J. Org. Chem. **1983**, *48*, 147–152

Synthesis and Characterization of the 3,5,5-Trimethyl-2-oxopiperazin-3-yl Radical. An Amino Carboxamido Type Merostabilized Free Radical

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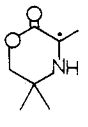
Received June 22, 1982

The synthesis, structure, and stability of 3,5,5-trimethyl-2-oxopiperazin-3-yl are described. The oxopiperazinyl radical (2) was formed by dissolution of the meso or *dl* dimer (6 or 7) of the radical and was characterized from its EPR spectrum and its reactivity. The meso and *dl* dimers were formed by photoreductive dimerization of 1,2,5,6-tetrahydro-3,5,5-trimethyl-2-pyrazinone (3) in 2-propanol solvent. The oxopiperazinyl radical disproportionated upon heating to a 1:1 mixture of 3 and 3,5,5-trimethyl-2-piperazinone (8), reduced isatin (9) to isatide (10), reduced di-*tert*-butyl nitroxide (DTBN) to di-*tert*-butylhydroxylamine, and was quantitatively oxidized by oxygen to 3. Reaction with DTBN was faster than recombination of 2 and was used to measure the kinetics of bond homolysis of 6 and 7. The activation enthalpies and entropies are 27.7 ± 0.2 kcal/mol and 5.8 ± 0.8 eu for the meso dimer 6 and 28.0 ± 0.3 kcal/mol and 6.6 ± 0.9 eu for the *dl* dimer 7. The *dl* dimer 7 was further characterized by single-crystal X-ray diffraction. The dimer crystallized in the monoclinic space group $P2_1/n$ with four dimeric molecules per unit cell of dimensions a = 8.502 (8) Å, b = 16.458 (8) Å, c = 11.377 (6) Å, and β = 106.98 (6)°. With 949 unique, observed reflections, the structure was solved and refined to final values for the discrepancy indices of R = 0.038 and R_w = 0.045. The central C(1)–C(7) bond is 1.581 (5) Å. The bond homolysis of 6 and 7 is compared with the bond homolysis of the meso and *dl* dimers of 3,5,5-trimethyl-2-oxomorpholin-3-yl and discussed in terms of dimer and radical structures.

Radical persistence is a function of electronic stabilization and steric inhibition.[1] Radicals bearing electron-withdrawing and electron-donating substituents show unusual electronic stabilization described by Katritzky as merostabilization,[2] by Balaban as push–pull stabilization,[3] and by Viehe as a captodative substituent effect.[4] The importance of this synergistic electronic effect was also noted in the early work of Kosower and co-workers on pyridinyl radicals[5] and of deVries on amino cyano radicals[6] and evaluated theoretically by von R. Schleyer and co-workers.[7] In our work on the 3,5,5-trimethyl-2-oxomorpholin-3-yl radical (1) we discussed the interplay of steric and electronic effects on persistence.[8,9] We now compare formation of 1 with formation of the carboxamido analogue 3,5,5-trimethyl-2-oxopiperazin-3-yl (2). The two radicals share almost identical steric stabilization.



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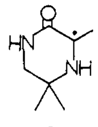

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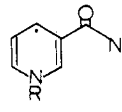
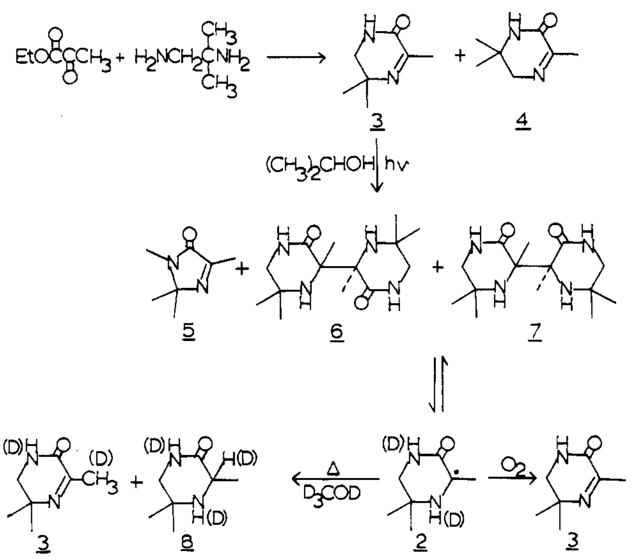


NAD·

The oxopiperazinyl radical 2 is significant because of its electronic resemblance to the nicotinamide adenine dinucleotide radical (NAD) and α-amino acid radicals in proteins and because its water solubility and reactivity as a mild reducing agent may result in important biomedical activity.[10]

Scheme I



Results and Discussion

Synthesis and Characterization of the Meso and *dl* Radical Dimers (6 and 7) of 3,5,5-Trimethyl-2-oxopiperazin-3-yl (2). Reaction of 1,2-diamino-2-methylpropane with ethyl pyruvate in refluxing toluene afforded a mixture of two regioisomeric tetrahydropyrazinones, 3 and 4.[11] The desired pyrazinone, 1,2,5,6-tetrahydro-3,5,5-trimethyl-2-pyrazinone (3), was obtained in 40% isolated yield after two recrystallizations from ether.

Irradiation of 3 (Scheme I) in 2-propanol solvent at −25 °C with a 400-W mercury lamp gave three products, 1,2,2,4-tetramethyl-3-imidazolin-5-one (5), *dl*-bi(3,5,5-trimethyl-2-oxopiperazin-3-yl) (7), and *meso*-bi(3,5,5-tri-

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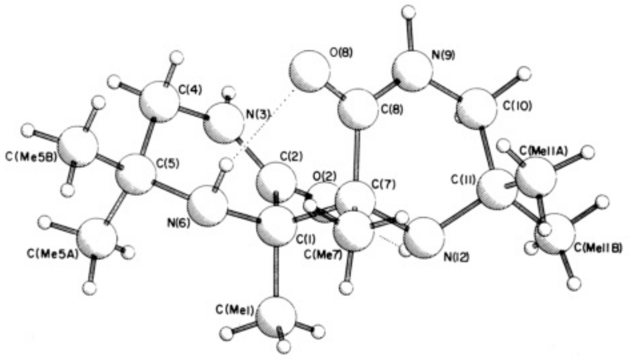


Figure 1. Perspective drawing[13] of *dl* dimer **7**, showing the numbering scheme adopted. The intramolecular hydrogen bonds H(1N6)···O(8) and H(1N12)···O(2) are indicated with dotted lines.

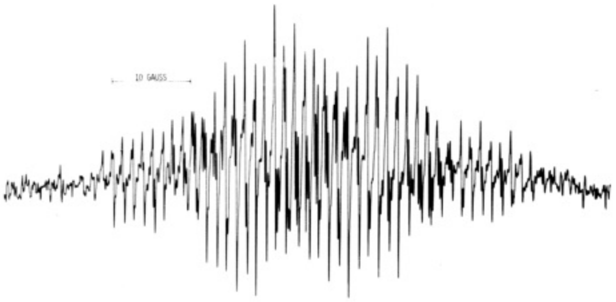


Figure 2. EPR spectrum of 3,5,5-trimethyl-2-oxopiperazin-3-yl (**2**) in chloroform from heating a mixture of the meso and *dl* dimers **6** and **7** at 90 °C.

methyl-2-oxopiperazin-3-yl) (**6**). The products were separated and purified by alumina and silica gel flash chromatography[12] and obtained in 16%, 38%, and 34% yields, respectively, after correction for recovered unreacted pyrazinone **3**. The imidazolone was characterized by comparison with a sample prepared earlier under different conditions that maximized its formation.[11] The structures for radical dimers **6** and **7** were assigned from spectroscopic and analytical data and characteristic reactivity (vide supra).

Stereochemical assignment and confirmation of structure were achieved by single-crystal X-ray analysis of the *dl* dimer **7**. The results of the structure determination are displayed as follows. Crystal data are given in the Experimental Section. The final atomic positional and thermal parameters are given in Table I (supplementary material). Table II (supplementary material) gives bond lengths and angles for the *dl* dimer **7**. A perspective drawing of **7** with the numbering scheme chosen to conform to that of the *dl* dimer of **1**[9] appears in Figure 1.

The mechanism of dimer formation is probably similar to that described for the formation of the dimers of **1**[8] and occurs via radical **2**. Radical dimers are the major products because radical combination occurs more rapidly than disproportionation.

Characterization and Reactivity of the 3,5,5-Trimethyl-2-oxopiperazin-3-yl Radical (2). An oxygen-degassed chloroform solution of the *meso* and *dl* dimers at 90 °C gives the EPR spectrum shown in Figure 2. The signal was assigned to the oxopiperazinyl radical **2** on the basis of the *g* factor and splitting pattern. The *g* factor is 2.0034, which is the same as the *g* factor for the oxomorpholinyl radical **1**. The splitting pattern was not easily assigned because of poor signal to noise. A reasonable fit to the spectrum was obtained with the coupling constants and splittings 11.73 (1:3:3:1, CH_3), 5.10 (1:1:1, amine N), 3.71 (1:1, amine N–H), 2.58 (1:1:1, amide N), and 1.26 G (1:1, amide NH) as shown by the simulated spectrum in Figure 3.

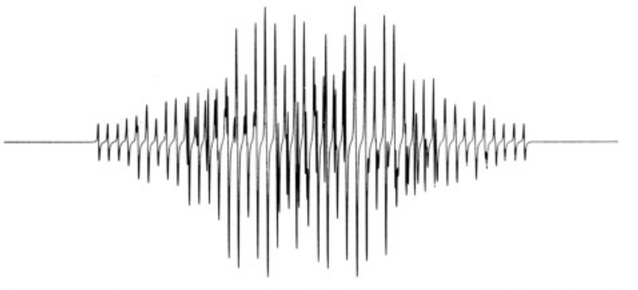
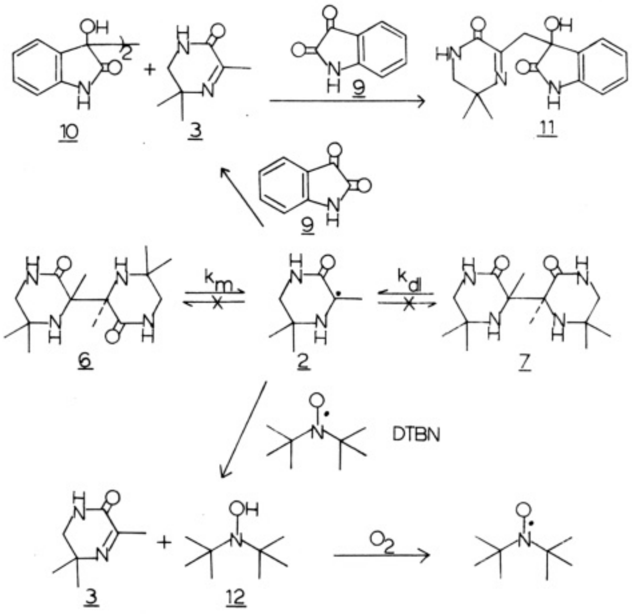


Figure 3. Computer-simulated EPR spectrum with the following splittings (line width of 0.1 G, and modulation of 0.1 G): 11.73 (1:3:3:1), 5.10 (1:1:1), 3.71 (1:1), 2.58 1:1:1), 1.26 G (1:1).

Scheme II



Reactivity of the meso and *dl* dimers **6** and **7** is consistent with the intermediacy of **2** as summarized in Scheme I. Heating freeze–pump–thaw degassed deuteriochloroform and tetradeuteriomethanol solutions of each dimer resulted in stereochemical equilibration and ultimate disproportionation to a 1:1 mixture of **3** and 3,5,5-trimethyl-2-piperazinone (**8**) as determined by ^1H NMR spectroscopy as a function of time. The 3-methyl group of **8** appeared as a singlet in the product mixture from reaction in tetradeuteriomethanol, indicating incorporation of deuterium at the 3-position. Deuterium incorporation is consistent with the net transfer of a deuterium atom from the nitrogen of **2**. A control experiment indicated that the proton at the 3-position of **8** did not exchange in tetradeuteriomethanol under the reaction conditions. Piperazinone **8** was characterized by comparison with a sample prepared by catalytic hydrogenation of **3**. In the presence of oxygen in refluxing methanol, the meso and *dl* dimers are quantitatively oxidized to pyrazinone **3**.

The oxopiperazinyl radical **2** reduces isatin (**9**) to isatide (**10**), analogous to the reduction of *N*-methylisatin observed earlier with the oxomorpholinyl radical **1**.[14] Because

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Table III. Rate Constants for Bond Homolysis of the Radical Dimers 6 and 7 as a Function of Temperature[a]

dimer	temp, K	10^{-6} rate constant,[b] s^{-1}
meso	313	3.83 ± 0.05
meso	318	12.42 ± 0.1
meso	323	24.0 ± 0.2
meso	328	46.7 ± 0.5
meso	333	91.5 ± 1
dl	313	4.92 ± 0.02
dl	318	10.30 ± 0.08
dl	323	20.2 ± 0.2
dl	328	39.5 ± 0.3
dl	333	79.7 ± 0.5

[a] The concentrations of the dimer and di-*tert*-butyl nitroxide were in the range of 0.1 M in methanol solvent. [b] All correlation coefficients exceeded 0.999.

N-methylisatin reacts faster with **1** than **1** recombines, the reaction was employed to measure the kinetics of bond homolysis. The reaction of **2** with **9** could not similarly be used because the product pyrazinone **3** undergoes a subsequent condensation reaction with isatin. This reaction interferes with the methods of analysis. The condensation product was assigned structure **11** (Scheme II) from spectroscopic and analytical data. The reaction probably results from the electrophilic attack by the carbonyl of isatin on the enamine tautomer of the pyrazinone. Formation of the enamine tautomer is consistent with the observation of facile exchange of the 3-methyl protons of **3** in tetradeuteriomethanol. Heating a sample of **3** in tetradeuteriomethanol at 60 ± 1 °C for 143 h results in 73% exchange of the protons at this position (Scheme I).

Di-*tert*-butyl nitroxide (DTBN) proved to be the reagent of choice for trapping the oxopiperazinyl radical **2**. DTBN reacts quantitatively with **2** to give di-*tert*-butylhydroxylamine **12** and pyrazinone **3**. The quantitative nature of the redox reaction was established from the decay in the DTBN absorption at 438 nm with regeneration upon air oxidation[15,16] and the quantitative formation of the pyrazinone **3**. The reactions with *N*-methylisatin and DTBN are summarized in Scheme II.

The reactions of the oxopiperazinyl radical most likely occur by one-electron transfer from the electron-rich π system followed by rapid proton transfer from the nitrogen at the 3-position. The net result is the transfer of a hydrogen atom equivalent. Evidence in support of this mechanism for the reactions of 3,5,5-trimethyl-2-oxomorpholin-3-yl (**1**) has been reported earlier.[17]

Kinetics of Bond Homolysis. The reaction of the meso and *dl* dimers **6** and **7** with DTBN in methanol was established as first order in dimer and zero order in DTBN from the following observations. The reaction followed first-order kinetics for over 95% of the destruction of DTBN as determined from the absorbance at 438 nm, and the measured first-order rate constant was independent of the concentration. No equilibration of meso and *dl* dimers had occurred when reactions of each dimer were stopped at an intermediate stage and analyzed by ^{1}H NMR spectroscopy after removal of unreacted DTBN.

The first-order rate constants as a function of temperature for each dimer are reported in Table III. Arrhenius plots of the kinetic data were linear and gave the activation parameters listed in Table IV.

Table IV. Comparison of Activation Parameters for Bond Homolysis of Radical Dimers

dimer	solvent	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	ref
meso-**13**	$CHCl_3$	26.5 ± 0.2	6.0 ± 0.7	14
dl-**14**	$CHCl_3$	27.3 ± 0.2	6.7 ± 0.5	14
dl-**14**	CH_3OH	22.6 ± 0.4	6.6 ± 0.5	10
meso-**6**	CH_3OH	27.7 ± 0.2	5.8 ± 0.8	this work
dl-**7**	CH_3OH	28.0 ± 0.3	6.6 ± 0.9	this work

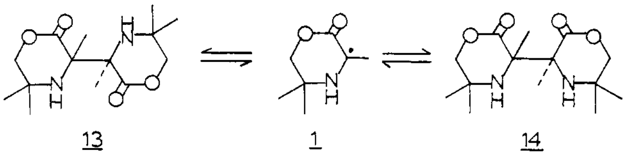
Further evidence substantiating that the measured rate constants are the rate constants for bond homolysis was obtained from a measurement of the rate of isomerization of pure meso dimer **6** in methanol to the equilibrium mixture of meso and *dl* dimers. The integrated rate equation for equilibration was derived earlier[14] and is as follows:

$$\ln\left\{\frac{(1+1/K)[\text{meso}]}{[\text{meso}]_0}-\frac{1}{K}\right\}=-\left\{\frac{k_m(1+1/K)}{k_m/(Kk_{dl})+1}\right\}t \qquad (1)$$

where $K = [dl]_e/[\text{meso}]_e$, $[dl]_e$ and $[\text{meso}]_e$ are the equilibrium conentration of **6** and **7**, and k_m and k_{dl} are the first-order rate constants for bond homolysis. Plotting the isomerization data according to this equation gives a slope equal to $-[(k_m(1 + 1K))/(k_m/(Kk_{dl}) + 1)]$, which can be calculated from K, k_m, and k_{dl}.

The rate of isomerization was observed at 50 ± 0.1 °C in tetradeuteriomethanol and monitored by ^{1}H NMR spectroscopy. The deuterated solvent introduces an isotope effect resulting from exchange of the N–H protons and from hydrogen-bonding effects. Consequently, k_m and k_{dl} were also determined in methanol-*d* solvent at 50 ± 0.1 °C to be $(1.78 \pm 0.02) \times 10^{-5}$ and $(1.38 \pm 0.01) \times 10^{-5}$ s^{-1}, respectively. These values together with the data in Table IV give an isotope effect of 1.4. The equilibrium constant K was 1.41 ± 0.01 as determined from the average of the last ten measurements in the rate of equilibrium experiment. These values of K, k_m, and k_{dl} predict a slope for the plot of the equilibration data according to eq 1 of $-(1.60 \pm 0.04) \times 10^{-5}$ s^{-1}. The observed slope was $-(1.71 \pm 0.07) \times 10^{-5}$ s^{-1}, which differs from the calculated slope by approximately 1 standard deviation. The near identity of the calculated and measured slopes confirms that the measured rate constants are those for bond homolysis and that DTBN does not influence the bond homolysis. Furthermore, DTBN is not reacting to any appreciable extent with a radical cage resulting from bond homolysis.

Bond Homolysis as a Function of Structure. The activation energies for bond homolysis of **6** and **7** are compared with those for bond homolysis of the meso and *dl* dimers **13** and **14** of the oxomorpholinyl radical **1** in Table IV. Replacing the oxygen of **13** and **14** with an NH results in an increase in ΔH^{*} of about 5 kcal/mol, an effect comparable with the increase associated with changing the solvent from methanol to chloroform. As discussed earlier for the formation of radical **1**,[8] the facility for bond homolysis results from structural features in the dimers that weaken the C(1)–C(7) bond (i.e., raise the energy of the dimers) and structural features in the radical that stabilize the radical center (i.e., lower the energy of the radical). Since the bond homolysis is endothermic, the transition



13 1 14

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Table V. Hydrogen Bonding Distances (Å) and Angles (deg)

A-H···B	A···B	A-H	H···B	<AHB	<ABH	<HAB
N(6)-H(1N6)···O(8)	2.884 (4)	0.98	2.09	137	13	30
N(12)-H(1N12)···O(2)	2.865 (4)	0.97	2.08	137	13	30
N(3)-H(1N3)···N(6)[a]	3.265 (5)	0.96	2.31	171	2	6
N(9)-H(1N9)···O(8)[b]	2.828 (4)	0.97	1.88	167	4	9

[a] Symmetry operations as denoted by superscripts: $^1/_2 + x, {}^1/_2 - y, {}^1/_2 + z$. [b] $1 - x, -y, -z$.

state will tend to resemble two incipient radicals and differences in radical stability should account for the major portion of the effect observed here.

Bond weakening in the dimers should result from steric and electronic factors, steric factors possibly from interactions of the methyl substituents and electronic factors from throughbond coupling of the functional groups in the two rings through the C(1)–C(7) bond.[18] Steric effects were anticipated to be similar in the two dimers, and through-bond coupling was anticipated to be more important in **14** than in **7** because of the larger electron-withdrawing effect of the ester functional group.

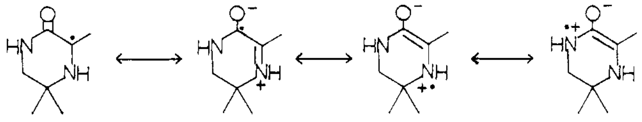
We had hoped that relative steric and electronic effects in the *dl* dimers **7** and **14** would be apparent from the crystallographic data reported here for **7** and earlier for **14**.[9] The C(1)–C(7) bond of **7** is 1.581 (5) Å, 0.01 Å shorter than the C(1)–C(7) bond of **14**. Any interpretation of this difference in bond lengths in terms of differences in solution reactivity and through-bond coupling, however, is clouded by differences in conformation and intramolecular hydrogen bonding in the respective crystals. Furthermore, the two bond lengths are within 2 standard deviations of each other.

The conformation of **7** about the C(1)–C(7) bond is apparently controlled by inter- and intramolecular hydrogen bonding as described in Table V. The molecules are paired about an inversion center by hydrogen bonding between H(1N3) and O(8). Hydrogen bonding of this type is typical of amides. These bonds, however, are significantly shorter than the average N–H···O length of 3.04 Å[19] and thus appear to be strong. The H(1N3)···N(6) interaction provides further intermolecular linking. H(1N6) and H(1N12), which are the only hydrogen atoms in **14** available for hydrogen bonding, are in **7** involved only in intramolecular hydrogen bonding, linking the two rings. Presumably this intramolecular hydrogen bonding also occurs in **14** in aprotic solvents and is not seen in that crystal structure because of crystal packing requirements. That is, H(1N6) and H(1N12) are required for intermolecular hydrogen bonding. The differences in hydrogen bonding between **7** and **14** are unfortunate because they lead to different conformations with respect to the C(1)–C(2) bond and make comparison of steric factors in the two structures difficult. Table VI gives selected intramolecular contacts. There are no significant intermolecular contacts. Steric crowding about the C(1)–C(7) bond of **7** appears to be less than that about the C(1)–C(7) bond of **14**, where there are two 2.6-Å contacts.

Table VI. Selected Intramolecular Contacts (Å)

C(2)-C(8)	2.810 (5)	C(ME1)-C(ME5A)	3.300 (6)
C(2)-N(12)	2.989 (5)	C(ME7)-C(ME11A)	3.292 (6)
N(3)-N(9)	3.649 (5)	C(ME1)-N(3)	3.570 (7)
N(6)-C(8)	3.001 (5)	C(ME7)-N(9)	3.556 (6)
C(ME7)-N(6)	2.819 (5)	C(ME1)-C(5)	3.357 (6)
C(ME1)-N(12)	2.821 (5)	C(ME7)-C(11)	3.357 (7)
C(ME1)-C(ME7)	3.125 (6)		

The relative stability of the two radicals is related to the magnitude of the hyperfine coupling constants for the 3-methyl substituents, if planar configurations for the radical centers are assumed.[20] The smaller the coupling constant, the more delocalized and stable is the radical. β-Proton hyperfine coupling constants for a series of radicals including some captodative substituted radicals have been compared by Viehe and co-workers.[4] The hyperfine coupling constants for the oxomorpholinyl radical **1** measured under identical experimental conditions are 11.00 (1:3:3:1, CH_3), 6.34 (1:1:1, amine N), 3.78 (1:1, amine N–H), and 0.28 G (1:2:1, CH_2). Hence, the methyl coupling constant for the oxopiperazinyl radical **2** is 0.73 G larger than the methyl coupling constant for the oxomorpholinyl radical **1**. Correspondingly, the amine N, amine N–H, and CH_2 splittings for the oxopiperazinyl radical are all smaller. In terms of resonance theory, the canonical forms **2a-c** contribute less to the structure of radical **2** than corresponding canonical forms to the structure of radical **1**, most likely because the carboxamido substituent is a poorer electron acceptor than the carboxyl substituent.[7]



2 2a 2b 2c

In summary, the data suggest that the 5 kcal/mol difference in activation energy for bond homolysis of radical dimers **7** and **14** are reflected in the greater stability of radical **1** compared with radical **2** and possibly in the greater stability of dimer **7** compared with dimer **14**. In the solid state the C(1)–C(7) bond of **7** appears to be stronger than the C(1)–C(7) bond of **14**; however, because of differences in conformation and intramolecular hydrogen bonding, the crystallographic data do not provide any basis for accurate comparison of relative dimer stabilities in solution.

Biological Relevance. The radical-stabilizing functionality of **2** is structurally related to that in an α-amino acid radical. Elad and co-workers[21] have shown that α-amino acids, peptides, and proteins can be alkylated at the α-carbon via a free-radical substitution reaction employing electronically excited ketones and peroxides as initiators. The initial chemical process has been shown to be the abstraction of a hydrogen atom on the α-carbon by the initiator to yield a radical stabilized by amino and carboxamido functional groups. Similar radicals ultimately result also from γ ray and X-ray irradiation of α-amino acids, peptides, and proteins.[22,23] Merostabilization is the most reasonable explanation for the regiospecificity observed in hydrogen abstraction by OH at the α-positions

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in dipeptides.[23] The radicals NAD·, resulting from one-electron oxidation of nicotinamide adenine dinucleotide (NADH),[24] and 1-alkyl-4-carboxamidopyridinyl[25] are also structurally related to 2 by similar zwitterionic canonical forms.

Experimental Section

Melting points were measured with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 337 infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained with Varian EM 390 and JEOL PFT-100 spectrometers, respectively. Chemical shifts are reported in parts per million on the δ scale from internal tetramethylsilane. The EPR spectrum was recorded with a Varian 109 E spectrometer, and mass spectral data were obtained with a Varian Mat CH-5 mass spectrometer. A Varian Aerograph Series 1700 gas chromatograph with thermal conductivity detector was used for preparative and analytical gas chromatography. A Varian Techtron Model 635 spectrophotometer was used to obtain ultraviolet and visible spectra. Microanalyses were performed by Atlantic Microlab, Atlanta, GA.

Materials. Ethyl pyruvate, 1,2-diamino-2-methylpropane, and isatin were obtained from Aldrich Chemical Co. Di-*tert*-butyl nitroxide was prepared from the reaction of 2-methyl-2-nitropropane with sodium as described by Hoffmann and Henderson.[16]

1,2,5,6-Tetrahydro-3,5,5-trimethyl-2-pyrazinone (3). Pyrazinone 3 was prepared by reaction of 1,2-diamino-2-methylpropane with ethyl pyruvate in refluxing toluene and isolated in 40% yield as colorless needles, mp 106–108 °C.[11]

3,5,5-Trimethyl-2-piperazinone (8). 1,2,5,6-Tetrahydro-3,5,5-trimethyl-2-pyrazinone (3, 0.80 g, 5.7 mmol) was dissolved in 10 mL of ethyl acetate and hydrogenated at 1 atm of hydrogen by using 0.090 g of 10% palladium on carbon catalyst. After 163 mL of hydrogen reacted (theoretical 169 mL), the catalyst was removed by suction filtration through Celite, and the solvent was removed by rotary evaporation. Recrystallization of the product in ether solvent yielded a white solid, mp 138–139 °C. The material was identified as 3,5,5-trimethyl-2-piperazinone (8) from the following spectral and analytical data: IR (KBr) 3.10, 3.17, 3.25, 3.38, 3.44, 3.49, 6.01 μm; ^{1}H NMR (CDCl$_3$) δ 1.18 (s, 3 H), 1.30 (s, 3 H), 1.39 (d, J = 8.0 Hz, 3 H), 1.50 (br, 1 H), 3.11, 3.26 (AB portion of an ABX pattern, J_{AB} = 13.0 Hz, J_{AX} = 4.8 Hz, J_{BX} = 0.8 Hz, J_{AX} and J_{BX} are of opposite sign; this pattern simplifies to an AB pattern in deuterium oxide), 3.62 (q, J = 8.0 Hz, 1 H), 7.10 (br, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 142 (77), 127 (28), 99 (36), 85 (38), 84 (91), 60 (28), 48 (100), 47 (22), 46 (29).

Anal. Calcd for $C_7H_{14}N_2O$: C, 59.12; H, 9.92; N, 19.70. Found: C, 59.04; H, 9.94; N, 19.68.

Photoreductive Dimerization of 1,2,5,6-Tetrahydro-3,5,5-trimethyl-2-pyrazinone (3). Pyrazinone 3 (16.1 g, 0.115 mol) was placed in a Pyrex immersion well apparatus and dissolved in 400 mL of 2-propanol solvent. The immersion well was immersed in a refrigerated cold bath at −25 °C and irradiated with a modified 400-W Westinghouse Lifeguard mercury street lamp for 498 h. During the irradiation the solution was continuously degassed with a slow stream of nitrogen. At termination the solvent was removed by rotary evaporation and the product starting material mixture divided into four portions for flash chromatography. The flash column was 6 cm in diameter packed to a height of 16 cm with 32–63-μm Woelm neutral alumina. The portions were in turn eluted with 6% methanol in methylene chloride. The fractions containing unreacted pyrazinone, 1,2,2,4-tetramethyl-3-imidazolin-5-one (5), and the *dl* reductive dimer 7 of 1,2,5,6-tetrahydro-3,5,5-trimethyl-2-pyrazinone (3) were combined. The fractions containing the meso reductive dimer 6 of 3 and a few low-R_f unidentified products were combined. The two combined fractions were then each flash chromatographed on silica gel after solvent rotary evaporation. A 6-cm diameter column was dry packed to a height of 16 cm with 32–63-μm silica gel. The fraction containing meso-dimer 6 was eluted with 11% methanol in methylene chloride. The fraction containing *dl* dimer 7 was similarly chromatographed in two equal portions with 11% methanol in methylene chloride eluent for 450 mL and then with 16% methanol in methylene chloride as further eluent for 750 mL. The following amounts were obtained after combining fractions and solvent rotary evaporation: *dl* dimer 7, 3.34 g (21%); meso-dimer 6, 3.03 g (19%); imidazolone 5, 1.46 g (9%); unreacted pyrazinone 3, 7.08 g (44%). The imidazolone 5 was characterized by comparison with a sample prepared earlier under different conditions that maximized its formation.[11] The meso-dimer 6 was characterized by the following physical and analytical properties: mp 171–172 °C dec; IR (KBr) 3.01, 3.06, 3.15, 3.30, 3.39, 3.43, 6.08 μm; ^{1}H NMR (CDCl$_3$) δ 1.11 (s, 6 H), 1.27 (s, 6 H), 1.44 (s, 6 H), 1.87 (br, 2 H), 2.84, 3.25 (AB portion of an ABX pattern, J_{AB} = 11.5 Hz, J_{AX} = 5.4 Hz, J_{BX} = 0.4 Hz, J_{AX} and J_{BX} were of opposite sign, 4 H; this pattern simplified to an AB pattern in deuterium oxide), 6.47 (br, 2 H); mass spectrum (70 eV), *m/e* (relative intensity) 142 (100), 141 (18), 140 (23), 83 (14), 82 (23), 57 (45).

Anal. Calcd for $C_{14}H_{26}N_4O_2$: C, 59.55; H, 9.28; N, 19.84. Found: C, 59.35; H, 9.28; N, 19.77.

The *dl* dimer 7 was characterized by the following physical and analytical properties: mp 182–183 °C dec; IR (KBr) 3.06, 3.30, 3.39, 6.04 μm; ^{1}H NMR (CDCl$_3$) δ 1.10 (s, 6 H), 1.22 (s, 6 H), 1.53 (s, 6 H), 2.17 (br, 2 H), 2.87, 3.29 (AB portion of an ABX pattern, J_{AB} = 11.5 Hz, J_{AX} = 7.7 Hz, J_{BX} = 1.7 Hz, J_{AX} and J_{BX} were of opposite sign, 4 H; this pattern simplified to an AB pattern in deuterium oxide), 6.10 (br, 2 H); mass spectrum (70 eV), *m/e* (relative intensity) 142 (71), 141 (18), 140 (32), 84 (18), 83 (19), 56 (65), 42 (100), 41 (40), 39 (22).

Anal. Calcd for $C_{14}H_{26}N_4O_6$: C, 59.55; H, 9.28; N, 19.84. Found: C, 59.28; H, 9.28; N, 19.77.

Molecular Structure Determination by X-ray Crystallographic Techniques. Crystals of the *dl* photoreductive dimer 7, colorless parallelepipeds, were recrystallized from ethanol and isooctane at −20 °C. The molecule crystallized in space group $P2_1/n$ with a = 8.502 (8) Å, b = 16.458 (8) Å, c = 11.377 (6) Å, and β = 106.98 (6)°. The cell volume was 1522 (2) Å^3, and for Z = 4, ρ_{calcd} = 1.24 g/cm^3. The observed density (floatation) was 1.21 g/cm^3. A crystal of approximate dimensions 0.06 × 0.06 × 0.07 mm was selected, mounted with epoxy resin, and used for all measurements. Cell parameters were determined by least-squares fit of the parameters to 30 centered reflections. These measurements and all intensity measurements were made on a Syntex (Nicolet) P$\bar{1}$ autodiffractometer with graphite-monochromatized Mo radiation, λ 0.71069. Standard θ–2θ scan techniques were employed.[7,25] Some 5580 reciprocal lattice points were surveyed within the whole sphere to $2\theta \leq 40°$. These were averaged to 1356 independent reflections. Of these, 949 were determined to have intensity significantly above background[9,26] and were used in the solution and refinement of the structure.

The structure was solved by direct methods and refined by using full-matrix least-squares techniques. Hydrogen atoms were located in a three-dimensional difference map. Final least-squares refinement, with non-hydrogen atoms treated anisotropically and hydrogen atoms included in fixed positions with isotropic thermal parameters, converged with R = 0.038 and R_w = 0.045. The scattering factors used were for neutral atoms.[27] The programs used were contained in or derived from the MULTAN 78 package,[28] the Northwestern University package,[29] and routines supplied by Syntex Analytical Instruments.

Oxidation of Radical Dimers 6 and 7 with Oxygen. The radical dimers 6 and 7 were each oxidized quantitatively to 1,2,5,6-tetrahydro-3,5,5-trimethyl-2-pyrazinone (3) by oxygen. In a typical experiment 18 mg (0.060 mmol) of radical dimer in 10

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mL of methanol was placed in a 25-mL two-neck round-bottom flask equipped with a condenser. Oxygen was introduced via a pipet held in place with a thermometer adapter. The oxygen was bubbled into the solution while the solution was heated to reflux for 2 days. The solvent was then removed by rotary evaporation. ^{1}H NMR analysis indicated that the only material present was the pyrazinone **3**.

Disproportionation of Radical Dimers 6 and 7. Radical dimers **6** and **7** both disproportionated to a mixture of 1,2,5,6-tetrahydro-3,5,5-trimethyl-2-pyrazinone (**3**) and 3,5,5-trimethyl-2-piperazinone (**8**) when heated in the absence of oxygen. In a typical experiment 9 mg (0.03 mmol) of radical dimer **6** or **7** was placed in an NMR tube that had a 9-mm attachment for connection to a vacuum line. To the tube was added 0.5 mL of deuteriochloroform or 0.5 mL of methanol-d_4. The solution was freeze (−196 °C)–pump (10^{-5} torr)–thaw (0 °C) degassed through five cycles and sealed at 10^{-5} torr. The sample was placed in a constant-temperature bath, and the reaction was periodically monitored by ^{1}H NMR spectroscopy. The NMR spectra showed both equilibration of radical dimer to a mixture of **6** and **7** and disproportionation of these dimers to a mixture of **3** and **8**. The final ^{1}H NMR spectrum in deuteriochloroform, taken after the total disappearance of absorptions due to dimers **6** and **7**, showed that **3** and **8** were formed in equimolar amounts. The relative yields were determined from integration of absorptions at δ 2.21 and 3.61. Integration of absorption at δ 2.21 and 3.61 in the experiment in methanol-d_4 was not useful because of deuterium exchange of the 3-methyl hydrogens of **3**. The disproportionation of **6** was complete in deuteriochloroform at 70 ± 0.1 °C after 97 h and in methanol-d_4 at 65 ± 0.1 °C after 108 h. In methanol-d_4 solvent the ^{1}H NMR absorption for the 3-methyl group of **8** appeared as a singlet, indicating incorporation of deuterium at the 2-position during the reaction.

Deuterium Exchange in 1,2,5,6-Tetrahydro-3,5,5-trimethyl-2-pyrazinone (3) and 3,5,5-Trimethyl-2-piperazinone (8) in Methanol-d_4 Solvent. To one NMR tube were added 9 mg (0.06 mmol) of **3** and 0.5 mL of methanol-d_4 and to another, 8 mg (0.06 mmol) of **8** and 0.5 mL of methanol-d_4. The samples were freeze–pump–thaw degassed as described above through three cycles and sealed at 10^{-5} torr. Initial ^{1}H NMR spectra were obtained and the samples were heated in a constant-temperature bath at 60 ± 0.1 °C. After 143 h 73% of the protons on the 3-methyl carbon of **3** had exchanged for deuterons as determined by integration. No measurable exchange was observed for protons bonded to the carbons of **8**.

Reaction of 1,2,5,6-Tetrahydro-3,5,5-trimethyl-2-pyrazinone (3) with Isatin. To a 100-mL round-bottom flask equipped with condenser was added 2.44 g (17.4 mmol) of **3**, 2.57 g (17.5 mmol) of isatin, and 50 mL of reagent grade methanol. The solution was heated to reflux for 5 days with a nitrogen atmosphere. The solvent was removed by rotary evaporation and the crude product flash chromatographed. A 6-cm flash column packed with 15 cm of 32–63-μm silica gel was eluted with 14% methanol in methylene chloride, and 20-mL fractions were collected. The product obtained was recrystallized three times in acetone–hexanes to give 2.73 g (55% yield) of an adduct with mp 167–169 °C. The material was assigned structure **11** from the following spectral and analytical data: IR (KBr) 3.03, 3.39, 3.44, 5.76, 5.86, 5.94, 6.10, 6.16 μm; ^{1}H NMR (CD$_3$OD) δ 0.97 (s, 3 H), 1.07 (s, 3 H), 2.85, 3.01 (AB pattern, J_{AB} = 14 Hz, 2 H), 2.98, 3.40 (AB pattern, J_{AB} = 15.3 Hz, 2 H), 6.85–7.37 (m, 4 H); ^{13}C NMR (CD$_3$OD) δ 180.9 (s), 159.7 (s), 158.5 (s), 143.1 (s), 131.7 (s), 130.5 (d), 125.3 (d), 123.2 (d), 110.8 (d), 76.6 (s), 55.8 (s), 49.2 (t), 40.5 (t), 26.3 (q), 25.4 (q); mass spectrum (70 eV), m/e (relative intensity) 287 (11), 148 (14), 147 (67), 141 (12), 140 (96), 125 (24), 120 (11), 119 (100), 97 (28), 91 (67), 90 (20), 82 (56), 81 (39), 64 (24), 63 (21), 58 (16), 57 (98), 55 (11), 43 (15), 42 (84), 41 (41).

Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.62. Found: C, 62.75; H, 5.97; N, 14.58.

Reaction of Isatin with Radical Dimer 6 in an NMR Tube. An NMR tube was charged with 15 mg (0.10 mmol) of isatin and 7.1 mg (0.025 mmol) of meso dimer **6**. Methanol-d_4 (0.5 mL) was added, and the sample was freeze–pump–thaw degassed as decribed above through four cycles and sealed. An initial ^{1}H NMR spectrum was taken, and the sample tube was placed in a constant-temperature bath maintained at 50 ± 0.1 °C. At various time intervals the tube was removed from the bath and the ^{1}H NMR spectrum observed. The spectra showed the formation of 1,2,5,6-tetrahydro-3,5,5-trimethyl-2-pyrazinone (**3**) and isatin adduct **11** as the only products from radical dimer **6**. After 991 min, when 70% of the dimer should have reacted as calculated from the known rate constant for bond homolysis at 50 °C, the mole ratio of **3**:**11** was 1.6.

Kinetic Measurements. Di-*tert*-butyl nitroxide and radical dimer **6** or **7** in a mole ratio approximately 1:1 were weighed into a 3-mL volumetric flask. The concentration of the dimer was in the range of 0.1 M for all experiments. The volumetric flask was then filled to a final volume of 3.0 mL with spectrograde methanol. The contents of the flask were then transferred to a Pyrex spectrophotometer cell with 1.00-cm path length and a 9-mm attachment for connection to the vacuum line. The cell was then freeze (−196 °C)–pump (10^{-5} torr)–thaw (−78 °C) degassed through five cycles and sealed. The reaction mixture was warmed to ambient temperature and an initial absorbance reading at 438 nm observed. The cell was placed in a constant-temperature bath thermostated to ±0.1 °C. At regular time intervals the sample was removed from the bath and immediately cooled with cold tap water. The progress of the reaction was then measured by visible spectroscopy at 438 nm. Reactions were followed to greater than 95% completion. The concentration of dimer (**6** or **7**) at any time was determined by substraction half of the amount of DTBN destroyed from the initial concentration of dimer. The concentration of DTBN was obtained from a Beer's law plot. Rate constants were obtained from the least-squares slopes of plots of ln ($[\text{dimer}]_0/[\text{dimer}]_t$) vs time. The errors reported are the standard deviations in the slopes. The activation energies and A factors were obtained from the least-squares slopes and intercepts of the Arrhenius plots, and the errors are the standard deviations from the least-squares analysis. The enthalpy of activation was calculated as $E_a - RT$ where T is the average temperature in degrees kelvin.

Isomerization of Radical Dimer 6 to the Equilibrium Mixture of Radical Dimers 6 and 7. To an NMR sample tube were added 18 mg (0.063 mmol) of meso dimer **6** and 0.5 mL of methanol-d_4. The reaction sample was freeze (−196 °C)–pump (10^{-5} torr)–thaw (0 °C) degassed through five cycles and sealed. An initial ^{1}H NMR spectrum was recorded, and the sample was placed in a constant-temperature bath at 50 ± 0.1 °C. ^{1}H NMR spectra were obtained and integrated at regular time intervals to measure the relative concentration of **6** and **7**. Disproportionation of the oxopiperazinyl radical **2** was not observed during the course of the isomerization. The equilibrium ratio of **6** to **7** was 1:1.41 ± 0.01, determined from the average of the last ten measurements.

Oxidation of Di-*tert*-butylhydroxylamine to Di-*tert*-butyl Nitroxide. When a kinetic experiment was completed, the spectrophotometer cell was opened and oxygen was bubbled through the solution intermittently for 3 h. The absorbance at 438 nm was then observed. In all such oxidations performed the absorbance returned to within 0.3% of the initial value. No significant evaporation of the methanol solvent occurred during the oxidation.

Acknowledgment. This investigation was supported by PHS Grant CA-24665 awarded by The National Cancer Institute, DHHS. Acknowledgment is also made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support. This research was assisted by computer time provided by the University of Colorado Computer Center.

Registry No. **2**, 83720-01-8; **3**, 82043-97-8; **5**, 82044-00-6; *meso*-**6**, 82044-03-9; (±)-**7**, 83720-02-9; **8**, 83720-03-0; **9**, 91-56-5; **11**, 83720-04-1.

Supplementary Material Available: Table I, atomic coordinates and thermal parameters, and Table II, bond lengths and angles for the *dl* dimer **7** (6 pages).[30] Ordering information is given on any current masthead page.

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[30] A table giving the observed and calculated structure amplitudes (×10) is available from the author.