solution (one test tube out of the four) to which the ylide solution was not added. The fractions of reaction were calculated for both reactants, and the reactivity ratio was computed according to the equation

$$k_A/k_B = \log (1 - f_A)/\log (1 - f_B)$$

Carbon-14 KIE Measurement. A THF solution of benzaldehyde-*carbonyl*-^{14}C (0.60 M, 25 mL) containing diphenyl ether (internal standard) was divided into six parts and transferred with a stainless steel needle into flame-dried test tubes capped with rubber septa. To these solutions were added preset amounts of benzylidenetriphenylphosphorane solution (0.3 M, THF) at 0 °C under stirring; the molar ratio of the ylide to the aldehyde was in the range 0.0–0.8. The solutions were stirred vigorously at 0 °C for 10 s and were then worked up in a usual manner and subjected to GC analysis to determine the fractions of reaction. Since we had encountered trouble in determining molar radioactivity of ^{14}C-labeled benzaldehyde in desired accuracy probably due to the difficulty in purifying, weighing, and transferring the liquid sample to a counting vial, we treated the recovered benzaldehyde with an excess amount of PhLi. The reaction of benzaldehyde with PhLi was known to give benzhydrol quantitatively with the carbonyl-^{14}C KIE of unity,[20] and therefore this procedure would have no influence on the radioactivity of the sample. The resulting benzhydrol was easy to handle and readily purified by recrystallization from hexane. The molar radioactivities were measured by a liquid scintillation counter (Beckman LS-9000) as reported previously,[21] and KIE was calculated by the least-squares method according to the equation[22]

$$\log R_r = \log R_0 - [1 - (^{14}k/^{12}k)] \log (1 - f)$$

Radioactivity data are listed in the supplementary material.

Cis–Trans Ratio. In a standard procedure, 1.0 mL of THF solution (1.0 M) of ylide was added at 0.0 ± 0.1 °C to a 1.0-mL of THF solution (1.0 M) of benzaldehyde, and the solution was allowed to react for 10 s under stirring. The reaction mixture was worked up in a usual manner and subjected to GC analysis to determine the product ratio. Similar experiments were carried out under a variety of conditions. Variables include reaction temperature, concentration, the mode of addition, and reaction time. Specific conditions were shown in Tables II–V.

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Supplementary Material Available: Tables of relative reactivities, molar radioactivities, and a list of ^1H NMR chemical shifts of substituted stilbenes (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Spectroscopic Evidence for a Spirooxirane Intermediate in the Synthesis of 4-(Hydroxymethyl)-2-[(dimethylamino)methyl]thiazole

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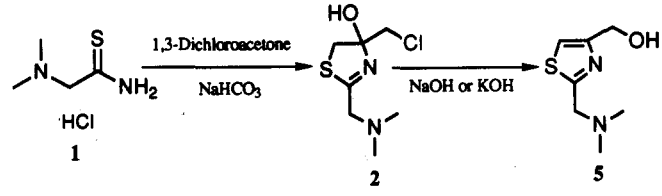
The synthesis of 4-(hydroxymethyl)thiazole derivatives from the corresponding 4-(chloromethyl)-4-hydroxythiazole derivatives have been speculated to proceed through spirooxirane intermediates. NMR spectroscopy was used to provide evidence for the existence of such an intermediate in the synthesis of 4-(hydroxymethyl)-2-[(dimethylamino)methyl]thiazole. Experimental conditions for the optimum formation and stabilization of a suspect intermediate were determined and spectral data obtained to support the speculated structure. Comparisons were made between couplings constants predicted in molecular models and the experimental data.

During our investigations of different synthetic routes toward functionalized thiazole ring systems,[1] methods to generate 4-(hydroxymethyl)-2-[(dimethylamino)methyl]-thiazole (**5**) became of interest. This compound is presently produced by the synthetic route shown in Scheme I. (Dimethylamino)thioacetamide hydrochloride (**1**) is treated with 1,3-dichloroacetone in the presence of $NaHCO_3$ to afford the thiazole derivative **2**. Compound **2** is then treated with either aqueous NaOH or KOH to afford **5**. Two possible mechanisms on comparable substrates have been proposed.[2] The mechanisms, using the substrate of primary interest, are shown in Scheme II. One mechanism starts with dehydration of **2** to the corresponding 4-(chloromethyl)thiazole **3** followed by chloride displacement to produce **5**. The other mechanism starts with abstraction of the hydroxyl proton from **2** followed by chloride displacement to afford the spirooxirane **4**. Subsequent proton abstraction from the thiazoline ring of **4** followed by rearrangement would result in the alkoxide of **5**.

Scheme I



Yield claims of 92% by Brown and Newberry[2] for the conversion of a thioamide to the corresponding 4-(hydroxymethyl)thiazole prompted our interest in the evalu-

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0022-3263/92/1957-2869$03.00/0

Scheme II

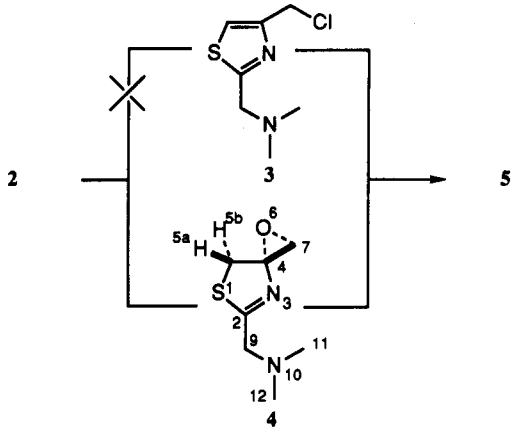

Table I. ^{1}H NMR Spectroscopic Data

compd	solvent	$H_{5a,b}$[a]	$H_{7a,7b}$	$H_{9a,9b}$	$H_{11,12}$[b]
2	toluene	3.22, 3.05 (d, 11.99)	3.67, 3.52 (d, 11.04)	3.10, 3.03 (d, 15.12)	2.03 (s)
5	toluene	6.98 (t, 0.87)	4.79 (s)	3.57 (d, 0.93)	2.09 (s)
4	toluene	2.81, 2.72 (d, 12.87)	3.12, 2.28 (d, 5.05)	3.06 (s)	1.94 (s)

[a] Only one proton for compound 5, H_5. [b] H_{11} and H_{12} consist of three protons each.

ation of this synthetic route. The reaction which produces the epoxide intermediate was indirectly supported by Brown and Newberry after they found no hydroxymethyl product formation when treating analogues of 3 with hydroxide anion. In our efforts to more thoroughly understand the reaction, we set out to find conditions for stable intermediate formation and then characterize the intermediate which was formed. If formation of 5 does proceed through 4, under stabilized conditions, a unique magnetic resonance pattern for 4 might be observed.[3] This made NMR spectroscopy an attractive investigative tool in our efforts to characterize the proposed epoxide intermediate.

It was previously speculated that proton abstraction from the hydroxyl group of 2 would be the initial result of base addition.[2] If correct, this would likely be followed by displacement of the chloride to give the spirooxirane. The following assumptions were considered in our plan to stabilize and characterize the spirooxirane intermediate.

(i) Addition of 2 to base should minimize formation of an intermediate by subjecting the substrate to an excess of base. This would allow immediate proton abstraction from an intermediate resulting in rearrangement to 5.

(ii) The use of a protic or even highly polar solvent might minimize intermediate stabilization by providing a medium for proton exchange.

(iii) Depending on the relative acidities of the hydroxyl proton and the thiazoline ring protons on 2, the reaction temperature and rate of base addition might impact relative conversion rates of 2 to 4 and subsequently 4 to 5. A slow base addition should maximize intermediate formation provided the relative pK_a's are sufficiently different.

(iv) The base stoichiometry should be maintained at less than 1.0 equiv since compound 4 could theoretically be catalytically converted to 5. The resulting alkoxide of 5 would act as the base for reaction propagation.

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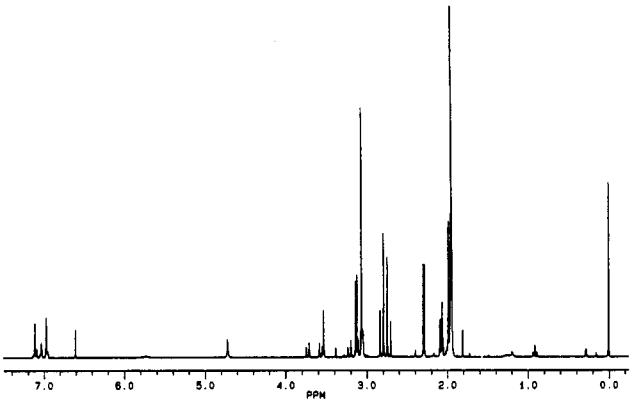

Figure 1. 300.13-MHz ^{1}H NMR spectrum of the optimized reaction mixture.

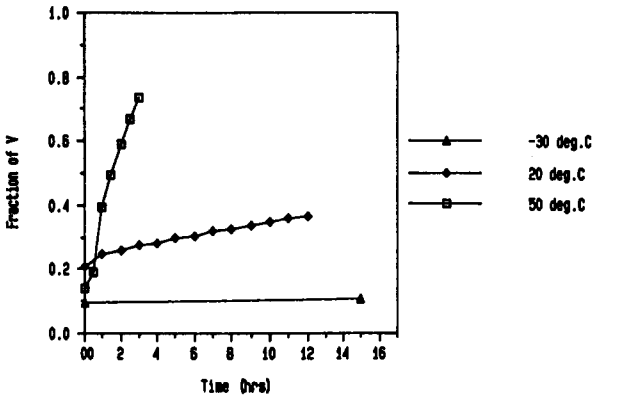

Figure 2. Temperature dependence of the rate of formation of 5.

Methods

Purified substrate 2 was utilized for this study. Benzene-d_6 was used as the initial solvent. Approximately 0.75 equiv of *n*-butyllithium was added to 2 in benzene-d_6 at room temperature. A precipitate (presumably LiCl) immediately formed. Filtration and subsequent evaluation by ^{1}H NMR indicated the substantial presence of a compound other than 2 or 5. Table I gives the ^{1}H NMR resonances for the reaction mixture as well as for compounds 2 and 5. Reaction conditions were further modified in an effort to maximize formation of the unknown compound. Attempts with $NaNH_2$ were unsuccessful, presumably because of slurry transfer difficulties thus resulting in poor reaction rate control. As predicted, the use of more polar solvents such as DMSO-d_6 and acetone-d_6 resulted in depression of the resonances associated with the unknown compound. With methanol-d_4, only 2 and 5 were observed during addition of either hydroxides or methoxides.

The best conversion of 2 to the unknown was obtained with sodium metal. Based on integration in the methyl region of the ^{1}H NMR resonances, the optimum reaction conditions resulted in mixtures of approximately 90% unknown with 5% each of both 2 and 5. Figure 1 shows the ^{1}H NMR spectrum for this reaction mixture. Table II gives the ^{13}C proton-decoupled and DEPT NMR results for the reaction mixture and for compounds 2 and 5. In the aliphatic region of both spectra for the unknown, four major resonances were observed. From the DEPT experiments, the resonance at 45.50 ppm was assigned to a methyl carbon and the other three resonances were assigned to methylene carbons. No resonances in the aromatic region were detected.

Table II. ^{13}C NMR Spectroscopic Data[a]

compd	solvent	$C_{11,12}$	C_9	C_2	C_5	C_4	C_7
2	toluene	45.40 (q)	61.14 (t)	178.78 (s)	39.09 (t)	107.65 (s)	50.13 (t)
5	toluene	45.29 (q)	60.70 (t)	171.02 (s)	115.03 (d)	157.62 (s)	60.73 (t)
4	toluene	45.40 (q)	61.59 (t)	179.24 (s)	33.51 (t)	87.06 (s)	53.54 (t)

[a] q = CH_3, t = CH_2, d = CH, s = C.

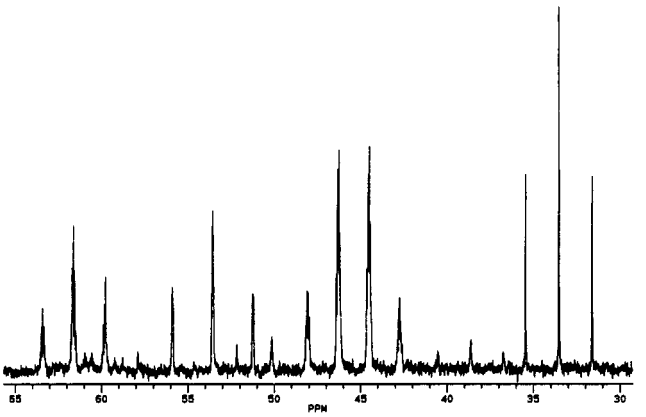

Figure 3. 75.47-MHz proton-coupled ^{13}C NMR spectrum of the aliphatic region of the optimized reaction mixture.

It was observed that over a period of time proton resonance areas associated with **5** spontaneously increased while the other resonances decreased. Because of the potential impact on subsequent lengthy acquisitions needed for some 1D and many 2D NMR experiments, the effects of temperature on this phenomena was studied. The solvent for this study was toluene-d_8 which allowed low-temperature experimentation. Figure 2 graphically shows the percentage of **5** formed over time at three different temperatures.[4] The good stability of the unknown at −30 °C allowed for experiments utilizing much longer acquisiton times. The NMR experiments of interest were the carbon–proton (HETCOR) and proton–proton (COSY) correlated 2D experiments and the ^{13}C gated-decoupled experiment. The HETCOR showed that the proton resonances centered at 3.12 and 2.28 ppm were attached to the same carbon, thus indicating the presence of two substantially nonequivalent protons. The ^{13}C gated-decoupled spectrum confirmed the DEPT NMR assignments of the methyl and methylene carbons. In addition, no doublets were observed. This supports the DEPT experimental results which showed that no aromatic carbons were present. Figure 3 shows the aliphatic region of the coupled carbon spectrum. Coupling information from the COSY and the HETCOR experiments indicated the triplet centered at 33.51 ppm was the methylene carbon in the thiazoline ring and the triplet centered at 61.59 ppm was the methylene carbon adjacent to the dimethylamino moiety. By the process of elimination, the triplet centered at 53.54 ppm was assigned to the methylene carbon of the suspect spirooxirane.

Discussion

The spectral data gives strong evidence for a spirooxirane intermediate in this reaction. The ^1H NMR spectrum shows evidence of three compounds as indicated by the three resolved peaks in the methyl region. Over time it was observed that **5** was formed in the reaction mixture at the expense of the large methyl and its related resonances. This indicated that the reaction mixture did indeed contain an intermediate leading to the formation of **5**. The proton spectrum shows the suspect epoxide methylene to be two doublets with a coupling constant of 5.05 Hz. This relatively small coupling is expected for the epoxide, since similar geminal coupling is observed in the analogous cyclopropane systems.[5] The constrained nature of the epoxide combined with the orthogonal location of the thiazole ring would create drastically different environments for the individual protons on the epoxide ring. The ^{13}C and DEPT NMR spectra show the suspect spirooxirane to have one type of methyl carbon, three methylene carbons, and two quaternary carbons. This also supports the spirooxirane structure. The lack of an aromatic carbon containing one proton eliminates **3** as a potential intermediate. Further evidence for the presence of an epoxide functionality can be seen in the ^{13}C gated-decoupled spectrum. The suspect epoxide methylene carbon has a chemical shift of 53.54 ppm with a coupling constant ($^1J_{CH}$) of 175.9 Hz. This chemical shift and coupling constant are characteristic of epoxides.[6]

Further efforts to support the conclusions included independent synthesis of **3**.[7] The compound is stable only as the dihydrochloride or other salt. However, under dilute conditions the spectra of **3** (as the free amine) were obtained. The proton spectrum does not contain a doublet of doublets as seen in the reaction mixture, and the ^{13}C and DEPT NMR spectra do show the expected thiazole aromatic carbons.

The unique geometry of the suspect spirooxirane allowed for the use of longer range coupling information. NOE experiments were undertaken to see if any interactions could be found. These experiments gave inconclusive results. Information taken from the ^{13}C gated-decoupled spectrum was then evaluated. Since predictions of $^3J_{CH}$ coupling constants based on Karplus-like dihedral angles have been empirically derived,[7] the experimental $^3J_{CH}$ coupling information was studied. On the basis of the spirooxirane structure, $^3J_{CH}$ coupling should be observed for the carbons at positions C_5 and C_7. However, as seen in Figure 3, the thiazoline methylene carbon centered at 33.51 ppm does not exhibit any $^3J_{CH}$ splitting while the epoxide methylene carbon does. This is attributed to the shielding effect of the sulfur atom adjacent to C_5. The $^3J_{CH}$ coupling constants of C_7 to H_{5a} and H_{5b} are 2.65 and 4.58 Hz, respectively. Using these values and the empirically derived equation,[8] the dihedral angles around

(4) The percentages of **5** were based on the integrations of the methylene singlet of **5** at 3.6 ppm (adjacent to the dimethylamino group) and the doublet of suspect **4** at 2.4 ppm (assumed to be one proton of a methylene group). The amount of **2** present in the samples was negligible.

(5) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. In *Spectroscopic Identification of Organic Compounds*, 4th ed.; John Wiley and Sons: New York, 1981; p 209.

(6) (a) Paschal, J. W.; Occolowitz, J. L.; Larsen, S. H.; Boeck, L. D.; Mertz, F. P. *J. Antibiotics* **1989**, *42*(4), 623. (b) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy, High Resolution Methods and Applications in Organic Chemistry and Biochemistry*; VCH: Weinheim, 1987; p 288. (c) Shapiro, M. J. *J. Org. Chem.* **1977**, *42*, 1434. (d) Eliel, E. L.; Pietrusiewicz, K. M. In *Topics in Carbon-13 NMR Spectroscopy*; Levy, G. C., Ed.; John Wiley and Sons: New York, 1979; p 174.

(7) See the experimental section for the synthetic procedure as well as the ^1H NMR spectral data.

(8) Marshall, J. D. In *Carbon–Carbon and Carbon–Proton NMR Couplings: Applications to Organic Stereochemistry and Conformational Analysis*; Verlag Chemie International: Deerfield Beach, 1983.

H_{5a}–C_5–C_4–H_7 and H_{5b}–C_5–C_4–H_7 were calculated to be 55° and 38°, respectively.

The empirically derived values were then compared with those obtained from a molecular model. The model was built using SYBYL.[9] In order to optimize geometry with respect to the dihedral angles around the C_4–C_5 bond, a series of conformers were generated by adjusting the dihedral angle from +40° to −40° around S_1–C_5–C_4–N_3. Initial geometric optimization on the resulting seven conformers was completed with MAXIMIN2. The final geometric optimization was completed using the semiempirical molecular orbital method AM1,[10] under the AMPAC option. All seven conformers converged to the same structure predicting dihedral angles of 30.3° for $H5_a$–C_5–C_4–H_7 and 96.5° for H_{5b}–C_5–C_4–H_7. These angles predict $^3J_{CH}$ coupling constants of 0.90 and 5.15 Hz based on the Karplus-like curve generated from propylene oxide data.

Conclusions

^{1}H NMR spectroscopy was utilized in the search for a proposed intermediate in the synthesis of **5**. Reaction conditions were discovered in which **2** was converted to an unknown that spontaneously transformed to **5**. This tool was also utilized in the optimization of the formation of the unknown to aid in full characterization.

The subsequent spectral data provide substantial evidence that the unknown is the spirooxirane **4**. The ^{13}C NMR data indicated the unknown contained three methylene groups. The 2D NMR COSY and HETCOR experiments indicated that in one of the methylene group the protons (separated by 0.8 ppm) were subjected to significantly different environments. In addition, as seen in Figure 1, protons on another methylene group were separated by 0.1 ppm. This indicated two of the methylene groups were not freely rotating which is consistent with the spirooxirane structure. The ^{13}C gated decoupled experiment showed a $^1J_{CH}$ coupling constant of 175.9 Hz for the methylene carbon bonded to the protons separated by 0.8 ppm. This coupling constant would be expected for the epoxide methylene moiety. Finally, the unique geometry and location of the methylene groups in the speculated spirooxirane allowed for evaluation of the $^3J_{CH}$ coupling constants. An energy-minimized model of the spirooxirane predicted $^3J_{CH}$ coupling constants of 0.90 and 5.15 Hz while the experimental data showed 2.65 and 4.58 Hz. The discrepancy between the predicted and experimental values are not of concern since the model utilizes propylene oxide for the generation of the empirical data. Therefore, the theoretical data are generated from a model which is structurally very different than the experimental system. The comparison, however, did indicate there was consistency with respect to degree of $^3J_{CH}$ splitting and to the approximate magnitude of the splitting generated as a result of dihedral angles. In our opinion, the spectroscopic data provides substantial evidence that the intermediate in the presented reaction is indeed the suspected spirooxirane **4**.

Experimental Section

General. All spectra were recorded on NMR spectrometers with ^{1}H and ^{13}C operating frequencies of 300.13 and 75.47 MHz, respectively. The number of scans needed for acceptable signal-to-noise ratio ranged from 128 to 6800 scans per FID. Chemical shifts are reported in ppm downfield relative to internal TMS. The deuterated solvents were purchased from the Aldrich Chemical Co.

Synthesis. 4-Hydroxy-4-(chloromethyl)-2-[(dimethylamino)methyl]thiazoline (2). A mixture of (dimethylamino)thioacetamide hydrochloride (1) (54.0 g, 350 mmol), 1,3-dichloroacetone (52.0 g, 409 mmol), and $NaHCO_3$ (64.0 g, 762 mmol) in toluene (300 mL) was stirred at 60 °C for 2 h. After the mixture was cooled, filtration afforded a toluene solution of **2**. Precipitation and filtration to afford 55.5 g (76%) of **2** was accomplished by the addition of an equal volume of petroleum ether. Next, 20 g (96 mmol) of **2** was placed in 100 mL of toluene and heated to approximately 60 °C, filtered, and slowly cooled to 10 °C. The resulting precipitate was filtered, washed with petroleum ether, and dried under nitrogen to afford 9.5 g (48%) of recrystallized **2**.

2-[(Dimethylamino)methyl]-4-exomethylenethiazoline Epoxide (4). To a solution of **2** (0.14 g, 0.67 mmol) in toluene-d_8 (5 mL) was added sodium metal (0.015 g, 0.65 mmol) which had been divided into five approximately equal pieces and washed with toluene-d_8. The resulting mixture was stirred under nitrogen for 1 h at 20–25 °C. TMS (one drop) was added, and the mixture was filtered and transferred to NMR tubes for analysis.

4-(Chloromethyl)-2-[(dimethylamino)methyl]thiazole (3). A mixture of (dimethylamino)thioacetamide hydrochloride (1) (25.35 g, 162 mmol), 1,3-dichloroacetone (24.4 g, 192 mmol), and $NaHCO_3$ (32.0 g, 381 mmol) in CH_2Cl_2 (70 mL) was stirred at 20–25 °C for 24 h. The resulting mixture was filtered and the filtrate added to a solution of phosphorus trichloride (12 mL) in CH_2Cl_2 (75 mL). The resulting slurry was filtered and washed with CH_2Cl_2 (100 mL), and the solids were dissolved in water (60 mL). After extracting with CH_2Cl_2, the water layer was vacuum distilled to afford **3** as the dihydrochloride salt (42.14 g).[11]

Approximately 0.2 g of the dihydrochloride salt of **3** was added to saturated $NaHCO_3$ (3 mL) and extracted with toluene-d_8. After separation, the toluene-d_8 layer was dried with $Na_2(SO_4)$ and filtered into an NMR tube. One drop of TMS was added prior to spectroscopic analysis: ^{1}H NMR (toluene-d_8) d 2.04 (6 H, s, CH_3), 3.46 (2 H, s, CH_2), 4.32 (2 H, s, CH_2), 6.66 (1 H, s, CH).

(9) *SYBYL Molecular Modeling System*; Tripos Associates, Inc., St. Louis, MO; Release 5.1, April 1988.

(10) (a) Dewer, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (b) QCPE No. 506, Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, Bloomington, IN. (c) Clark, T. A. In *A Handbook of Computational Chemistry; A Practical Guide to Chemical Structure and Energy Calculations*; John Wiley and Sons: New York, 1985.

(11) This sample was provided by Ms. M. K. Neeb, Eli Lilly and Co., Tippecanoe Laboratories, Lafayette IN.