a spiro link at C-8 to a tricyclic portion. All the rings are joined trans except the spiro ring, and all have chair conformation. The carboxymethyl groups at C-9 and C-9′ are equatorial while at the spiro C-8 the oxygen is equatorial and C-12 is axial. The hydroxyl at C-7 is equatorial but the peak corresponding to the C-7 hydrogen was large enough (approximately three electrons at a distance of 1.22 Å) to suggest that there might be some disorder at C-7 involving axial attachment of the hydroxyl.

The structure of officinalic acid is unique in comparison with those of known triterpenes, but it has some similarity to the onoceranes. While the onoceranes are likely derived from squalene, extensive rearrangement of a squalene precursor would be required to give the carbon skeleton of officinalic acid.

Supplementary Material Available: Lists of atomic coordinates, temperature parameters, torsion angles, and bond distances (17 pages). Ordering information is given on any current masthead page.

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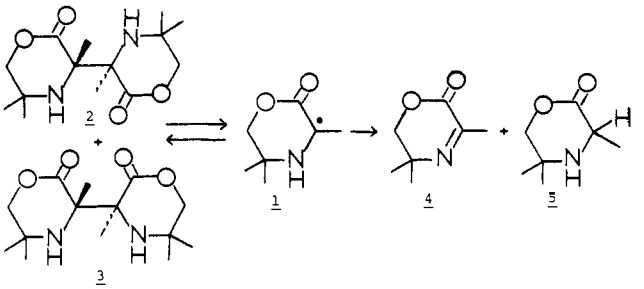
Received December 1, 1978

Electron-Transfer Chemistry of the 3,5,5-Trimethyl-2-morpholinon-3-yl Radical

Sir:

Previously we have reported that the 3,5,5-trimethyl-2-morpholinon-3-yl radical (**1**) is formed when a mixture of the meso and *dl* dimers (**2** and **3**, respectively) of the radical are dissolved in benzene, chloroform, or ethanol solvent at ambient temperature.[1,2] Upon being heated to 80 °C **1** disproportionates to a 50:50 mixture of 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**4**) and 3,5,5-trimethyl-2-morpholinone (**5**). The methylmorpholinonyl radical **1** is analogous to some free radicals described by Katritzky as merostabilized radicals.[3]

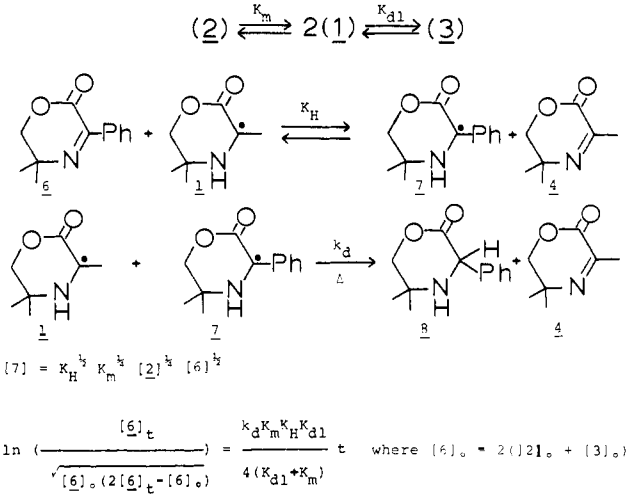


We now report (1) that the morpholinonyl radical **1** is capable of serving as a mild reducing agent by formally transferring a hydrogen atom to an appropriate acceptor, (2) that as a hydrogen atom donor it is capable of generating other stable free radicals and serving as a selective reducing agent for some functional groups, and (3) that the mechanism of hydrogen atom transfer is actually a rate-controlling electron transfer followed by a rapid proton transfer.

When a degassed mixture of the meso and *dl* radical dimers **2** and **3** and 5,6-dihydro-5,5-dimethyl-3-phenyl-1,4-oxazin-2-one (**6**)[4] is dissolved in methanol solvent, a new radical species is observed in the EPR spectrum which has been identified as the 5,5-dimethyl-3-phenyl-2-morpholinon-3-yl radical (**7**). The spectrum has a *g* value of 2.00399 and the following splitting pattern N, 1:1:1, 6.52; N-H, 1:1, 3.95; ortho and para H, 1:3:3:1, 2.01; meta H, 1:2:1, 0.81 G. The phenylmorpholinonyl radical **7** is persistent at ambient temperature for a period of days, does not dimerize, and is further reduced quantitatively to 5,5-dimethyl-3-phenyl-2-morpholinone (**8**) upon prolonged heating.

A mechanism for the production of the phenylmorpholinone **8** is shown in Scheme I and is suggested by the following evidence. The intensity of the EPR spectrum of the phenylmorpholinonyl radical **7** at ambient temperature is directly proportional to the square root of the concentration of the phenyloxazinone **6** and the fourth root of the concentration of the radical dimers **2** and **3**. Furthermore, the intensity of the EPR spectrum of **7** is significantly diminished upon the addition of trimethyloxazinone **4**. Under the conditions of the intensity

Scheme I



measurements, the reduction of **7** to **8** was slow and the concentration of the methylmorpholinonyl radical **1** was low relative to the concentration of the phenylmorpholinonyl radical **7**. The rate of reduction of the phenyloxazinone **6** to the phenylmorpholinone **8** is consistent with the kinetic expression shown in Scheme I for over 90% of the reaction at 35 °C for a methanol solution that is 0.250 M in **6** and 0.125 M in radical dimers **2** and **3**. In the absence of an excess of **6**, disproportionation of **1** is competitive with reduction of **7** toward the end of the reaction. The kinetic measurements were inconsistent with disproportionation of **7** as the rate-controlling step for production of **8**. A plot of $\ln \{[\mathbf{6}]_t/\sqrt{[\mathbf{6}]_0(2[\mathbf{6}]_t - [\mathbf{6}]_0)}\}$ vs. t was linear with a slope of $(7.9 \pm 0.3) \times 10^{-3}$ s^{-1}. A deuterium-labeling experiment indicates that the hydrogen ultimately transferred from the methylmorpholinonyl radical **1** is the hydrogen bonded to nitrogen rather than a hydrogen bonded to the 3-methyl carbon. Heating a mixture of N,N-dideuterated radical dimers **2** and **3** with the phenyloxazinone **6** in methanol-d_4 solvent gives 3-deuterio-5,5-dimethyl-3-phenyl-2-morpholinone quantitatively as shown by ^{1}H NMR spectroscopy.

The methylmorpholinonyl radical **1** also formally transfers a hydrogen atom to the carbonyl of 4-(diphenylmethylene)-2,5-cyclohexadienone[5] (fuchsone, **9**). A solution of **2**, **3**, and fuchsone in chloroform solvent at ambient temperature gives an EPR signal with a g value of 2.00353 and approximately the following splitting pattern: ortho H, 1:6:15:20:15:6:1, 2.57; meta H, 1:6:15:20:15:6:1, 1.13; para H, 1:2:1, 2.80; O-H, 1:1, 0.12 G. The EPR spectrum was assigned to the diphenyl-*p*-hydroxyphenylmethyl radical (**10**). Upon prolonged heating of fuchsone with radical dimers **2** and **3** quantitative reduction to diphenyl-*p*-hydroxyphenylmethane occurs.

Radical **1** selectively reduces the carbonyl functional group of 2-benzoyl-4,4-dimethyl-2-oxazoline (**11**)[6] to give 2-(hydroxyphenylmethyl)-4,4-dimethyl-2-oxazoline (**12**)[6] and selectively reduces one carbonyl of benzil to give benzoin, both in chloroform solvent. Intermediate radicals other than **1** are not observed in the EPR spectrum, and both reductions are quantitative in radical dimers **2** and **3** when approximately a 100% excess of the carbonyl compound is employed. In the absence of a large excess of the carbonyl compound, disproportionation of the methylmorpholinonyl radical **1** to **4** and **5** is competitive with reduction of the carbonyl compound. The rate of reduction of oxazoline **11** in a chloroform solution that is 0.50 M in oxazoline, 0.25 M in radical dimers **2** and **3**, and 0.50 M in methyloxazinone **4** is consistent with a mechanism analogous to that proposed in Scheme I for the reduction of the phenyloxazinone **6**. In the absence of the initial concentration of methyloxazinone **4**, the rate-controlling step shifts from the first hydrogen atom transfer to the second hydrogen atom transfer as the reaction proceeds. A plot of the kinetic expression for the indicated reaction conditions

$$\ln ([\mathbf{11}]_t^3/\{4[\mathbf{11}]_0([\mathbf{11}]_t - 1/2[\mathbf{11}]_0)^2\})$$

vs. t is linear for over 90% of the reaction with slope equal to $(4.0 \pm 0.1) \times 10^{-4}$ s^{-1}.

The redox reactions described for the methylmorpholinonyl radical **1** could occur by two distinct mechanisms, direct hydrogen atom transfer or electron transfer followed by proton transfer. We have probed two of the redox reactions of **1** for evidence which might distinguish between these mechanistic alternatives. First, the deuterium kinetic isotope effect for the disproportionation of methylmorpholinonyl radical **1** to **4** and **5** was measured. The deuterium kinetic effect was determined by examining deuterium incorporation at the 3 position of 3,5,5-trimethyl-2-morpholinone (**5**) from <20% disproportionation of a solution in which the ratio of the concentration of methylmorpholinonyl radical to *N*-deuteriomethylmorpholinonyl radical was 47:53. The mixture of deuterated and undeuterated radicals was prepared from partially deuterated radical dimers **2** and **3**, and the ratio was measured by double integration of a region of the EPR spectrum in which the absorptions of the two radicals were distinct and equally intense. A deuterium kinetic isotope effect of 1.16 ± 0.09 was calculated from the integration of the ^{1}H NMR spectrum of the reaction mixture with the single assumption that, for a rate-controlling hydrogen atom transfer, the possible secondary deuterium isotope effects with respect to the hydrogen atom acceptor are equal. The magnitude of the kinetic isotope effect is inconsistent with a rate-controlling hydrogen atom transfer or proton transfer and suggests that the rate-controlling step is electron transfer. The measured isotope effect then is the secondary isotope effect on the electron donor.

The second redox reaction probed for evidence of the mechanism for hydrogen atom transfer was the reduction of benzil to benzoin. The effect of substituents in the 4 and 4′ positions on the rate in chloroform solvent was measured. For at least the first 30% of reaction, the rates of reduction of benzil and the 4,4′-disubstituted benzils were consistent with the first hydrogen atom transfer, analogous to step 3 of Scheme I, being the rate-controlling step. The electron-withdrawing substituent, chlorine, enhanced the rate of reduction and the electron-donating substituents methyl and methoxyl retarded the rate of reduction. All of these substituents should stabilize the transition state for formation of a free-radical intermediate and should correspondingly enhance the rate of a direct hydrogen atom transfer; however, only the chlorine substituent should enhance the rate of electron transfer. The kinetic data were linear in σ^+ and a plot of $\log(k/k_0)$ vs. σ^+ gave a ρ of 1.7 ± 0.1. The sign of ρ and correlation with σ^+ are both consistent with a mechanism for hydrogen atom transfer by a rate-controlling electron transfer followed by a rapid proton transfer.[7]

The hydrogen atom transfer reactions of the methylmorpholinonyl radical **1** find precedent in photoreduction reactions. Reversible hydrogen atom transfer has been proposed as part of the reaction mechanism for the photoreduction of benzophenone by ethers[8] and for the chemical sensitized photoreduction of imines.[9]

Analogous electron-transfer mechanisms have been proposed for the reaction of pyridinyl radicals with acyl peroxides[10] and for the reaction of 1-ethyl-4-carbomethoxypyridinyl radical with *p*-nitrobenzyl chloride.[11]

Acknowledgment. We thank Professors Shelby Sherrod and Edward King for helpful discussions and Joseph Keute for the synthesis of fuchsone. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We thank the General Medical Institute (GM-18349) and the National Cancer Institute (CA-24665) of the National Institutes of Health and the Biomedical Research Support Grant Program of the National Institutes of Health for financial assistance.

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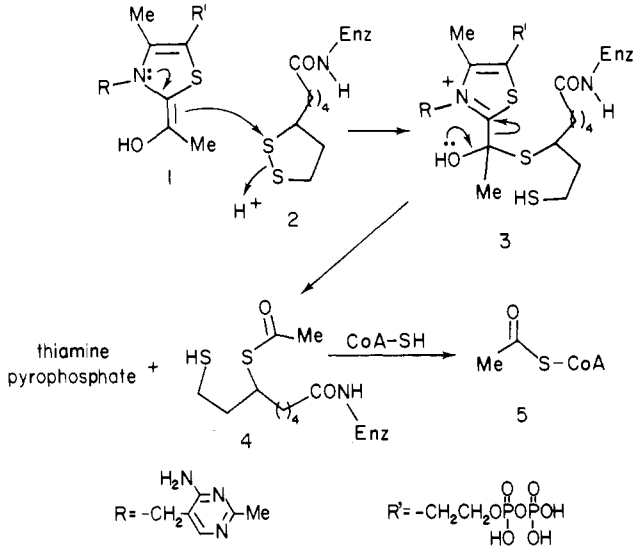
Received October 20, 1978

On the Involvement of Lipoic Acid in α-Keto Acid Dehydrogenase Complexes

Sir:

Herein we report the reactivity of thiazolium salt derived acyl anion equivalents (see **1**, Scheme I) toward sulfur electrophiles and provide a model for the thioester-forming step catalyzed by the lipoic acid containing enzymes (**2**), the α-keto acid dehydrogenases.[1,2] This class of enzymes mediates the production of energy-rich thioesters of coenzyme A (e.g., acetyl coenzyme A, **5**) by oxidative decarboxylation of α-keto acids (e.g., pyruvate). Our work, detailed below, focuses on the formation of the intermediate thioester **4** and supports the direct reductive acylation step[3] depicted in Scheme I.

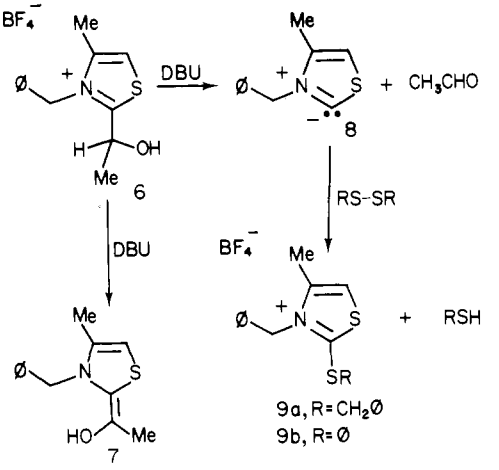
Scheme I



In our model system an equivalent of the biological "active aldehyde" (**1**) is generated by proton abstraction from the crystalline precursor **6** (Scheme II).[4] Table I shows results of the trapping of in situ generated enamine **7** by a variety of electrophiles. As precedented,[2g] **7** transfers the acetyl moiety to methyl vinyl ketone (entries 1 and 2). The reactions of **7** with sources of electrophilic sulfur (entries 3–6) mimic the pyruvate dehydrogenase mediated production of enzyme-bound acetyldihydrolipoic acid (**4**, Scheme I).

Competing, base-promoted reaction pathways exist for precursor **6** (Scheme II). Treatment of **6** with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) not only generates enamine **7**, but, as well, induces fragmentation of **6** to ylide **8** and acetaldehyde.[5] Reaction of **7** with disulfides yields thioesters and thiols; competing reaction of **8** with disulfides yields sulfenylated products (e.g., **9a,b**) and thiols. Thus, the yield of thiols produced in the model reaction of **6** with disulfides substantially exceeds the yield of thioesters (Table I, entries 4 and 5).[6] In an independent experiment, the ylide **8**, generated from 3-benzyl-4-methylthiazolium tetrafluoroborate[7] and DBU reacted rapidly with benzyl disulfide yielding benzylthiol (79%, GLC yield) and sulfenylated product **9a; 9b** was isolated[8] (74%) from the reaction of ylide **8** with *N*-(phenylthio)-phthalimide[9] (PhS-Phth).

Scheme II



The facile sulfenylation of ylide **8** (Scheme II) precludes efficient generation of thioesters starting from ylide **8** plus acetaldehyde and disulfides. One (1.0) equivalent of acetaldehyde reacts with 5.0 equiv of diphenyl disulfide in tetrahydrofuran (THF) containing 1.0 equiv of 3-benzyl-4-methylthiazolium tetrafluoroborate[7] and 1.0 equiv of DBU (cf. Table I, entry 4) producing <1% yield of acetylthiophenol but a 73% yield of thiophenol (GLC yields based on CH_3CHO).

The base-initiated fragmentation of precursor **6** can be blocked using the methylated derivative **10**.[10] In situ enamine generation from **10** and trapping with *N*-(phenylthio)-

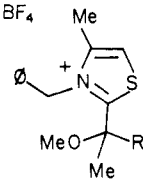


Table I. Reactions of 2-(α-Hydroxyethyl)-3-benzyl-4-methylthiazolium Tetrafluoroborate (**6**) as an Acyl Anion Equivalent

entry	electrophile	solvent, base	conditions, time (temp)	product (% yield)
1	methyl vinyl ketone[a]	EtOH, DBU[b]	0.5 h (ambient temp)	2,5-hexanedione (40)[c]
2	methyl vinyl ketone[a]	EtOH, Et_3N[d]	15 h (reflux), plus 20 h (ambient temp)	2,5-hexanedione (49)[e]
3	PhS-Phth[a]	THF, DBU[b]	16 h (ambient temp)	CH_3COSPh (42)[f,i]
4	PhS-SPh[g]	THF, DBU[b]	5 min (ambient temp)	CH_3COSPh (32),[c,i] PhSH (74)[c,i]
5	$PhCH_2S$-SCH_2Ph[g]	THF, DBU[b]	5 min (ambient temp)	CH_3COSCH_2Ph (13),[c,i] $PhCH_2SH$ (88)[c,i]
6	EtS-SEt[g]	THF, DBU[b]	5 min (ambient temp)	CH_3COSEt (33),[c,i] EtSH[h]

[a] 1.0 equiv used vs. **6**. [b] 1.0 equiv of DBU (1,5-diazabicyclo[5.4.0]undec-5-ene) used vs. **6**. [c] GLC yield (4.1% SE-30 on Chromosorb G, 7 ft), determined relative to hydrocarbon standard. [d] 7.2 equiv of Et_3N used vs. **6**. [e] Isolated yield as bisoxime, mp 129–132 °C. [f] Isolated yield. [g] 5.0 equiv of disulfide used vs. **6**. [h] EtSH yield not determined owing to interfering solvent peak in GLC run. [i] Identity confirmed by GLC–mass spectrum (comparison with authentic sample).

0002-7863/79/1501-2752$01.00/0