabilization of the incipient radicals.[15]

The nonconjugative electronic effects observed here can be explained in terms of substituent stabilization or destabilization of resonance structure **18**. Electron-withdrawing groups at ring position 5 should destabilize **18** because of unfavorable interaction with the positive charge on nitrogen, whereas electron-withdrawing substituents at ring position-3 should stabilize **18** because of favorable interaction with the enolate anion.

In summary we have observed that relatively small structural changes in the oxomorpholinyl radicals, not at the radical center, induce surprisingly large changes in their ease of formation.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 337 or 727B grating spectrophotometer and NMR spectra on a Varian EM-390 spectrometer. Chemical shifts are reported in parts per million on the δ scale from internal tetramethylsilane or sodium 3-(trimethylsilyl)propanesulfonate. UV–visible spectra and kinetic measurements were determined with a Cary 219 spectrophotometer. EPR measurements were made with a Varian 109 E spectrometer and mass spectral measurements with a Varian MAT CH5 mass spectrometer. Melting points were determined by using a Thomas-Hoover apparatus and are uncorrected. GLC analyses were performed with a Varian Aerograph Model 1700 gas chromatograph equipped with a thermal-conductivity detector. The flash chromatography used in the following procedures was essentially that described by Still, Kahn, and Mitra.[29] Columns were packed to a height of 15 cm with Merck silica gel 60 (40–63 μm) and eluted at 2.5 cm/min, collecting 20-mL fractions. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

5,6-Dihydro-5,5-bis(hydroxymethyl)-3-methyl-1,4-oxazin-2-one (15). To a refluxing solution of 3.0 g (0.025 mol) of tris(hydroxymethyl)aminomethane (Sigma) in 100 mL of reagent grade butanol was added 2.90 g (0.025 mol) of ethyl pyruvate (Aldrich). The solution was refluxed for 4 h, cooled, and concentrated under reduced pressure to afford 6.8 g of a crude yellow oil. Flash chromatography of the oil on a 50-mm diameter column, eluting with 5% methanol in ethyl acetate (R_f 0.37), afforded 2.4 g (55%) of **15** of sufficient purity for use in subsequent reactions. The following NMR data were obtained for material which had been chromatographed several times: ^{1}H NMR (D_2O) δ 2.24 (s, 3 H), 3.59, 3.78 (AB pattern, J_{AB} = 12 Hz, 4 H), 4.60 (s, 2 H). Analytically pure material could not be obtained.

5,5-Bis(acetoxymethyl)-5,6-dihydro-3-methyl-1,4-oxazin-2-one (7). To 6.9 g of crude **15** in 25 mL of fractionally distilled acetic anhydride was added 3 mL of pyridine distilled from calcium hydride. The solution was stirred at room temperature for 12 h and concentrated under reduced pressure to afford 11 g of a crude orange oil. Fractional distillation (250 μm, 138–140 °C) through a 20-cm Vigreux column afforded 1.98 g (31% based on ethyl pyruvate) of **7** as a viscous orange oil. An analytical sample was prepared by GLC on a 0.64 × 300 cm column of 7.5% SE-30 on 60/80-mesh Chromasorb W (acid wash/DMCS) at 200 °C (He flow rate 60 mL/min): ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 6 H), 2.28 (s, 3 H), 4.01, 4.32 (AB pattern, J_{AB} = 11 Hz, 4 H), 4.39 (s, 2 H); IR (neat) 3.39, 5.75, 6.10 μm; mass spectrum (70 eV), m/e (relative intensity) 257 (12.1), 230 (9.3), 185 (51.1), 172 (70.6), 156 (11.7), 140 (24.2), 130 (14.5), 114 (13.1), 113 (24.9), 112 (99.1), 103 (47.7), 99 (19.4), 98 (85.7), 97 (base), 95 (53.7), 80 (15.5), 73 (11.8), 70 (12.5), 69 (16.4), 68 (18.4), 61 (14.2), 44 (14.7), 43 (58.3), 42 (48.0). Anal. Calcd for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.44. Found: C, 51.35; H, 5.91; N, 5.40.

Photolysis of 5,5-Bis(acetoxymethyl)-5,6-dihydro-3-methyl-1,4-oxazin-2-one (7). A solution of 1.20 g (4.67 mmol) of oxazinone **7** in 50 mL of isopropyl alcohol was purged with nitrogen for 20 min and then irradiated with a Hanovia 450-W mercury vapor lamp under nitrogen at −40 °C through a Pyrex filter for 38 h. A white precipitate was collected (20 mg) and found to be one diastereomer of **3** by analytical TLC (R_f 0.53, 50% ethyl acetate in methylene chloride) and ^{1}H NMR spectroscopy. This same diastereomer could also be obtained pure by flash chromatograph of the crude oil (800 mg) after evaporation of the solvent. Flash chromatography on a 25-mm column, eluting with 50% ethyl acetate in methylene chloride (R_f 0.53), afforded 340 mg (28%) of the diastereomer of the radical dimer **3**. The other diastereomer was found to be intractable. The diastereomer **3** (mp 144–146 °C) had the following spectral properties: ^{1}H NMR ($CDCl)_3$) δ 1.69 (s, 6 H), 1.95 (d, J = 3 Hz, 2 H), 2.09 (s, 12 H), 3.95 (s, 4 H), 4.17 (s, 4 H), 4.22 (dd, J = 3, 12 Hz, 2 H), 4.53 (d, J = 12 Hz, 2 H); IR ($CHCl_3$) 3.02, 3.33, 3.41, 5.82 μm; mass spectrum (70 eV), m/e (relative intensity) 259 (17.1), 217 (4.8), 216 (4.4), 200 (4.1), 186 (31.1), 185 (14.0), 172 (23.9), 155 (23.8), 144 (19.5), 142 (14.0), 141 (10.3), 113 (14.1), 112 (32.9), 103 (15.6), 99 (13.5), 98 (base), 97 (28.5), 95 (21.0) 81 (11.2), 70 (10.7), 68 (16.2), 56 (10.0), 44 (13.9), 43 (92.5), 41 (12.3). Anal. Calcd for $C_{22}H_{33}N_2O_{12}$: C, 51.16; H, 6.25; N, 5.42. Found: C, 51.24; H, 6.27; N, 5.39.

5,5-Bis[(caproyloxy)methyl]-5,6-dihydro-3-methyl-1,4-oxazin-2-one (8). To 2.37 g (13.7 mmol) of oxazinone **15** in 10 mL of dry pyridine was added 6.46 g (30.2 mmol) of hexanoic anhydride (Aldrich). The solution was stirred at room temperature for 4 h and concentrated under reduced pressure. The oil was poured into 100 mL of a 2% aqueous sodium hydroxide solution and extracted with 200 mL of ether. The ether layer was washed with 100 mL of water and 50 mL of brine, dried over anhydrous magnesium sulfate, and filtered. Concentration under reduced pressure afford 4.2 g of a yellow oil. The oil was purified by flash chromatography on a 50-mm column, eluting with 50% ether–hexane, which afforded 2.15 g (24% based on ethyl pyruvate) of the oxazinone **8** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 6 H), 1.15–1.82 (m, 12 H), 2.30 (s, 3 H), 2.30 (t, J = 7 Hz, 4 H), 4.06, 4.36 (AB pattern, J_{AB} = 12 Hz, 4 H), 4.43 (s, 2 H); IR ($CHCl_3$) 3.39, 3.50, 5.75, 6.10 μm; UV (2-propanol) λ_{max} 320 nm (ϵ 120); mass spectrum (70 eV), m/e (relative intensity) 369 (7.6), 169 (6.5), 100 (6.5), 99 (base), 96 (11.9), 71 (28.9), 43 (43.2), 41 (11.8).

This material could not be sufficiently purified for combustion analysis.

Photolysis of 5,5-Bis[(caproyloxy)methyl]-5,6-dihydro-3-methyl-1,4-oxazin-2-one (8). A solution of 1.11 g (3.01 mmol) of oxazinone **8** was similarly irradiated at −50 °C for 48 h. A white precipitate (32 mg) was collected, washed with cold isopropyl alcohol, and dried under vacuum. This precipitate appeared to be one diastereomer of **4** by ^{1}H NMR spectroscopy and analytical TLC [R_f 0.21 (50% ether–hexane)]. The mother liquor was concentrated under pressure to yield 1.11 g (99%) of a mixture of the diastereomeric dimers **4** as judged by analytical TLC [R_f 0.21, 0.13 (50% ether–hexane)]. The white precipitate (mp 75–76

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°C) had the following spectral properties: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, 6 H), 1.10–1.83 (m, 16 H), 1.69 (s, 6 H), 1.92 (d, J = 2 Hz, 2 H), 2.33 (t, J = 7 Hz, 4 H), 3.96 (s, 4 H), 4.17 (s, 4 H), 4.21 (dd, J = 2, 12 Hz, 2 H), 4.52 (d, J = 12 Hz, 2 H); IR ($CHCl_3$) 3.40, 5.80 μm; mass spectrum (70 eV), m/e (relative intensity) 372 (12.0), 371 (10.4), 370 (42.8), 350 (15.9), 242 (35.0), 212 (10.8), 169 (10.8), 161 (33.7), 99 (base), 98 (17.5), 97 (11.9), 71 (27.0), 43 (32.6). Anal. Calcd for $C_{38}H_{64}N_2O_{12}$: C, 61.60; H, 8.71; N, 3.78. Found: C, 61.43; H, 8.74; N, 3.75.

5,5-Bis(acetoxymethyl)-5,6-dihydro-3-ethyl-1,4-oxazin-2-one (9). To a refluxing solution of 3.0 g (0.025 mol) of tris(hydroxymethyl)aminomethane in 100 mL of *n*-butyl alcohol was added 3.25 g (0.025 mol) of ethyl α-oxobutyrate. The solution was refluxed for 18 h, cooled, and concentrated under reduced pressure. Flash chromatography on a 50-mm diameter column, eluting with 5% methanol in ethyl acetate (R_f 0.50), afforded 1.95 g of a yellow oil. To this oil in 25 mL of acetic anhydride was added 3 mL of pyridine. The solution was stirred for 15 h and concentrated under reduced pressure to yield 2.4 g of an orange oil. Flash chromatography on a 50-mm diameter column, eluting with 30% tetrahydrofuran in hexane (R_f 0.40), yielded 1.05 g (14%) of **9**: ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7 Hz, 3 H), 2.02 (s, 6 H), 2.67 (q, J = 7 Hz, 2 H), 4.01, 4.35 (AB pattern, J_{AB} = 11 Hz, 4 H), 4.38 (s, 2 H): IR (neat) 3.35, 5.75, 6.10 μm; UV (2-propanol) λ_{max} 320 nm (ε 105); mass spectrum (70 eV), m/e (relative intensity) 271 (5.3), 241 (0.8), 229 (1.5), 228 (1.0), 199 (20.9), 172 (49.0), 154 (17.1), 130 (10.2), 113 (20.1), 112 (base), 111 (47.3), 110 (32.5), 103 (28.1), 98 (11.9), 58 (11.5), 56 (25.2). Anal. Calcd for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.16. Found: C, 52.95; H, 6.37; N, 5.13.

Photolysis of 5,5-Bis(acetoxymethyl)-5,6-dihydro-3-ethyl-1,4-oxazin-2-one (9). A solution of 1.0 g (3.7 mmol) of oxazinone **9** was similarly irradiated at −30 °C for 65 h. The white precipitate formed was collected by filtration, washed several times with cold isopropyl alcohol, and dried under vacuum to afford 657 mg (65%) of **5** as a mixture of inseparable diastereoisomers: mp 97.5–99.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7 Hz, 6 H), 1.67 (q, J = 7 Hz, 4 H), 2.10 (s, 12 H), 3.90–4.63 (m, 12 H); IR ($CHCl_3$) 2.98, 3.37, 5.75 μm; mass spectrum (70 eV), m/e (relative intensity) 274 (6.3), 273 (38.2), 231 (15.3), 214 (19.6), 200 (33.7), 199 (21.3), 172 (71.4), 170 (32.4), 158 (15.0), 156 (20.6), 155 (12.3), 154 (28.9), 130 (17.2), 129 (10.6), 128 (10.8), 114 (13.3), 113 (50.9), 112 (base), 111 (57.2), 110 (38.5), 103 (32.4), 98 (18.9), 58 (23.0), 45 (91.7), 43 (91.7). Anal. Calcd for $C_{24}H_{36}N_2O_{12}$: C, 52.94; H, 6.66; N, 5.14. Found: C, 52.85; H, 6.68; N, 5.08.

3-(Chloromethyl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one. To 4.82 g (34 mmol) of 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**17**)[18] in 150 mL of dry dichloromethane under nitrogen at 0 °C in the dark was added slowly 3.90 g (4.3 mL, 35 mmol) of *tert*-butyl hypochlorite. The reaction was stirred in the dark at 0 °C for 3 h. The solvent was evaporated to yield a pale yellow oil. The *tert*-butyl alcohol formed from the reaction was removed by high-vacuum rotary evaporation to afford 6.05 g (98%) of crude product with the following spectral properties: IR (neat) 5.76, 6.10 μm; NMR ($CDCl_3$) δ 1.33 (s, 6 H), 4.20 (s, 2 H), 4.33 (s, 2 H); mass spectrum (70 eV), m/e (relative intensity) 175 (7), 117 (20), 81 (50), 76 (8), 72 (6), 57 (100) 42 (38), 41 (52). The product was unstable with respect to purification.

3-(Acetoxymethyl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (10). To 14 g (170 mmol) of sodium acetate in 150 mL of dry dimethylformamide under nitrogen was added 6 g (35 mmol) of crude 3-(chloromethyl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one in 10 mL of *N,N*-dimethylformamide. The reaction mixture was stirred at 50–55 °C for 18 h, cooled to 25 °C, and then diluted with 150 mL of ether. The solution was filtered, and the solvents were rotary evaporated to give 6 g of a brown oil which was purified by flash column chromatography on a 50-mm diameter column, eluting with 20:1 dichloromethane–ether, to yield 3.4 g (49%) of **10**: IR (neat) 5.78 (br), 6.08 μm; NMR ($CDCl_3$) δ 1.27 (s, 6 H), 2.10 (s, 3 H), 4.13 (s, 2 H), 4.90 (s, 2 H); mass spectrum (70 eV), m/e (relative intensity) 199 (7), 100 (13), 98 (36), 82 (18), 71 (11), 56 (100), 55 (13), 43 (52). An analytical sample was prepared by preparative GLC with a column of 7.5% SE-30 on 60/80-mesh high-performance Chromosorb W at 170 °C (He 60 mL/min). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.00; H, 6.61; N, 6.95.

Photolysis of 3-(Acetoxymethyl)-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (10) in 2-Propanol. A solution of 3.39 g (17 mmol) of oxazinone **10** was similarly irradiated at −50 °C or 48 h. The white precipitate formed was collected by filtration, washed several times with cold 2-propanol followed by cold ether, and dried under vacuum to give 1.21 g (36%) of **6** as a mixture of diastereomers: mp 103–105 °C dec; IR (KBr) 3.05 (sharp, NH), 5.80 (br, C=O); NMR ($CDCl_3$) δ 1.10–1.40 (overlapping s, 6 H), 1.50–1.80 (br s, 1 H), 1.95–2.10 (overlapping s, 3 H), 3.50–4.95 (m, 4 H); mass spectrum (70 eV), m/e (relative intensity) 199 (6, $M^+/2 - 1$), 141 (28), 99 (24), 82 (43), 81 (12), 71 (9), 58 (25), 43 (68), 42 (100). Flash chromatography of 850 mg of a mixture of meso and *dl* dimers was performed in a cold room at −18 °C. A 50-mm column was eluted with 33% tetrahydrofuran in hexane, and 10-mL fractions were collected. Fractions 27–39 afforded 122 mg of a white solid which was judged to be one diastereomer of the radical dimer **6** from the following ^{1}H NMR spectrum ($CDCl_3$): δ 1.20 (s, 3 H), 1.33 (s, 3 H), 1.60 (br s, 1 H), 2.04 (s, 3 H), 3.90, 4.61 (AB q, J = 11 Hz, 2 H), 4.47, 4.72 (AB q, J = 12 Hz, 2 H). The material was not sufficiently stable for elemental analysis.

Oxidation of 3, 5, and 6. To 20 mg (0.05 mmol) of radical dimer **3** in an NMR tube was added 0.5 mL of deuteriochloroform. The tube was maintained at 35 °C, and oxygen was continually bubbled into the solution. After 2 weeks, approximately 10% conversion to the oxazinone **7** was observed as judged by ^{1}H NMR spectroscopy.

To 12 mg (0.022 mmol) of dimer **5** in an NMR tube was added 0.5 mL of methanol-d_4. After 5 h at room temperature and exposure to air, oxidation to the oxazinone **9** was complete as determined by ^{1}H NMR spectroscopy.

Oxygen was bubbled through a solution of 30 mg (0.075 mmol) of **6** in 5 mL of absolute methanol for 0.5 h. Evaporation of the solvent yielded 30 mg (100%) of the oxazinone **14** as determined by ^{1}H NMR spectroscopy.

EPR Spectra. EPR samples were each prepared by dissolving 190 ± 70 mg of the appropriate dimer in 0.5 mL of spectrograde chloroform and adding the solution to a 3-mm quartz EPR tube. Samples were freeze (−196 °C)–pump (10^{-5} torr)–thaw (25 °C) degassed and sealed at a pressure of 10^{-5} torr. Spectra were observed at 60 °C unless otherwise indicated. EPR spectra in other solvents were obtained with saturated solutions.

Establishment of 2,2-Diphenyl-1-picrylhydrazyl (DPPH) as a Viable Radical Scavenger. To 1.50 mL of a 6.70×10^{-5} M solution of bi(5,5-bis(acetoxymethyl)-3-methyl-2-oxomorpholin-3-yl) (**3**) in chloroform in a quartz cuvette was added 1.65 mL of a 1.01×10^{-4} M solution of DPPH in chloroform. The cell was freeze–thaw degassed and sealed at a pressure of 10^{-5} torr. The reaction was heated at 60 °C for 48 h to ensure completion, and a UV–visible spectrum was taken. The spectrum showed one maximum at 321 nm with log ε = 4.07 (lit.[30] λ_{max} = 319 nm, log ε = 4.19), indicating at least 97% conversion to 2,2-diphenyl-1-picrylhydrazine.

In a separate experiment 29 mg (0.102 mmol) of **3** was added to 69 mg (0.175 mmol) of DPPH in a reaction tube followed by 3 mL of chloroform. After degassing, the reaction mixture was heated at 60 °C for 48 h and then concentrated under reduced pressure. Preparative layer chromatography on Merck silica gel PF254 in 10% tetrahydrofuran-hexane (R_f 0.31) afforded 37 mg (54%) of 2,2-diphenyl-1-picrylhydrazine mp 167–169 °C (lit.[30] 170–172 °C).

A third experiment was carried out in which the unimolecular rate constant for bond homolysis of *meso*-bi(3,5,5-trimethyl-2-oxomorpholin-3-yl) (**2a**) was measured by using DPPH as a radical scavenger. The rate constant was determined to be $(2.08 \pm 0.05) \times 10^{-4}$ s^{-1} at 49.1 ± 0.1 °C as compared with $(1.77 \pm 0.03) \times 10^{-4}$ s^{-1} at 50 °C on using *N*-methylisatin as a scavenger.[15] Measurements were performed as for **3**.

Kinetic Measurements of the Unimolecular Bond Homolysis of 3. About 12.5 mg (0.032 mmol) of 2,2-diphenyl-1-picrylhydrazyl (DPPH) was dissolved in 100 mL of chloroform, and 1.5 mL of this solution was added to a Pyrex cuvette. To this was added about 1.5 mL of a 1×10^{-3} M solution of one diastereomer of the dimer **3** in chloroform. The solution was freeze–thaw

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degassed three times and sealed at a pressure of 10^{-5} torr. The sealed cell was then placed in the thermostated compartment of a Cary 219 spectrophotometer. The absorbance at 525 nm was recorded at a constant chart speed until a stable infinity reading was reached. Concentrations of DPPH were calculated from the absorbance readings based on an extinction coefficient of 12670. For each absorbance reading $-\ln((2[\text{dimer}]_0 - [\text{DPPH}]_0 + [\text{DPPH}]_t)/2[\text{dimer}]_0)$ was plotted vs. time. Rate constants were obtained from least-squares slopes of these plots. The errors reported are the standard deviations in the slopes. The activation energy and A factor were obtained from the least-squares slopes and intercepts of the Arrhenius plot, and the errors are the standard deviations from the least-squares analysis. The enthalpy and entropy of activation were calculated as described earlier.[15] The error in the free energy of activation was obtained through a propagation of error technique for the errors associated with enthalpy of activation and the entropy of activation.

Kinetic Measurements of the Unimolecular Bond Homolysis of 5 and 6. In a typical experiment, 1.50 mL of a 6.30×10^{-3} M solution of *N*-methylisatin in spectral quality chloroform was added to 1.50 mL of a 3×10^{-3} M solution of radical dimer or mixture of radical dimers in chloroform in a Pyrex cuvette. The solution was degassed, sealed, and placed in the thermostated compartment of a Cary 219 spectrophotometer. The absorbance at 420 nm was recorded at a constant chart speed until a stable infinity reading was reached. For each absorbance reading $-\ln(A_t - A_\infty)$ was plotted vs. time where A_∞ is the infinity absorbance reading. Rate constants were obtained from least-squares slopes of these plots. At this point calculations were carried out exactly as described for the kinetics with DPPH as a trapping agent.

Acknowledgment. This investigation was supported by PHS Grant No. CA-24665 awarded by the National Cancer Institute, DHHS. R.J.H. and A.D.B. thank the AMC Cancer Research Center for graduate fellowships, and T.H.K. thanks the University of Colorado Council on Research and Creative Work for a faculty fellowship. We also thank Melvin Hanna for a helpful discussion.

Registry No. 1, 57765-64-7; 3, 86527-90-4; (*R**,*R**)-4, 86527-91-5; (*R**,*S**)-4, 86527-92-6; (*R**,*R**)-5, 86527-93-7; (*R**,*S**)-5, 86527-94-8; 6, 86527-95-9; 7, 86527-96-0; 8, 86527-97-1; 9, 86527-98-2; 10, 86527-99-3; 11, 86528-01-0; 13, 86528-02-1; 14, 86528-03-2; 15, 86528-00-9; 17, 53153-46-1.

Intramolecular [3 + 2] Cycloaddition Routes to Carbon-Bridged Dibenzocycloheptanes and Dibenzazepines†

Pat N. Confalone* and Edward M. Huie

Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

Received February 14, 1983

Utilization of several intramolecular [3 + 2] cycloaddition reactions for the synthesis of functionalized carbon-bridged dibenzocycloheptanes and dibenzazepines is described. Reaction of the aldehydes **4**, **7**, and **10** with *N*-methylhydroxylamine led to the formation of the bridged polycyclic isoxazolidines **14**, **15**, and **17**, respectively. Dissolving metal reduction of these compounds afforded representatives of the title compounds **1** and **2** (X = OH, Y = $NHCH_3$). Alternatively, reaction of **7** with the acylhydrazine **18** yielded directly the diaza cycloadduct **20**, a precursor to **1** and **2** (X = NHR, Y = NHR). A novel [3 + 2] cycloaddition was observed when **7** was reacted with sarcosine ethyl ester (**21**), leading to the polycyclic proline derivative **23**, presumably via the zwitterionic intermediate **22**.

The synthesis of bridged polycyclic molecules has long been of importance to organic chemists, primarily because of a theoretical interest in the physical properties of such systems.[1] More recently, reports of significant biological activities in certain of these classes have appeared, thus sparking a renewed interest in their synthesis.[2] We describe a novel preparation of carbon-bridged dibenzocycloheptanes[1a] and dibenzazepines of general structures **1** and **2**, respectively, relying on key intramolecular [3 + 2] cycloadditions for their construction. The use of this reaction mode has increased in recent years and has proven valuable for the preparation of complex ring systems[3] as well as several natural products.[4] A further advantage of

1 X = OR, NHR; Y = NHR; Z = $(CH_2)_n$, n = 0,1 **2**

† Contribution 3183.

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