Kinetic Procedure. The addition, isomerization H-D isotope effect measurement, and tritium incorporation reactions were carried out similarly to the previously published procedure[1] with the major exception being that the reaction solution was quenched with dilute acetic acid in alcohol rather than in water.

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References and Notes

(1) Cyclobutane-Bicyclobutane System. 3. For part 2 in this series see: Hoz, S.; Albeck, M.; Livneh, M. *J. Am. Chem. Soc.* **1979**, *101*, 2475-2480.
(2) For review of carbanion chemistry, see: (a) Cram, D. J. "Fundamentals of Carbanion Chemistry"; Academic Press: New York, 1965. (b) Buncel, E. "Carbanions: Mechanistic and Isotopic Aspects"; American Elsevier: New York, 1975. (c) Cram, D. J.; Cram, J. M. *Intra-Sci. Chem. Rep.* **1973**, *7*, 1-17.
(3) Wang, S. M.; Fischer, H. P.; Cram, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 2235-2243.
(4) For a review of cyclobutane stereochemistry, see: Morlarty, R. M. *Top. Stereochem.* **1974**, *8*, 271-423.
(5) Wiberg, K. B.; Lampman, G. M. *J. Am. Chem. Soc.* **1966**, *88*, 4429-4433.
(6) DiBiase, S. A.: Gokel, G. W. *J. Org. Chem.* **1978**, *43*, 447-452.
(7) Baciocchi, E.; Corsano, S.; Ruzziconi, R. *J. Chem. Soc., Perkin Trans. 2* **1977**, 436-439.
(8) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549-557. Zimmerman, H. E.; Nevis, T. E. *J. Am. Chem. Soc.* **1957**, *79*, 6559-6561. Zimmerman, H. E.; Mariano, P. S. *Ibid.* **1968**, *90*, 6091-6096. Malhotra, S. K.; Johnson, F. *Ibid.* **1965**, *87*, 5492-5493. Bordwell F. G.; Yee, C. K. *Ibid.* **1970**, *92*, 5939-5944.
(9) Cram, D. J.; Gosser, L. *J. Am. Chem. Soc.* **1964**, *86*, 5445-5457. Kollmeyer, W. D.; Cram, D. J. *Ibid.* **1968**, *90*, 1779-1784. Ford, W. T.; Cram, D. J. *Ibid.* **1968**, *90*, 2612-2622. Roltman, N. J.; Cram, D. J. *Ibid.* **1971**, *93*, 2231-2234.
(10) Chu, K. C.; Cram, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 3521-3531. Almy, J.; Hoffman, D. H.; Chu, K. C.; Cram, D. J. *Ibid.* **1973**, *95*, 1185-1190.
(11) Reference 2b, p 27.
(12) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439-2443.
(13) Bordwell, F. G.; Bartmess, J. E.; Drucker, G. E.; Margolin, Z.; Matthews, W. S. *J. Am. Chem. Soc.* **1975**, *97*, 3226-3227.
(14) Hibbert, F.; Long, F. A.; Walters, E. A. *J. Am. Chem. Soc.* **1971**, *93*, 2829-2835.
(15) (a) Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354-360. (b) Dahlberg, D. B.; Kresge, A. J.; Lin, A. C. *J. Chem. Soc. Chem. Commun.* **1976**, 35-36. The β value of these two reactions is the sum of the individual βs of each of the steps involved in the deprotonation reactions. The overall $\beta > 1$ value observed is probably due to this fact.
(16) von Schleyer, P. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377-2386.
(17) Hoz, S.; Aurbach, D., unpublished results. Calculations using an STO-3G and 4-31G basis sets gave inversion barriers of ca. 14 and 2 kcal/mol, respectively.
(18) Bunnett, J. F. *Tech. Chem. (N.Y.)* **1974**, *6*, 472-475.
(19) Kwok, K. W.; Lee, W. G.; Miller, S. I. *J. Am. Chem. Soc.* **1969**, *91*, 468-476.
(20) McLennan, D. J. *Q. Rev., Chem. Soc.* **1967**, *21*, 490-506.
(21) Williams, A.; Douglas, K. T.; Loran, J. S. *J. Chem. Soc., Chem. Commun.* **1974**, 689-690. King, J. F.; Beatson, P. R. *Tetrahedron Lett.* **1975**, 973-976.
(22) Hall, K. H.; Blanchard, E. P.; Cherkofsky, S. C.; Sleja, J. B.; Sheppard, W. A. *J. Am. Chem. Soc.* **1971**, *93*, 111-120.
(23) Hoz, S.; Aurbach, D. *Tetrahedron* **1979**, *35*, 881-883.
(24) Gokel, G. W.; Cram, J. D.; Liotta, C. L.; Harris, H. P.; Cook, F. L. *J. Org. Chem.* **1974**, *39*, 2445-2446.

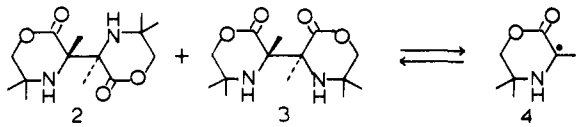
Formation Kinetics of an Amino Carboxy Type Merostabilized Free Radical

Richard W. Bennett, Donald L. Wharry, and Tad H. Koch*

Contribution from the Department of Chemistry, University of Colorado, Boulder, Colorado 80309. *Received October 12, 1979*

Abstract: The reduction of isatin (**5**) and *N*-methylisatin (**6**) by the merostabilized free radical 3,5,5-trimethyl-2-morpholinon-3-yl (**4**) to isatide (**7**) and *N,N'*-dimethylisatide (**8**) is described. The reaction rates are first order in the meso and *dl* dimers (**2** and **3**) of **4** and zero order in *N*-methylisatin. The rate of reaction is a measure of the rate of bond homolysis of the meso or *dl* dimer. Rate constants and activation parameters are reported. The free energies of activation for homolysis of **2** and **3** in chloroform solvent are 24.6 ± 0.3 and 25.1 ± 0.2 kcal/mol, respectively. The enthalpy of activation for recombination of **4** is estimated at 4-5 kcal/mol. Measured rate constants for bond homolysis were consistent within one standard deviation with the observed kinetics of isomerization of the meso dimer (**2**) to the equilibrium mixture of the meso and *dl* dimers. The activation parameters in part are a measure of the effect of merostabilization on radical stability.

We have reported that the meso and *dl* dimers (**2** and **3**, respectively) resulting from photoreduction of 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**1**) in 2-propanol solvent exist in equilibrium with the unusually persistent carbon free radical, 3,5,5-trimethyl-2-morpholinon-3-yl (**4**).[1,2] The facile bond



2 3 4

homolysis, which has a $\Delta H°$ of 22 ± 1 kcal/mol in chloroform solvent, has been discussed in terms of steric and electronic factors.[2,3] The 3,5,5-trimethyl-2-morpholinon-3-yl radical is one of the simplest examples of a relatively new class of free radicals which are stabilized by dipolar resonance structures[2] and which have been named merostabilized free radicals.[4] The structure and reactivity of **4** are especially significant because of a probable relationship with the pyridinyl radicals, especially the radical of NAD.[5,6]

We have recently described some of the reactivity of 3,5,5-trimethyl-2-morpholinon-3-yl (**4**).[5] Specifically **4** is a mild reducing agent and reacts via the net transfer of a hydrogen atom. The hydrogen-atom transfer most likely occurs by electron transfer followed by rapid proton transfer. Reduction of a variety of functional groups in one-electron steps often with the intermediacy of other persistent free radicals has been achieved. In this context we now report the reactivity of 3,5,5-trimethyl-2-morpholinon-3-yl (**4**) with isatin (**5**) and *N*-methylisatin (**6**) and the application of this reaction to the measurement of the kinetic parameters for the primary bond homolysis of both the meso and *dl* dimers (**2** and **3**) of the morpholinonyl radical **4**.

Results and Discussion

Reactivity of 1 and 2 with Isatin and *N*-Methylisatin. A mixture of the meso and *dl* dimers of 3,5,5-trimethyl-2-morpholinon-3-yl cleanly reacts with isatin (**5**) in degassed dimethyl sulfoxide solvent to give 5,6-dihydro-3,5,5-trimethyl-

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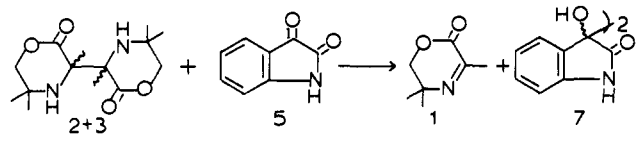
Table I. Effect of Concentration on Reaction Rate[a]

dimer	[dimer][b]	[*N*-methylisatin][b]	first-order rate constant, s^{-1}
meso (**2**)	0.075	0.154	$(3.27 \pm 0.10) \times 10^{-4}$
meso (**2**)	0.075	0.302	$(3.25 \pm 0.10) \times 10^{-4}$
dl (**3**)	0.073	0.145	$(1.20 \pm 0.02) \times 10^{-4}$
dl (**3**)	0.073	0.294	$(1.19 \pm 0.02) \times 10^{-4}$

[a] Rate measurements were performed in deuteriochloroform solvent at 55 ± 0.1 °C. [b] Concentrations are given in mol/L.



1,4-oxazin-2-one (**1**) and isatide (**7**) as the only observed products. In a small-scale reaction isatide was isolated in 75% yield. The products were characterized by comparison of physical and spectroscopic properties with those of authentic samples.[1,7]

When a degassed dimethyl sulfoxide solution of isatin (1.56 M) and a mixture of the meso and *dl* dimers (**2** and **3**, 0.52 M) was examined by EPR spectroscopy no EPR signal was observed including the signal normally observed for the morpholinonyl radical **4** under similar conditions in the absence of isatin.[2] This result suggests that isatin might be an efficient scavenger of the morpholinonyl radical and that measurement of the rate of reaction with isatin might yield the rate constants for bond homolysis of **2** and **3**.

Further experiments were subsequently performed with the reaction of *N*-methylisatin and **2** or **3** in chloroform solvent. Chloroform was selected as the solvent because the enthalpy of bond dissociation of a mixture of **2** and **3** had been previously measured in chloroform solvent, and *N*-methylisatin was selected because of its solubility in chloroform. When a degassed chloroform solution of the meso dimer (**2**) of 3,4,4-trimethyl-2-morpholinon-3-yl and *N*-methylisatin was reacted at 34 °C and monitored by ^{1}H NMR spectroscopy over a 48-h period, the only products observed were 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**1**) and a mixture of the meso and *dl* isomers of *N*,*N*′-dimethylisatide (**8**). Under these conditions none of the *dl* dimer (**3**) was observed during the course of the reaction and the half-life of the meso dimer (**2**) was 10.6 h. Since the *dl* dimer (**3**) is the thermodynamically more stable stereoisomer (vide infra), it should have been observed if it were formed to any reasonable extent during the course of the reaction. This result then suggests that *N*-methylisatin and probably also isatin react with 3,5,5-trimethyl-2-morpholinon-3-yl (**4**) much faster than two morpholinonyl radicals recombine.

The reactions of **4** with isatin and *N*-methylisatin undoubtedly yield dioxindolyl radicals **9** and **10**, respectively, as intermediates. These radicals are also merostabilized carbon radicals in that the radical center lies between the electron-donating hydroxy substituent and the electron-withdrawing carbamido substituent. Radicals **9** and **10** have not been observed by EPR spectroscopy, although isatin radical anion has been reported by Russell and co-workers.[8] Possible evidence for the formation of **9** via bond homolysis of isatide comes from the further reaction of **4** with isatide. Heating a mixture of isatide and stereoisomeric dimers **2** and **3** at 50 °C yielded 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**1**), 3,5,5-trimethyl-2-morpholinone (**11**), and dioxindole (**12**). Formation of 3,5,5-trimethyl-2-morpholinone indicates that some disproportionation of **4** occurred during the course of the reaction.[2] A reasonable pathway for formation of dioxindole is the reaction of the morpholinonyl radical **4** with the dioxindolyl radical **9** resulting from homolysis of isatide. A radical-induced homolysis of isatide is, however, also a possibility.

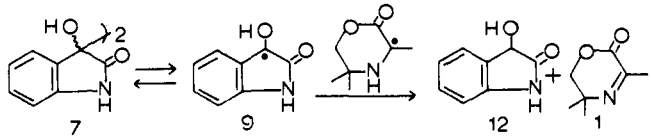
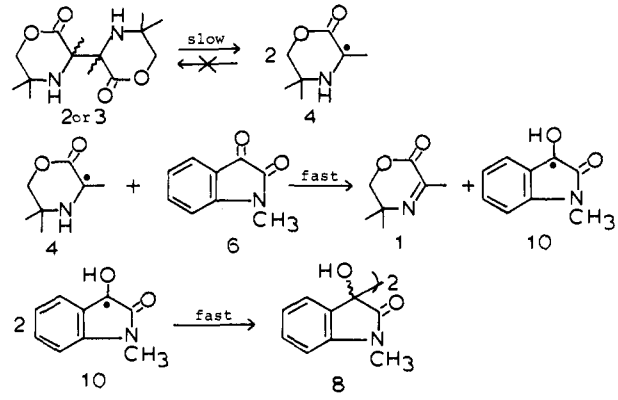


Table II. Rate Constants for Bond Homolysis of the Meso and *dl* Dimers (**2** and **3**) as a Function of Temperature[a]

dimer	temp; K	$\tau_{1/2}$, min	rate constant, s^{-1}	corr coeff
meso (**2**)	298	2424	$(4.76 \pm 0.14) \times 10^{-6}$	0.998
meso (**2**)	303	1110	$(1.04 \pm 0.03) \times 10^{-5}$	0.998
meso (**2**)	313	255	$(4.53 \pm 0.09) \times 10^{-5}$	0.999
meso (**2**)	318	133	$(8.66 \pm 0.18) \times 10^{-5}$	0.999
meso (**2**)	323	65.3	$(1.77 \pm 0.03) \times 10^{-4}$	0.999
meso (**2**)	328	35.3	$(3.27 \pm 0.10) \times 10^{-4}$	0.998
meso (**2**)	333	20.8	$(5.56 \pm 0.16) \times 10^{-4}$	0.998
meso (**2**)	338	10.3	$(1.13 \pm 0.02) \times 10^{-3}$	0.999
dl (**3**)	303	3082	$(3.75 \pm 0.07) \times 10^{-6}$	0.999
dl (**3**)	323	179	$(6.46 \pm 0.10) \times 10^{-5}$	0.999
dl (**3**)	328	96.7	$(1.20 \pm 0.02) \times 10^{-4}$	0.999
dl (**3**)	333	45.7	$(2.52 \pm 0.06) \times 10^{-4}$	0.999
dl (**3**)	338	24.9	$(4.64 \pm 0.09) \times 10^{-4}$	0.999
dl (**3**)	343	14.0	$(8.24 \pm 0.07) \times 10^{-4}$	0.999

[a] The concentration of dimer was in the range of 0.07 M and the concentration of *N*-methylisatin was in the range of 0.14 M in deuteriochloroform solvent.

Scheme I



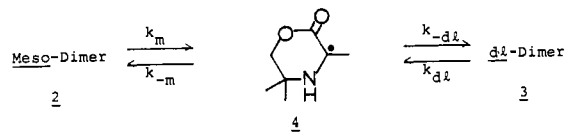
Kinetic Measurements. The qualitative experiments described above suggest that the reaction of the meso and *dl* dimers with *N*-methylisatin is first order in dimer and zero order in *N*-methylisatin. This order was established for the reaction of both dimers from the observation that the rate of reaction with each dimer is independent of the concentration of *N*-methylisatin and follows first-order kinetics with respect to dimer over 90% of the reaction as shown in Table I. The rate-controlling step of the reduction reaction then is the bond homolysis of either the meso or *dl* dimer, and recombination is slow relative to reduction of *N*-methylisatin (see Scheme I). The rate constant for bond homolysis of the meso dimer is approximately three times the rate constant for bond homolysis of the *dl* dimer.

The rate constants for bond homolysis of each dimer were then determined as a function of temperature over a 40 °C temperature range as shown in Table II. Plots of ln *k* vs. reciprocal temperature were linear, and activation energies, *A* factors, and enthalpies, entropies, and free energies of activation are reported in Table III. The kinetic parameters confirm the qualitatively apparent greater reactivity of the meso dimer and are consistent with the previously measured[2] average enthalpy of bond homolysis.

Table III. Activation Parameters for Bond Homolysis of the Meso and *dl* Dimers (**2** and **3**)

dimer	A, s^{-1}	E_a, kcal/mol	corr coeff	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$, kcal/mol
meso (**2**)	3.76×10^{14}	27.1 ± 0.2	0.999	26.5 ± 0.2	6.0 ± 0.7	24.6 ± 0.3
dl (**3**)	5.39×10^{14}	28.0 ± 0.2	0.999	27.3 ± 0.2	6.7 ± 0.5	25.1 ± 0.2

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 (**2**) to the equilibrium mixture of meso and *dl* dimers. The slope of the line obtained from plotting the isomerization data according to the integrated rate expression can be exactly calculated from the rate constants reported above and the equilibrium constant for the equilibrium between the meso and *dl* dimers. The derivation of the integrated rate expression is shown as follows:



Let meso ≡ meso dimer, R ≡ morpholinonyl radical, and *dl* ≡ *dl* dimer. The rate of disappearance of meso dimer is given by

$$-\mathrm{d[meso]}/\mathrm{d}t = k_m[\mathrm{meso}] - k_{-m}[\mathrm{R}]^2$$

As observed by EPR spectroscopy, equilibrium between dimer and radical is rapidly achieved. Hence the concentration of radical does not change and

$$\mathrm{d[R]}/\mathrm{d}t = 0 = k_m[\mathrm{meso}] + k_{dl}[dl] - k_{-m}[\mathrm{R}]^2 - k_{-dl}[\mathrm{R}]^2$$

Therefore

$$[\mathrm{R}] = \left\{\frac{k_m[\mathrm{meso}] + k_{dl}[dl]}{(k_{-m} + k_{-dl})}\right\}^{1/2}$$

and

$$\frac{-\mathrm{d[meso]}}{\mathrm{d}t} = k_m[\mathrm{meso}] - k_{-m}\left\{\frac{k_m[\mathrm{meso}] + k_{dl}[dl]}{(k_{-m} + k_{-dl})}\right\} = \frac{k_m[\mathrm{meso}]k_{-dl} - k_{-m}k_{dl}[dl]}{(k_{-m} + k_{-dl})}$$

Substituting $[dl] = [\mathrm{meso}]_0 - [\mathrm{meso}]$ and rearranging

$$\frac{\mathrm{d[meso]}(k_{-m} + k_{-dl})}{(k_m k_{-dl} + k_{-m}k_{dl})[\mathrm{meso}] - k_m k_{dl}[\mathrm{meso}]_0} = -\mathrm{d}t$$

Upon integration and simplification

$$\ln\left\{\frac{(k_m k_{-dl} + k_{dl}k_{-m})[\mathrm{meso}] - k_{dl}k_{-m}[\mathrm{meso}]_0}{k_m k_{-dl}[\mathrm{meso}]_0}\right\} = -\left\{\frac{k_{-dl}k_m + k_{-m}k_{dl}}{k_{-m} + k_{-dl}}\right\}t$$

Let $K = [dl]_e/[\mathrm{meso}]_e = (k_m k_{-dl})/(k_{-m}k_{dl})$, where $[dl]_e$ and $[\mathrm{meso}]_e$ are the dimer concentrations at equilibrium. Substituting into the integrated rate expression:

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

The slope of a plot of

$$\ln\left\{\frac{(1 + 1/K)[\mathrm{meso}]}{[\mathrm{meso}]_0} - 1/K\right\}$$

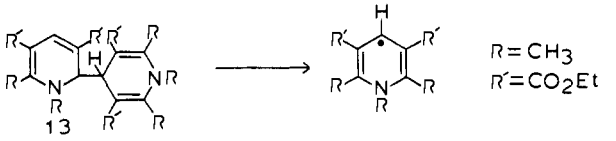
vs. time is $[k_m(1 + 1/K)]/[k_m/(Kk_{dl}) + 1]$, which can be calculated from the known rate constants and measured equilibrium constant.

When the kinetic data for the isomerization of meso dimer to *dl* dimer at 30 ± 0.1 °C were plotted according to the integrated rate law, the slope of the plot was $(6.86 \pm 0.23) \times 10^{-6}$ s^{-1} with a correlation coefficient of 0.995. The equilibrium constant K for the equilibrium between meso and *dl* dimer at 30 °C was determined to be 2.20. Using this value for the equilibrium constant and the rate constants for bond homolysis of the meso and *dl* dimers at 30 °C from Table II, the calculated slope is 6.70×10^{-6} s^{-1}, which is within one standard deviation of the measured slope. The near identity of the calculated and measured slopes for the plot of the integrated rate expression confirms that the measured rate constants are those for bond homolysis and that *N*-methylisatin does not influence the bond homolysis. Furthermore, *N*-methylisatin is not reacting to any appreciable extent with a radical cage resulting from bond homolysis.

The activation parameters are compared in Table IV with those for homolysis of the triphenylmethyl dimer to triphenylmethyl[9] and homolysis of benzpinacol to diphenylhydroxymethyl.[10] As can be seen the activation energies for homolysis of the meso and *dl* dimers (**2** and **3**) are of intermediate value. Both steric and electronic effects undoubtedly contribute to all three of the facile carbon-carbon bond homolyses. Inspection of CPK models suggests that steric crowding is less severe in the meso and *dl* dimers **2** and **3**. Electronic effects include electron delocalization in the late transition state analogous to the electron delocalization which is apparent in the radicals. As stated previously a significant contribution to the electron delocalization in radical **4** results from charge transfer type resonance structures. CPK models also suggest that electron delocalization concomitant with bond homolysis of **2** or **3** requires little molecular reorganization. Intramolecular hydrogen bonding is also a potential attractive interaction in benzpinacol and the meso and *dl* dimers **2** and **3**.

The enthalpies of activation from Table III together with the previously measured average enthalpy of formation indicate that the enthalpy of activation for radical combination is in the range of 4–5 kcal/mol. The enthalpy of activation for combination of two triphenylmethyl radicals is 6.1 kcal/mol[9] and for combination of two diphenylhydroxymethyl radicals is 1.0 kcal/mol.[10]

It is interesting also to compare the activation energies and A factors with those reported by Huyser and co-workers for the related 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 (**13**).[11] The A factor is 1.1×10^{12} and E_a



13

is 28.5 kcal/mol. Although the activation energy is almost identical with the activation energies for homolysis of the meso and *dl* dimers (**2** and **3**), the A factor is significantly smaller. As discusssed by Huyser, the low A factor indicates a conformational requirement to achieve resonance stabilization of the transition state during bond homolysis, namely, that in which the σ bond that is broken is in an axial-like position with respect to both rings. We propose that the conformations of two or more of the carboethoxy substituents of **13** are also important because, without resonance interaction of the incipient radical centers with the carboethoxy substituents, merostabilization

Table IV, Comparison of Activation Parameters for Carbon–Carbon Bond Homolyses

dimer	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	ref[c]
triphenylmethyl dimer[a]	16.9	−1.5	9
benzpinacol[a]	33.5	17.5	10
meso (**2**)[b]	26.5	6.0	this work
dl (**3**)[b]	27.3	6.7	this work

[a] Measurement performed in benzene solvent. [b] Measurement performed in chloroform solvent. [c] The data in ref 9 and 10 are also compared in S. F. Nelson and R. T. Landis, II, *J. Am. Chem. Soc.*, **95**, 8707 (1973), with data for homolysis of a hydrazine derivative.

of the transition state will be poor. The homolysis of **2** and **3** is similar to the homolysis of **13** in that an axial-like transition state will be important but differs in that the carboxyl groups are locked into the proper conformation for merostabilization of the incipient radicals in the transition state. Consequently, the entropy of activation for homolysis of **2** and **3** is positive and in the range expected for a unimolecular fragmentation reaction involving the breaking of a single σ bond.[12]

In summary we have reported (1) that 3,5,5-trimethyl-2-morpholinon-3-yl efficiently and cleanly reduces isatin and *N*-methylisatin to isatide and *N,N'*-dimethylisatide, (2) that reduction is much faster than radical combination under the reaction conditions, (3) the rate constants for bond homolysis of **2** and **3**, and (4) the activation parameters for bond homolysis. The rate constants and activation parameters in part reflect the significance of merostabilization on radical stability.

Experimental Section

^{1}H NMR spectral data were obtained with a Varian Associates EM-390 NMR spectrometer and chemical shifts are reported in parts per million on the δ scale from internal tetramethylsilane. Mass spectral data were obtained with a Varian MAT CH-5 mass spectrometer and infrared spectra were recorded on a Perkin-Elmer Model 337 infrared spectrophotometer.

Isatide (7). Isatide was synthesized via the base-catalyzed condensation of dioxindole with isatin according to the procedure of Sumpter.[7] The yellow powder obtained from the reaction decomposed, turning orange before melting at 200–202 °C (lit.[7] mp 228–230 °C dec). Isatide had the following spectral properties: IR (KBr) 3.06, 5.88, 6.18, and 6.80 μm; NMR (Me_2SO-d_6) δ 6.20 (s, 2 H), 6.8–7.36 (m, 8 H), and 10.37 ppm (broad s, 2 H); mass spectrum *m/e* (rel intensity) 149 (90), 147 (83), 121 (30), 119 (99), and 92 (100).

Reaction of Isatin (5) with Radical Dimers (2 + 3) in an NMR Tube. An NMR sample tube was charged with 36.8 mg (0.25 mmol) of isatin and 35.5 mg (0.125 mmol) of a mixture of the stereoisomeric radical dimers (**2** + **3**). Then 0.5 mL of dimethyl-d_6 sulfoxide was added, and the reaction solution was freeze (−196 °C)-pump (10^{-5} Torr)-thaw degassed through three cycles and sealed. After thawing, an initial ^{1}H NMR spectrum was obtained and the NMR sample tube was immersed in a thermostated water bath at 35 ± 0.1 °C. The reaction was monitored by periodically obtaining an ^{1}H NMR spectrum. As the reaction progressed the only products observed in the ^{1}H NMR spectrum were isatide and 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**1**). The color of the initial reaction solution was orange owing to the isatin and the color of the reaction solution at termination was light yellow. The solvent and trimethyloxazinone (**1**) were removed by high-vacuum rotary evaporation (25 °C, 0.5 Torr). Isatide was the only nonvolatile product as determined by silica gel, thin layer chromatography eluting with 25% acetonitrile in benzene solvent, IR, NMR, and mass spectrometry.

Preparative-Scale Reduction of Isatin with Radical Dimers (2 + 3). A test tube (15 × 150 mm) was charged with 294 mg (2.00 mmol) of isatin, 274 mg (0.96 mmol) of a mixture of the stereoisomeric radical dimers (**2** + **3**), and 5 mL of dimethyl sulfoxide. A serum stopper was placed on the test tube and the reaction solution was degassed by constantly bubbling argon through the solution. The orange color of the reaction solution faded to light yellow after 17 h at 28 °C and the reaction was allowed to continue for an additional 24 h to ensure complete reaction. Pure isatide (222 mg) was isolated in 75% yield via trituration with chloroform after removal of dimethyl sulfoxide and trimethyloxazinone **1** with a high-vacuum rotary evaporator (25 °C, 0.5 Torr). The isatide prepared had physical (mp 200–202 °C dec) and spectral properties identical with those of the isatide prepared by the procedure of Sumpter.[7]

Examination of the Isatin Radical Dimer (2 + 3) Solution by EPR Spectroscopy. To a 1-dram sample vial were added 115 mg (0.78 mmol) of isatin and 75 mg (0.26 mmol) of a mixture of the stereoisomeric dimers (**2** + **3**). The sample vial was fitted with a serum stopper, 0.50 mL of reagent grade dimethyl sulfoxide was added via syringe, and the resultant solution was degassed by a stream of argon for 10 min using syringe needles for inlet and outlet. After degassing 0.60 mL of the reaction solution was transferred via syringe to a 5-mm quartz EPR sample tube which had also been degassed with argon. The sample tube was placed in the EPR cavity, and the spectrum was scanned at temperatures ranging from 25 to 80 °C. No radical was detected including the trimethylmorpholinonyl radical **4**, which would have been observed in the absence of isatin.[2]

Reaction of Isatide with the Meso and *dl* Radical Dimers (2 and 3). An NMR sample tube was charged with 29.6 mg (0.100 mmol) of isatide and 28.4 mg (0.100 mmol) of a mixture of the meso and *dl* dimers **2** and **3**. Then 0.50 mL of dimethyl-d_6 sulfoxide was added and the reaction solution was freeze (−196°C)-pump (10^{-5} Torr)-thaw degassed and sealed. The reaction mixture was heated at 50 °C for 65 h. The products of the reaction as identified by ^{1}H NMR analysis were 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**1**), 3,5,5-trimethyl-2-morpholinone (**11**), and dioxindole (**12**). The ratio of **1**:**11**:**12** as determined by integration of the ^{1}H NMR spectrum was 3:2:1. The observed ratio was consistent with 50% reduction of isatide and 50% disproportionation of the morpholinonyl radical **4**. The product identification was facilitated by comparison of the ^{1}H NMR spectrum of the reaction mixture with the ^{1}H NMR spectra of authentic samples. Dioxindole was prepared by the reduction of isatin with sodium dithionite in aqueous solution as described by Marschalk.[13] 3,5,5-Trimethyl-2-morpholinone was obtained previously from the disproportionation of radical **4**.[2]

***N*-Methylisatin (6).** *N*-Methylisatin was prepared by the reaction of the sodium salt of isatin with methyl iodide using a procedure analogous to that described by Heller.[11] The product, recrystallized from water, melted at 129–131 °C (lit.[14] mp 134 °C) and gave the following spectral absorptions: NMR ($CDCl_3$) δ 3.30 (s, 3 H), 6.8–7.3 (m, 2 H), and 7.5–7.8 ppm (m, 2 H); mass spectrum *m/e* (rel intensity) 161 (28), 133 (10), 125 (19), 104 (23), and 77 (12).

Preparation and Separation of the Stereoisomeric Dimers of 3,5,5-Trimethyl-2-morpholinon-3-yl. A mixture of the meso and *dl* dimers of 3,5,5-trimethyl-2-morpholinon-3-yl was prepared by photoreductive dimerization of 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**1**) in 2-propanol solvent as previously described.[1] The meso and *dl* isomers (**2** and **3**, respectively) were efficiently separated by flash column chromatography.[15] A chromatography column 3 cm in diameter was dry packed to a height of 15 cm with 32–60 μm Woelm neutral alumina. The column was then charged with the eluting solvent, 2% acetone in methylene chloride. A mixture of the meso and *dl* radical dimers (0.50 g) was dissolved in 2 mL of 2% acetone in methylene chloride and added to the top of the column. The column was then eluted with 2% acetone in methylene chloride with a positive pressure of nitrogen in a cold room at 10 °C collecting 10-mL fractions. The *dl* dimer was eluted, and the eluting solvent was then changed to acetone to quickly elute the meso dimer. The solvent was quickly removed from the combined fractions by high-vacuum rotary evaporation (25 °C, 0.5 Torr). The materials obtained were the pure, separated meso and *dl* dimers as indicated by ^{1}H NMR spectroscopy and alumina TLC chromatography.

Reaction of *N*-Methylisatin (6) with the Meso Radical Dimers (2) in an NMR Tube. An NMR sample tube was charged with 11.4 mg (0.0708 mmol) of *N*-methylisatin and 9.1 mg (0.032 mmol) of the meso dimer (**2**) of 3,5,5-trimethyl-2-morpholinon-3-yl. Deuteriochloroform (0.5 mL) was added, and the sample tube was freeze (−196 °C)-pump (10^{-5} Torr)-thaw degassed and sealed. An initial ^{1}H NMR spectrum was obtained, and the NMR tube was placed in a constant-temperature bath at 35 ± 0.1 °C for a period of 48 h. During the reaction period the ^{1}H NMR spectrum was periodically scanned. The only products observed were the meso and *dl* isomers of *N,N'*-dimethylisatide (**8**) and 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**1**). No formation of the *dl* dimer (**3**) of 3,5,5-tri-

methyl-2-morpholinon-3-yl was observed. The half-life of the meso dimer of 3,5,5-trimethyl-2-morpholinon-3-yl under these conditions was 10.6 h. Formation of a mixture of the meso and *dl* isomers of *N,N'*-dimethylisatide was evident from the ^{1}H NMR spectrum which showed two *N*-methyl singlets at δ 3.00 and 3.14 ppm and a four-proton complex multiplet at δ 6.5–7.8 ppm.

Kinetic Measurements. A weighed amount of *N*-methylisatin (**6**) and either the meso or *dl* dimer of 3,5,5-trimethyl-2-morpholinon-3-yl in a slightly greater than 2:1 mole ratio was added to an NMR tube adapted with a 9-mm vacuum line attachment. The concentration of the dimer was in the range of 0.07 M for all experiments. The bottom of the NMR tube was then cooled in liquid nitrogen and 0.50 mL of deuteriochloroform containing 1% tetramethylsilane was added. The NMR tube was attached to the vacuum line with an Ultra Torr union, freeze (−196 °C)-pump (10^{-5} Torr)-thaw (0 °C) degassed through four cycles, and sealed. The reaction mixture was then thawed at 0 °C and placed in a constant-temperature bath thermostated to ±0.1 °C. The time was noted as $t = 0$. At various times the sample was removed from the bath and immediately frozen in a dry ice-acetone bath, and the time recorded. The progress of the reaction was then monitored by ^{1}H NMR spectroscopy. The concentration of dimer (**2** or **3**) was determined by integration of the methyl singlet of 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**1**) at 2.27 ppm and the corresponding methyl singlet of the dimer (**2** or **3**), i.e., the methyl singlet resulting from the 3- and 3'-methyl groups. The ratio of the area of the dimer methyl singlet to the sum of the area of the dimer methyl singlet plus the area of the oxazinone methyl singlet gave the fraction of remaining dimer (**2** or **3**). The concentration of dimer was calculated as the product of this fraction and the original concentration of dimer. Reactions were monitored to approximately 90% completion. Rate constants were obtained from the least-squares slopes of plots of −ln [dimer] 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 K, R is the gas constant, and E_a is the Arrhenius activation energy, and the entropy of activation was calculated as $R \ln (AN_a h/eRT)$ where A is the frequency factor, N_a is Avagadro's number, h is Planck's constant, $e = 2.7183$, R is the gas constant, and T is the average temperature in K. The error in the free energy of activation was obtained through a propagation of error technique upon the errors associated with the enthalpy of activation and the entropy of activation.

Isomerization of the Meso Dimer (2) to the Equilibrium Mixture of Meso and *dl* Dimers (2 + 3). To an NMR sample tube were added 9.2 mg (0.032 mmol) of meso dimer (**2**) and 0.50 mL of deuteriochloroform. The reaction sample was freeze (−196 °C)-pump (10^{-5} Torr)-thaw degassed through four cycles and sealed, and an initial ^{1}H NMR spectrum recorded. The reaction sample tube was then placed in a constant-temperature bath at 30 ± 0.1 °C. ^{1}H NMR spectra were obtained and integrated at various times to measure the relative concentration of the meso and *dl* dimers. A small amount of disproportionation of the radical (**4**) was observed during the course of the isomerization. The rate of disproportionation, however, was much slower than the rate of isomerization. At the time the last integration of the NMR spectrum was obtained for the plot of the integrated rate law (vide supra), the extent of disproportionation was approximately 6%. The equilibrium mixture of *dl* to meso dimer was observed to be 2.20.

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References and Notes

(1) T. H. Koch, J. A. Olesen, and J. DeNiro, *J. Org. Chem.*, **40**, 14 (1975).
(2) T. H. Koch, J. A. Olesen, and J. DeNiro, *J. Am. Chem. Soc.*, **97**, 7285 (1975).
(3) R. C. Haltiwanger, T. H. Koch, J. A. Olesen, C. S. Kim, and N. K. Kim, *J. Am. Chem. Soc.*, **99**, 6327 (1977).
(4) R. W. Baldock, P. Hudson, A. R. Katritzky, and F. Soti, *J. Chem. Soc., Perkin Trans. 1*, 1423 (1974). Radicals of this type have also been described as stabilized by "captodative substitution" by L. Stella, Z. Janousek, R. Merenyi, and H. G. Viehe, *Angew. Chem., Int. Ed. Engl.*, **17**, 691 (1978), and by a "push–pull effect" by A. T. Balaban, M. T. Caproin, N. Negoita, and R. Baican, *Tetrahedron*, **33**, 2249 (1977).
(5) J. M. Burns, D. L. Wharry, and T. H. Koch, *J. Am. Chem. Soc.*, **101**, 2750 (1979).
(6) E. M. Kosower, A. Tenerstein, H. D. Burrows, and A. J. Swallow, *J. Am. Chem. Soc.*, **100**, 5185 (1978).
(7) W. C. Sumpter, *J. Am. Chem. Soc.*, **54**, 2917 (1932).
(8) G. A. Russell, C. L. Meyers, P. Bruni, F. A. Neugebauer, and R. Blankespoor, *J. Am. Chem. Soc.*, **92**, 2762 (1970).
(9) F. S. D'iachkovskii, N. N. Bubnov, and A. E. Shilov, *Dokl. Akad. Nauk. SSSR*, **122**, 629 (1958).
(10) S. A. Weiner, *J. Am. Chem. Soc.*, **93**, 6978 (1971).
(11) F. T. McNamara, J. W. Nieft, J. F. Ambrose, and E. S. Huyser, *J. Org. Chem.*, **42**, 988 (1977).
(12) See A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2d ed., Wiley, New York, 1961, pp 109–115.
(13) C. Marschalk, *Chem. Ber.*, **45**, 582 (1912).
(14) C. Heller, *Chem. Ber.*, **40**, 1291 (1907).
(15) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).