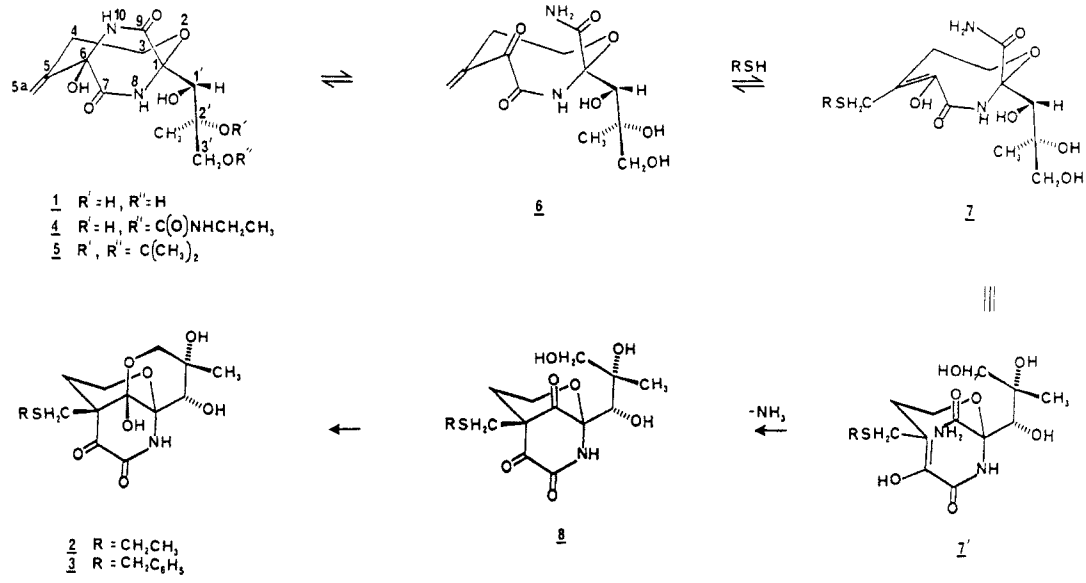
Scheme I. Proposed Pathway for the Generation of Compounds 2 and 3



Several experiments afforded information concerning this unique transformation. First, no significant consumption of bicyclomycin was observed by using the prescribed experimental conditions in the absence of ethyl mercaptan.[14] Second, treatment of an aqueous solution of **1** with ethyl mercaptan without tetrahydrofuran furnished **2** in lower amounts (TLC analysis). Third, repetition of the initial experiment using benzyl mercaptan gave **3** (53% yield).[16,17] Fourth, addition of ethyl mercaptan to a 3:1 tetrahydrofuran–water solution containing either the 3′-*O*-ethyl carbamate derivative **4**[19] or the acetonide **5**[20] led to no significant reaction after 24 h.[14] At higher "pH" values (10.2–12.5), treatment of **5** with mercaptans furnished the unrearranged C_{5a}-substituted sulfide.[4,5]

These results are in agreement with the pathway depicted in Scheme I.[21] Drug activation is envisioned to occur by initial ring cleavage of the hemiaminal bond to furnish **6**. Subsequent addition of ethyl mercaptan to the α,β-unsaturated carbonyl system generates **7** which is ideally situated to undergo an *intramolecular mixed-Claisen condensation* to produce **8** and ammonia. Cyclization of **8** in the final step yields the observed hemiketal **2**.

The isolation of compounds **2** and **3** and the accompanying experimental observations provide new information concerning the chemical pathway(s) for the activation of bicyclomycin which demand further study. The lack of reactivity of carbamate **4** and acetonide **5** and the enhanced activity of **1** in tetrahydrofuran–water mixtures versus water alone suggest that drug activation is facilitated by intramolecular hydrogen bonding of the triose ring hydroxyl groups with the 2,5-piperazinedione unit in **1**. Significantly, the observed intramolecular mixed-Claisen transformation generates **8** under exceedingly mild conditions. This reactive species[22] may be capable of undergoing further chemical transformations necessary for drug function. The mechanism and implications of this reaction are currently being pursued.

Acknowledgment. We thank the National Institutes of Health (GM37934) and the Robert A. Welch Foundation (E-607) for their support of this research. The National Science Foundation (CHE-8616352) is gratefully acknowledged for providing matching funds for the purchase of a high field NMR spectrometer. Special thanks are given to Dr. James D. Korp for performing the X-ray crystallographic analysis of compound **2** and Dr. Simon Gaskell (Baylor College of Medicine) for obtaining the mass spectral results. We also express our appreciation to Dr. K. Inokuchi and the Fujisawa Pharmaceutical Co., Ltd, Japan, for providing us with a gift of bicyclomycin.

(14) A similar result was observed for dihydrobicyclomycin.[15]

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(16) Select data for compound **3**: mp 108–110 °C; R_f 0.75 (10% methanol–chloroform); IR 1730, 1680 cm^{-1}; ^1H NMR (CD_3OD) δ 1.13 (s, 3 H), 1.86 (d, 1 H, J = 14.1 Hz), 2.23 (ca. dt, J = 7.4, 14.1 Hz), 2.80 (1/2 AB_q, 1 H, J = 14.0 Hz), 2.93 (1/2 AB_q, 1 H, J = 14.0 Hz), 3.59 (d, 1 H, J = 11.9 Hz), 3.70–3.80 (m, 3 H), 3.88 (s, 1 H), 3.96 (d, 1 H, J = 11.9 Hz), 3.92–4.05 (m, 1 H), 7.20–7.35 (m, 5 H); M_r 409.1191 (calcd for $C_{19}H_{23}NO_7S$, 409.1195).

(17) Use of select secondary amines (i.e., morpholine, ethyl 1-piperazinecarboxylate) gave a comparable result.[18]

(18) Abuzar, S.; Kohn, H., unpublished results.

(19) Muller, B. W.; Zak, O.; Kump, W.; Tosch, W.; Wacker, O. *J. Antibiot.* **1977**, *32*, 689.

(20) Kamiya, T.; Maeno, S.; Kitaura, Y. Belgium Patent 847 475.

(21) Alternatively, thiol- or hydroxyl-mediated cleavage of the amide bond at carbon-9 may have occurred to generate the corresponding thiol ester or ester, respectively, prior to cleavage of the hemiaminal bond and addition of the mercaptan to the exomethylene group.

(22) Compound **8** can be viewed as a masked derivative of 2,4,5-trioxooctanoic acid.

O–H Bond Dissociation Energies in Para-Substituted Phenols[1]

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Hammett substituent effects in free-radical chemistry have intrigued chemists for some considerable time.[3] Classical studies[4-9] focused on hydrogen abstraction at substituted toluenes,

(1) National Research Council of Canada. Issued as NRCC publication 28927.

(2) University of Leiden.

(3) (a) Arnold, D. R. *Substituent Effects in Radical Chemistry*; Viehe, H. E., Janousek, Z., Merényi, R., Eds. Reidel: Dordrecht, Holland, 1986; NATO ASI, Series C, Vol. 189, p 171. (b) Creary, X. *Substituent Effects in Radical Chemistry*; p 245. (c) Timberlake, J. W. *Substituent Effects in Radical Chemistry*; p 271 and references cited therein.

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Table I. O–H Bond Dissociation Energies in para-Substituted Phenols and Rate Constants, k_2, for Hydrogen Abstraction at 25 °C

X	BDE(p-XC_6H_4O-H),[a] kcal mol^{-1}	$k_2 \times 10^{-8}$,[b] M^{-1} s^{-1}
CF_3	87.2	1.3[c]
Cl	84.4	2.9
H	84.0[d]	3.3
t-Bu	82.1	5.6
MeO	78.1	18

[a] Measured with respect to phenol; relative error ±0.5 kcal mol^{-1}. [b] Reference 14. [c] McPhee, D. J., unpublished results. [d] o-Hydroxybenzophenone used as standard; absolute error ±1 kcal mol^{-1}.

where relative rate constants broadly correlated with the σ^+ parameter. Recently, serious attempts[3] have been made to disentangle polar and homolytic contributions from substituents so that a free radical $\sigma^\bullet$ scale might be established. Despite this intense activity, almost nothing is known about the effect of substituents on homolytic bond strengths.[10]

In a highly innovative study,[11] Mahoney and DaRooge combined kinetic and thermochemical methods in an attempt to measure substituent effects on the O–H bond strengths of phenols but were ultimately unable to separate the bond dissociation energies from activation energies for radical–radical reactions. In this work, we have used photoacoustic calorimetry to measure such O–H bond strengths. So far as we are aware, the data represent the first direct thermodynamic measurements of Hammett substituent effects on homolytic bond dissociation energies.

The photoacoustic technique has been described in detail elsewhere,[12,13] and its time scale is such that it can be used to measure the thermochemistry for radical formation. In a flow system, a mixture of di-*tert*-butyl peroxide and an appropriate phenol (p-XC_6H_4OH) was photolyzed in a standard UV flow cell by using laser pulses at 337 nm ($h\nu$ = 84.8 kcal mol^{-1}). The photolysis led to reactions 1 and 2, and the heat evolved in the

$$t\text{-BuOOBu-}t \xrightarrow{h\nu} 2t\text{-BuO}^\bullet \quad (1)$$

$$2t\text{-BuO}^\bullet + 2p\text{-}XC_6H_4OH \rightarrow 2t\text{-BuOH} + 2p\text{-}XC_6H_4O^\bullet \quad (2)$$

solution produced a shock wave that was detected by a transducer clamped to the cell wall. Signals resulting from 1280 laser pulses were stored and averaged in an oscilloscope. The system was calibrated[13] by using o-hydroxybenzophenone which effectively converts all of the light energy into heat.

The technique requires that the heat of reactions 1 and 2 be completely released in a time that is short compared to the instrumental response. We established this limit in experiments on phenol itself, where the concentration was varied over a wide range (10^{-4} to 2 M). Above 0.05 M phenol, the amplitude of the photoacoustic wave reached a maximum and remained constant. Since the rate constant for hydrogen abstraction, k_2, is 3.3×10^8 M^{-1} s^{-1},[14] this implies that the lifetime for reaction 2 must be <60 ns for accurate measurement. Rate constants, k_2, for the substituted phenols are given in Table I, and concentrations were always used that met this time constraint.[15,16]

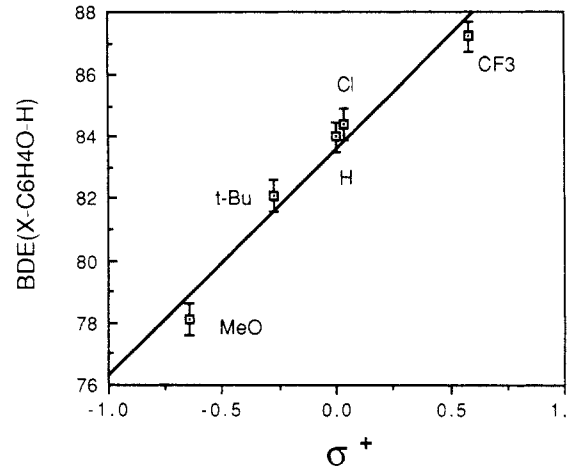

Figure 1. Hammett plot for bond dissociation energies (kcal mol^{-1}) in para-substituted phenols versus σ^+.

The observed heat deposition, ΔH_{obsd}, is related to the thermochemistry of interest via eq 3 and 4,[13] where Φ is the quantum

$$\Delta H_{obsd} = \Delta H_{1,2^\bullet}\cdot\Phi + 84.8 \quad (3)$$

$$\text{BDE}(p\text{-}XC_6H_4O\text{–H}) = \Delta H_{1,2}/2 + 86.1 \text{ kcal mol}^{-1} \quad (4)$$

yield for photolysis of di-*tert*-butyl peroxide in benzene (Φ = 0.85).[18] Taking the heats of formation of t-BuOH,[19] t-BuOO-Bu-t,[20] and H$^\bullet$[19] leads to the bond dissociation energies, BDEs, of the phenols, eq 4, Table I. The result obtained for phenol itself is in excellent agreement with the literature value for this bond strength (85.1 ± 1.0 kcal mol^{-1}),[21,22] and phenol was generally used as the standard against which the substituted phenols were compared.

The data for BDE show a very strong dependence on the electronegativity of the substituents. Interestingly, plots of BDE(p-XC_6H_4O–H) correlate very well with both σ^+ (r = 0.98; Figure 1)[23] and rate constants, k_2, for hydrogen abstraction by *tert*-butoxyl (r = 0.99, Table I). The results are summarized in eq 5 and 6. This observation appears to support the suggestion

$$\text{BDE}(p\text{-}XC_6H_4O\text{–H}) = 83.6 + 7.3\sigma^+ \text{ kcal mol}^{-1} \quad (5)$$

$$\text{BDE}(p\text{-}XC_6H_4O\text{–H}) = 160.2 - 8.97 \log (k_2) \text{ kcal mol}^{-1} \quad (6)$$

made by Zavitsas and Pinto[24] that substituent effects on radical abstractions actually reflect variations in bond strengths rather than polar contributions to the reaction transition state. However, whether these effects are separable or not remains a moot point—post hoc, ergo propter hoc.

The substituents investigated cause a surprisingly large (9 kcal mol^{-1}) spread in the O–H bond strengths of the para-substituted phenols. We suspect that this may be an extreme case because of the polarity of the O–H bond and that less polar bonds, such as C–H bonds in substituted toluenes, will not show much dramatic effects.

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Registry No. H_2, 1333-74-0; p-$F_3CC_6H_4OH$, 402-45-9; p-ClC_6H_4OH, 106-48-9; PhOH, 108-95-2; p-HOC_6H_4Bu-t, 98-54-4; p-$MeOC_6H_4OH$, 150-76-5.

Synthesis, Characterization, and X-ray Crystal Structure of a Donor-Stabilized Bis(silylene)iron Complex

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Silylene complexes have been proposed as reactive intermediates in a number of reactions[1] and as products in a few reactions,[2] but there has been no report on the X-ray crystal structure analysis of stable silylene complexes until recently. In 1987, two groups reported one after the other the syntheses and crystal structures of donor-stabilized silylene complexes: $[(OC)_4Fe{=}Si(O\text{-}t\text{-}Bu)_2{\cdot}HMPT]$[3] and $[Cp'(Me_3P)_2Ru{=}SiPh_2{\cdot}NCMe](BPh_4)$ ($Cp' = \eta^5\text{-}C_5Me_5$).[4] We now report the first synthesis and X-ray crystal structure determination of a donor-stabilized bis(silylene)iron complex.

Recently, Pannell's group[5] and we[6] independently observed an unusually fast alkyl scrambling between silicon atoms in the photoinduced conversion of $CpFe(CO)_2SiR_2SiR_3$ to $CpFe(CO)_2SiR_3$ (R = alkyl, aryl). Silyl(silylene)iron intermediates were postulated as key intermediates of this reaction, but these were too unstable to isolate. Thus, our efforts have focused on searching substituents on silicon atoms which effectively stabilize the silyl(silylene)iron complexes, and we have finally found that these can be stabilized as donor-stabilized bis(silylene)iron complexes by introducing alkoxy groups.

The starting complex $Cp'Fe(CO)_2SiMe_2SiMe(OMe)_2$ (**1**)[7] was prepared as follows: $Na[Cp'Fe(CO)_2]$ was allowed to react with $ClMe_2SiSiMeCl_2$, and then the product was treated with methanol and pyridine to give **1** and its isomer $Cp'Fe(CO)_2SiMe(OMe)$-$SiMe_2(OMe)$ in 32% and 9% overall yields, respectively. Irradiation of **1** in C_6D_6 or toluene (ca. 0.1 M) with a medium pressure Hg arc lamp resulted in the quantitative conversion to a mixture of diastereomers of bis(silylene) complexes **2**[8] and **3**[8] (optical isomerism is ignored) with loss of 1 equiv of CO within several minutes (eq 1). The ratio of **2** and **3** is approximately 2:1

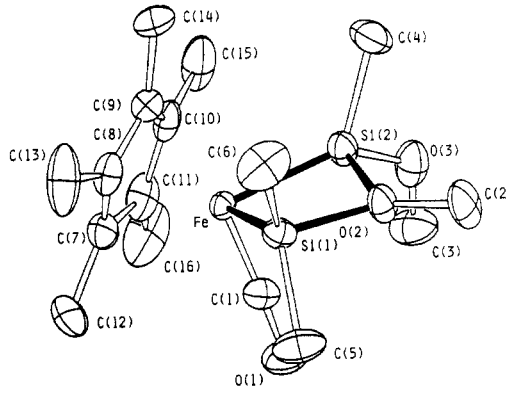


Figure 1. ORTEP view of **2** with thermal elipsoids at 30% probability level. Selected distances (Å) and angles (deg): Fe–Si(1), 2.222 (3); Fe–Si(2), 2.207 (3); Fe–C(1), 1.676 (11); Si(1)–C(5), 1.88 (2); Si(1)–C(6), 1.88 (2); Si(1)–O(2), 1.793 (9); Si(2)–O(2), 1.799 (8); Si(2)–O(3), 1.632 (9); Si(2)–C(4), 1.94 (2); O(2)–C(2), 1.45 (2); O(3)–C(3), 1.41 (2); O(1)–C(1), 1.198 (14); Si(1)···Si(2), 2.622 (4); Fe···O(2), 2.962 (7); O(1)···C(3), 3.33 (2); C(4)···C(14), 3.59 (2); C(6)···C(13), 3.54 (2); Si(1)–Fe–Si(2), 72.6 (1); Fe–Si(1)–O(2), 94.5 (3); Fe–Si(2)–O(2), 94.8 (3); Si(1)–O(2)–Si(2), 93.8 (4); Fe–Si(1)–C(5), 123.1 (5); Fe–Si(1)–C(6), 123.6 (6); C(5)–Si(1)–C(6), 105.8 (7); Fe–Si(2)–O(3), 126.9 (4); Fe–Si(2)–C(4), 127.2 (5); O(3)–Si(2)–C(4), 98.5 (6); Si(1)–O(2)–C(2), 131.6 (7); Si(2)–O(2)–C(2), 132.4 (8); Si(1)–Fe–C(1), 84.9 (4); Si(2)–Fe–C(1), 91.7 (4).

Chart I

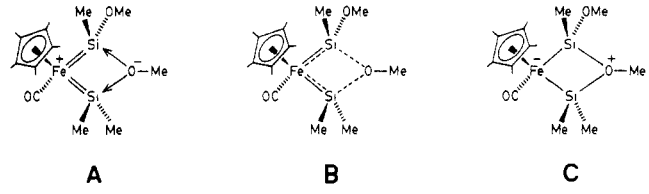
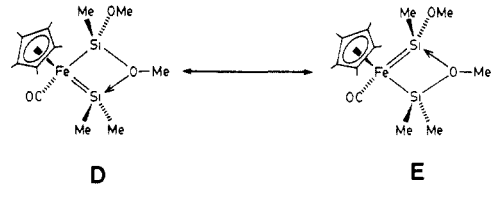
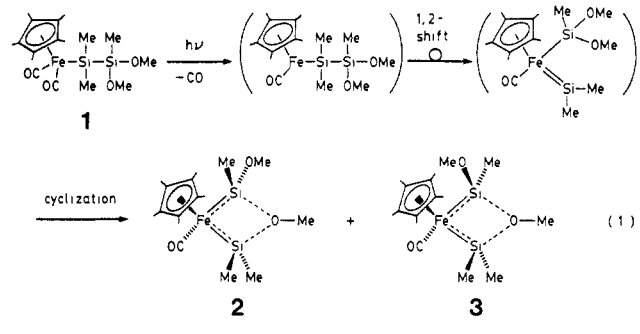


Chart II





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(7) For **1**: ^1H NMR (90 MHz, C_6D_6) δ 3.50 (s, 6 H, OMe), 1.62 (s, 15 H, Me of Cp'), 0.72 (s, 6 H, Si–Me), 0.41 (s, 3 H, Si–Me); ^{13}C NMR (22.5 MHz, C_6D_6) δ 217.8 (CO), 95.2 (Cp' ring carbon), 50.1 (OMe), 9.8 (Me of Cp'), 3.5 (Si–Me), −2.2 (Si–Me); ^{29}Si NMR (17.8 MHz, C_6D_6) δ 10.7, 4.6; IR (C_6D_6) ν(CO) 1920 vs, 1972 vs cm^{-1}; Anal. Calcd for $C_{17}H_{30}FeO_4Si_2$: C, 49.75; H, 7.39. Found: C, 49.74; H, 7.35.

(8) For a mixture of **2** and **3** in the ratio of ca. 2:1 (assignments of signals for NMR spectra were done if possible): ^1H NMR (90 MHz, C_6D_6) δ 3.70 (s, 3 H, OMe, **2**), 3.37 (s, 3 H, OMe, **3**), 2.89 (s, 3 H, OMe, **2**), 2.82 (s, 3 H, OMe, **3**), 1.90 (s, 15 H, Me of Cp', **3**), 1.82 (s, 15 H, Me of Cp', **2**), 0.57 (s, 3 H, Si–Me, **2** and **3**), 0.55 (s, 3 H, Si–Me, **3**), 0.47 (s, 3 H, Si–Me, **3**), 0.43 (s, 3 H, Si–Me, **2**), 0.40 (s, 3 H, Si–Me, **2**); ^{13}C NMR (22.5 MHz, C_6D_6) δ 221.0 (CO, **2**), 220.0 (CO, **3**), 90.0 (Cp' ring carbon, **3**), 89.8 (Cp' ring carbon, **2**), 51.9 (OMe), 51.8 (OMe), 51.0 (OMe), 11.6 (Me of Cp'), 9.9 (Si–Me), 7.3 (Si–Me), 6.5 (Si–Me), 5.8 (Si–Me), 5.2 (Si–Me), 3.3 (Si–Me); IR (C_6D_6) ν(CO) 1875 cm^{-1}; MS (10 eV), m/e 382 (100, M^+); exact mass calcd for $C_{16}H_{30}FeO_3Si_2$ 382.1083, found 382.1086.

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