Gas-Phase Acidities of *cis*- and *trans*-2-*tert*-Butyl-1,3-dithian-5-ol

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The gas-phase acidities (ΔG_{acid}) of *cis*- and *trans*-2-*tert*-butyl-1,3-dithian-5-ol (**1** and **2**, respectively) have been determined to be 354.9 ± 1.2 and 350.2 ± 2.8 kcal/mol, respectively, by using the Cooks' kinetic method and acid−base bracketing in a flowing afterglow-triple quadrupole apparatus. The difference in the acidities of these diastereoisomers is unexpectedly large (4.7 kcal/mol) and significantly greater than that of epimeric 4-methylcyclohexanols ($\Delta\Delta G_{\mathrm{acid}} = 1.1$ kcal/mol). The large difference is due to the unusually low acidity of **1**, which is rationalized by an unfavorable electrostatic repulsion between the oxygen lone pairs of the corresponding axial alkoxide and the ring sulfur lone pairs. This interaction is not present in the conjugate base of **2**, in which the negatively charged group is in an equatorial position. Density functional theory calculations (B3LYP/6-311+G(2d,p)) predict the axial 1,3-dithian-5-oxide ($C_4H_7S_2O^-$) to be higher in energy than the equatorial 1,3-dithian-5-oxide by 6.5 kcal/mol (298 K), in agreement with our hypothesis. The gas-phase acidities of **1** and **2** are predicted by theory (same level as above) to be 365.1 and 356.2 kcal/mol, respectively, corresponding to a $\Delta\Delta G_{\mathrm{acid}}$ of 8.9 kcal/mol. Although there is a marked difference between the theoretical and experimental values of $\Delta\Delta G_{\mathrm{acid}}$, both values point to unusually low gas-phase acidity for **1** relative to its diastereomer.

Introduction

The thermochemical properties of alcohols are of long-standing interest. Several experimental[1−3] and theoretical[4−6] investigations have focused on gas-phase acidities of alcohols to better understand the role that substituents play in the reactivity of alcohols. The intrinsic acidity of an alcohol is ultimately determined by intramolecular steric and electrostatic interactions in conjunction with inductive effects. However, it is particularly difficult to experimentally characterize the intrinsic acidity of an alcohol in solution because of the strong environmental influences that exist for both the alcohol and its conjugate base. The masking of both the intramolecular steric and electrostatic interactions by the solvent is evident in the reversal observed in the gas-phase acidity and basicity trends of alcohols upon going from aqueous solution to the gas phase.[7−9] To probe the intrinsic thermochemical properties of alcohols, it is necessary to examine them in the gas phase where all environment effects, such as solvent, ion-pairing and counterion effects, are absent.

Various methods are available for the measurement of gas-phase acidities. Direct and indirect measurements of equilibrium constants for bimolecular proton transfer reactions usually provide accurate values of gas-phase acidities.[10,11] However, the accuracy of the values may be diminished by a slow approach to equilibrium. In addition, specialized instrumentation, such as pulsed chemical ionization in ion cyclotron resonance mass spectrometers, are often necessary to perform these experiments.[12] The kinetic method, developed by Cooks and coworkers,[13,14] can be implemented on a wide variety of commercial, as well as home-built instruments. This method is a thermokinetic method founded on the rates of competitive dissociation of molecular cluster ions and provides for fast and accurate measurement of gas-phase acidities, as long as certain criteria are met regarding the nature of the functional group involved.[13,14] The method has been successfully applied to the determination of gas-phase proton affinities,[15] basicities, and ionization energies of organic compounds as well as electron affinities of alkyl radicals.[17]

In a recent investigation, a variant of the Cooks method was employed to examine the intrinsic diastereoselectivity of reduction of a series of cyclic ketones by pentacoordinate silicon hydride ions.[18,19] The method relies on differences in the rates of dissociation of diastereomeric dialkoxysiliconates and proton-bound clusters upon collisional activation. In the course of these studies, it was discovered that collision-induced dissociation (CID) of proton-bound clusters of *cis*- and *trans*-2-*tert*-butyl-1,3-dithian-5-oxide with a 2,2,2-trifluoroethanol reference alcohol yields a dramatic reversal of the CID alkoxide product ratio (Figure 1), suggesting relatively large differences in the gas-phase acidities of the corresponding epimeric dithianols. This result was surprising as simple epimeric cycloalkanols, such as *cis*- and *trans*-2-methylcyclohexanol and *cis*- and *trans*-4-methylcyclohexanol, exhibit only a small $\Delta\Delta G_{\mathrm{acid}}$ of approximately 1 kcal/mol. These findings led to the study reported here in which the gas-phase acidities of *cis*- and *trans*-2-*tert*-butyl-1,3-dithian-5-ol (**1** and **2**, respectively) were measured by the use of the kinetic method and acid−base bracketing.

Experimental Section

All gas-phase experiments described in this paper were performed at room temperature in a flowing afterglow triple-quadrupole apparatus[21,22] and a 3-T Fourier transform ion cyclotron mass resonance (FT-ICR) mass spectrometer.[23] The total pressure and flow rate of the helium buffer gas in the 1 m

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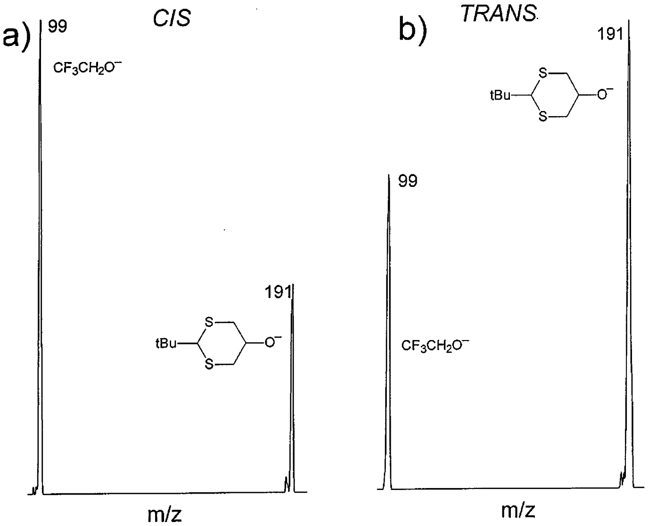


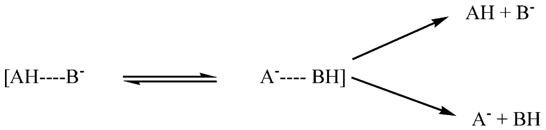
Figure 1. Partial CID spectra measured for (a) $(C_2H_2F_3O^-)$(*cis*-$C_8H_{15}S_2O^-$)H^+ and (b) $(C_2H_2F_3O^-)$(*trans*-$C_8H_{15}S_2O^-$)H^+. $E_{\text{collision}} = 20$ eV (laboratory frame). $P_{\text{argon}} = 250 \times 10^{-6}$ Torr.

× 7.3 cm flow reactor of the flowing afterglow triple-quadrupole apparatus were 0.4 Torr and 200 STP cm^3/s, respectively, with a bulk flow velocity of 9700 cm/s. Fluoride and amide ions were generated by electron ionization of NF_3 and NH_3, respectively. Reagent ions formed in the source were transported by flowing helium through the reactor, where they were allowed to react with the gaseous neutral reagents introduced via leak valves. All reference compounds used in the acid−base bracketing experiments were deprotonated by NH_2^-. The NH_2^- ions generated in the source region were completely quenched by alcohol being deprotonated downstream in the flow reactor. The alkoxide ions of *cis*- and *trans*-2-tert-*butyl*-1,3-dithian-5-ol were generated by deprotonation with F^-. Proton-bound clusters were formed by addition of the alkoxides to alcohols that were introduced downstream. The ions were thermalized to ambient temperature by ca. 10^5 collisions in the helium buffer gas. Negative ions were extracted from the flow reactor through a 0.5 mm orifice in a nose cone and then focused into an EXTREL triple quadrupole analyzer for mass spectrometric analysis.

Collision-induced dissociation experiments were performed in the triple-quadrupole analyzer using argon as target gas. The target pressure in the central, gastight quadrupole collision chamber (Q2) was maintained in the 0.24−0.26 mTorr range, which corresponds to multiple collision conditions.[24] The collision energy was set to 30 eV (laboratory frame). Mass-analyzed ions were detected with an electron multiplier. The voltage bias of the third quadruple (Q3) was adjusted to optimize product ion collection. The Q3 mass resolution and other tuning conditions of the triple quadrupole analyzer were adjusted to achieve maximum reproducibility (±10% absolute) in the quantitative measurement of the CID product yield ratios. Ion intensities were recorded using a digital counter operating at a 10 s gate time. The ion intensity values represent an average of at least 10 replicate measurements. The ion intensity measurements follow a Poisson distribution. Therefore, the uncentainty in each counter measurement was calculated by taking the square root of the intensity. Uncertainties in the yield ratios were determined by using standard error propagation procedures.[25]

The anionic products' assigned structures were verified by allowing synthesized[26] C-5 deuterated *cis*- and *trans*-2-*tert*-butyl-1,3-dithian-5-ol to react with fluoride ions in a 3-T Fourier transform ion cyclotron mass resonance (FT-ICR) mass spectrometer. Fluoride ions were generated via electron ionization

SCHEME 1



(in the negative ion mode) of fluorine gas in the FT-ICR mass spectrometer. The neutral C5-deuterated *cis*- and *trans*-2-tert-*butyl*-1,3-dithian-5-ol were introduced into the analyzer side of the dual cell at a nominal pressure of 2.7×10^{-8} Torr (measured by an ionization gauge). The fluoride ions were transferred from the source into the analyzer side of the dual cell where they were isolated via the application of a series of stored-waveform inverse Fourier transform (SWIFT) pauses on the cell plates. The isolated ions were allowed to react with the C5-deuterated *cis*- or *trans*-2-tert-*butyl*-1,3-dithian-5-ol for a variable period of time. Chirp excitation was employed for detection of the ions. Background reaction spectra, collected in the absence of the fluoride ions, were subtracted from the spectra measured for different reaction times to remove peaks that are not associated with reaction product of fluoride ions. All spectra were collected as 64k data points and subjected to one zero-fill before Fourier transformation. Reactions of the *cis*-alkoxide with C5-deuterated *trans*-2-*tert*-butyl-1,3-dithian-5-ol, and *trans*-alkoxide with C5-deuterated *cis*-2-*tert*-butyl-1,3-dithian-5-ol, were also examined in the FT-ICR. The alkoxide ions (cis and trans) were generated via deprotonation by fluoride ions and transferred into the other cell where they were isolated, and allowed to react with C5-deuterated trans and *cis*-2-*tert*-1,3-dithian-5-ol, respectively.

Density functional theory calculations were performed with Becke's three-parameter hybrid functional using the Lee−Yang−Parr correction functional as implemented in the Gaussian 98 computational package.[33] Optimized geometries, zero-point energies, and 298 K enthalpy corrections were derived from harmonic vibrational frequencies obtained at the B3LYP/6-311+G(2d,p) level of theory (not scaled).

Cis- and *trans*-2-tert-*butyl*-1,3-dithian-5-ol (deuterated and nondeuterated) were synthesized using literature methods.[26] All other reagents were obtained from commercial sources and used as supplied, except for degassing of liquid samples prior to use. Gas purities were as follows: He (99.995%), NF_3 (99%), NH_3 (99%).

Results

To determine the gas-phase acidity (ΔG_{acid}) of an alcohol (HA) via the kinetic method, the relative yield of A^- and B^- obtained from the competitive dissociation of a cluster ion $(AHB)^-$ (Scheme 1) is measured. The logarithm of the yield ratio of ionic products A^- and B^- is proportional to $\Delta\Delta G_{\text{acid}}$ (eq 1), where R is the ideal gas constant and T is the effective temperature (a measure of the average internal energy of the activated cluster ion).[13,14,27−29] The unknown ΔG_{acid} is taken as the intercept value on the abscissa in a plot of the natural logarithm of the ion abundance ratios, ln[dithianoxide$^-$/Ref$^-$] vs the ΔG_{acid} of reference compounds.[29]

$$\ln\left(\frac{I[B^-]}{[A^-]}\right) \approx \frac{\Delta(\Delta G_{\text{acid}})}{RT} \qquad (1)$$

In this work, A^- corresponds to the conjugate base anions formed by deprotonation of **1** and **2** with F^-, and B^- corresponds to the base anions of the reference acids (Table 1). The proton bound clusters $(AHB)^-$ were formed by direct addition of A^-

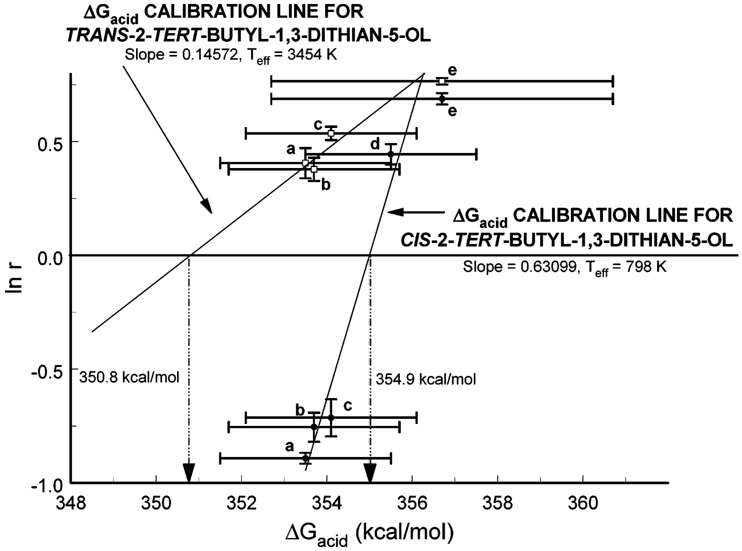


Figure 2. Plot of the natural logarithm of the fragment ion abundance ratios (r) of the proton-bound clusters as a function of the ΔG_{acid} of the reference compounds. Reference compounds: a, 1,1,1-trifluoro-2-methyl-2-propanol; b, 1,1,1-trifluoro-2-propanol; c, 2,2,2-trifluoroethanol; d, 1,5-pentanediol; e, 1,3-difluoro-2-propanol.

TABLE 1: Gas-Phase Acidity of Reference Compounds and Natural Logarithm of CID Product-Ion Production Abundance Ratios of Proton-Bound Clusters of *cis*- and *trans*-2-*tert*-Butyl-1,3-dithian-5-oxide and Reference Compounds

		[dithianoxide$^-$/Ref$^-$]	
reference compound	gas-phase acidity (ΔG_{acid}, kcal/mol)^a	*cis*-2-*tert*-butyl-1,3-dithian-5-oxide	*trans*-2-*tert*-butyl-1,3-dithian-5-oxide
1,3-difluoro-2-propanol	356.7 ± 4.0	1.99 ± 0.05	2.1 ± 0.03
1,5-pentanediol	354.4 ± 2.0	1.56 ± 0.07	∼
2,2,2-trifluoroethanol	354.1 ± 2.0	0.49 ± 0.04	1.71 ± 0.05
1,1,1,trifluoro-2-propanol	353.7 ± 2.0	0.47 ± 0.03	1.46 ± 0.07
1,1,1,-trifluoro-2-methyl-2-propanol	353.5 ± 2.0	0.41 ± 0.01	1.5 ± 0.1

TABLE 2: Acid−Base Bracketing Results for *trans*-2-*tert*-Butyl-1,3-dithian-5-ol^a

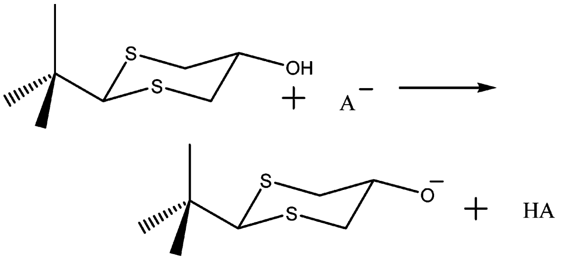
Ref$^-$	ΔG_{acid} of Ref−H (kcal/mol)^a	deprotonation of HY observed?
triethyl siloxide	351.5 ± 2.0	yes
pyrrolide	350.9 ± 2.0	yes
m-(trifluoromethyl)anilide	349.6 ± 2.0	no
$CH_2{=}CH{-}CH{=}CHO$-	348.1 ± 2.0	no

^{a} HY + Ref$^-$ → Y$^-$ + Ref-H, where HY = *trans*-2-*tert*-butyl-1,3-dithian-5-ol.

to a BH reference in the flow reactor, purified using the first quadrupole, and subjected to collisions with an argon target in the gastight collision cell. Finally, the ionic CID fragmentation products were mass-selected with the third quadrupole. Ions exiting the third quadrupole were detected with an electron multiplier.

Two plots obtained using the kinetic method are shown in Figure 2. These plots yield the ΔG_{acid} values of 354.9 ± 1.2 and 350.8 ± 4.9 kcal/mol for **1** and **2**, respectively. The uncertainties associated with these values arise mainly from the uncertainties in the literature values of the reference ΔG_{acid} (Table 1), the major contributor to the total uncertainty being that of 1,3-difluoro-2-propanol ($\Delta G_{acid} = 356.7 \pm 4.0$ kcal/mol). The fact that only four suitable reference bases were found for the determination of the ΔG_{acid} of **2** (CID of the corresponding proton-bound clusters with **2** were the only ones that produced measurable and reliable product intensity ratios) introduces a large uncertainty in the ΔG_{acid} value obtained for **2** relative to **1**, whose ΔG_{acid} determination employed five reference compounds. The low volatility of the problematic reference compound, 1,5-pentanediol, combined with the low volatility of **2** (**1** is more volatile than **2** because of its more spherical geometry relative to **2**), made it impossible to obtain a reasonable signal intensity of the corresponding proton-bound cluster. A third contributor to the uncertainty of the ΔG_{acid} measured for **2** is the lack of suitable reference alcohols whose ΔG_{acid} values are known to lie in the 345−352 kcal/mol range. This means that the calibration curve constructed for **2** is in reality an extrapolation and not the "ideal" interpolation that was achieved in the calibration curve for **1**.

A "reverse" gas-phase acid−base bracketing experiment was carried out to corroborate the value obtained for the ΔG_{acid} of **2**, and to resolve the overlap in the uncertainties of the values obtained for **1** and **2** by kinetic method. In these experiments, reference anions (B^-) were generated by proton abstraction with a strong base (NH_2^-) from the corresponding neutral precursors with known[30] ΔG_{acid}. Compound **2** was subsequently added downstream into the flow reactor and allowed to react with the reference bases (eq 2). The appearance of deprotonated **2** and disappearance of B^- were monitored. The bracketing results are summarized in Table 2. Compound **2** was deprotonated by triethylsiloxide and pyrrolide but not by *meta*-(trifluoromethyl)-anilide or $CH_2{=}CH{-}CH{-}CHO^-$. These results set an upper



(2)

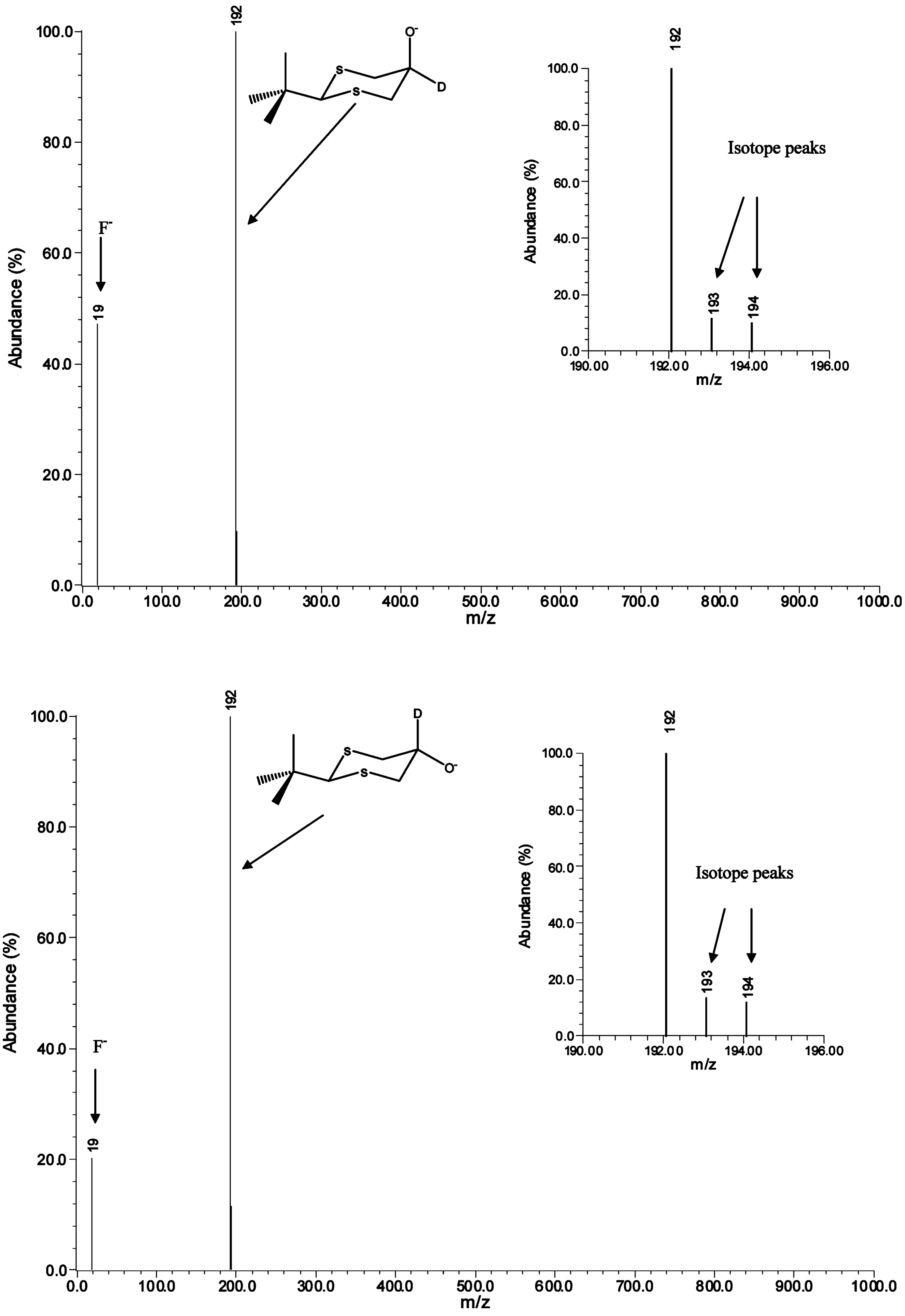


Figure 3. (a) Mass spectra of the reactions of C5-deuterated *cis*-2-*tert*-butyl-1,3-dithian-5-ol (with OH group is in axial position) with fluoride ion. (b) Mass spectra of the reactions of C5-deuterated *trans*-2-*tert*-butyl-1,3-dithian-5-ol (with OH group is in equatorial position) with fluoride ion.

limit for the ΔG_{acid} value of **2** at 350.2 ± 2.8 kcal/mol, in agreement with the value obtained by the kinetic method. The lower uncertainty associated with the ΔG_{acid} value of **2** obtained by the bracketing experiments compared to that obtained by the kinetic method effectively resolves the overlap in the uncertainties of the ΔG_{acid} obtained by the kinetic method for **1** and **2**. Unfortunately, the measurement of a lower limit for the ΔG_{acid} of **2** by a "forward" acid−base bracketing experiment, in which *trans*-2-*tert*-butyl-1,3-dithian-5-oxide is allowed to react with reference acids, could not be carried out. The low volatility of **2** precluded a complete quenching of the primary ion (NH_2^-) coming from the source region. Therefore, it is

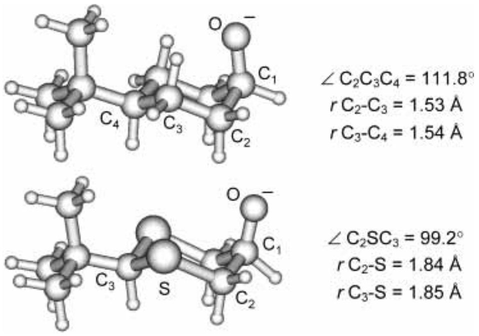
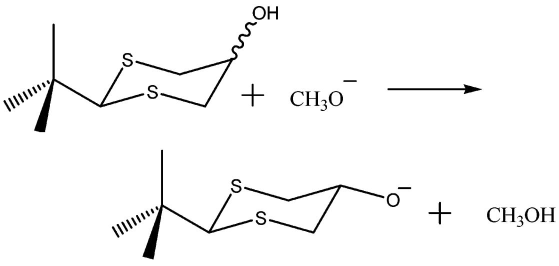


Figure 4. Geometries of *cis*-4-*tert*-butylcyclohexanoxide and *cis*-4-*tert*-butyl-1,3-dithian-5-oxide predicted by density functional theory at the B3LYP/6-311+G(2d,p) level.

unclear whether deprotonation of the reference alcohols was caused by the dithianoxide or by residual NH_2^- in the flow reactor.

Bartmess and co-workers[34] have reported an E2 reaction to be in competition with deprotonation at the C2 position upon the treatment of 1,3-dithiane with an anionic base in an ion cyclotron resonance mass spectrometer. To ensure that the product observed here is due to proton loss from the OH group of the alcohol rather than from C-5 via an E2 elimination reaction, the reactions of C5-deuterated *cis*- and *trans*-2-*tert*-butyl-1,3-dithian-5-ol with F^- were examined in a FT-ICR mass spectrometer. Only proton abstraction was observed, as shown in Figure 3. Further, the nondeuterated *cis*- and *trans*-alkoxides were allowed to react with the labeled *trans*- and *cis*-alcohols, respectively, to provide qualitative evidence in support of their acidity ordering. As expected, the *cis*-alkoxide abstracts a proton from the C5-deuterated *trans*-2-*tert*-butyl-1,3-dithian-5-ol, whereas the *trans*-alkoxide does not abstract a proton from the C5-deutrated *cis*-2-*tert*-butyl-1,3-dithian-5-ol.

The geometries and thermochemical properties of **1** and **2** and their conjugate base anions were examined computationally using density functional theory at the B3LPY/6-311+G(2p,d)+ZPVE level of theory. Predicted absolute energies, enthalpies, and ΔG_{acid} values are shown in Table 3. The predicted ΔG_{acid} values were derived from an isodesmic reaction involving proton transfer from **1** and **2** to CH_3O^- (eq 3), where $\Delta G_{\text{acid}}(\mathbf{X}) = \Delta G_{\text{rxn}} + \Delta G_{\text{acid}}(CH_3OH)$ and **X** is 1 or 2.



(3)

Discussion

The experimental $\Delta\Delta G_{\text{acid}}$ value of 4.1 kcal/mol found for **1** and **2** is substantially greater than those reported by Cooks et al.[20] for the epimeric 2- and 4-methylcyclohexanols. For the two sets of epimers, the *cis*-isomer is a stronger acid ($\Delta G_{\text{acid}} =$ 364.1 ± 0.1 and 365.1 ± 0.1 kcal/mol for *cis*-2-methylcyclohexanol and *cis*-4-methylcyclohexanol, respectively) than the

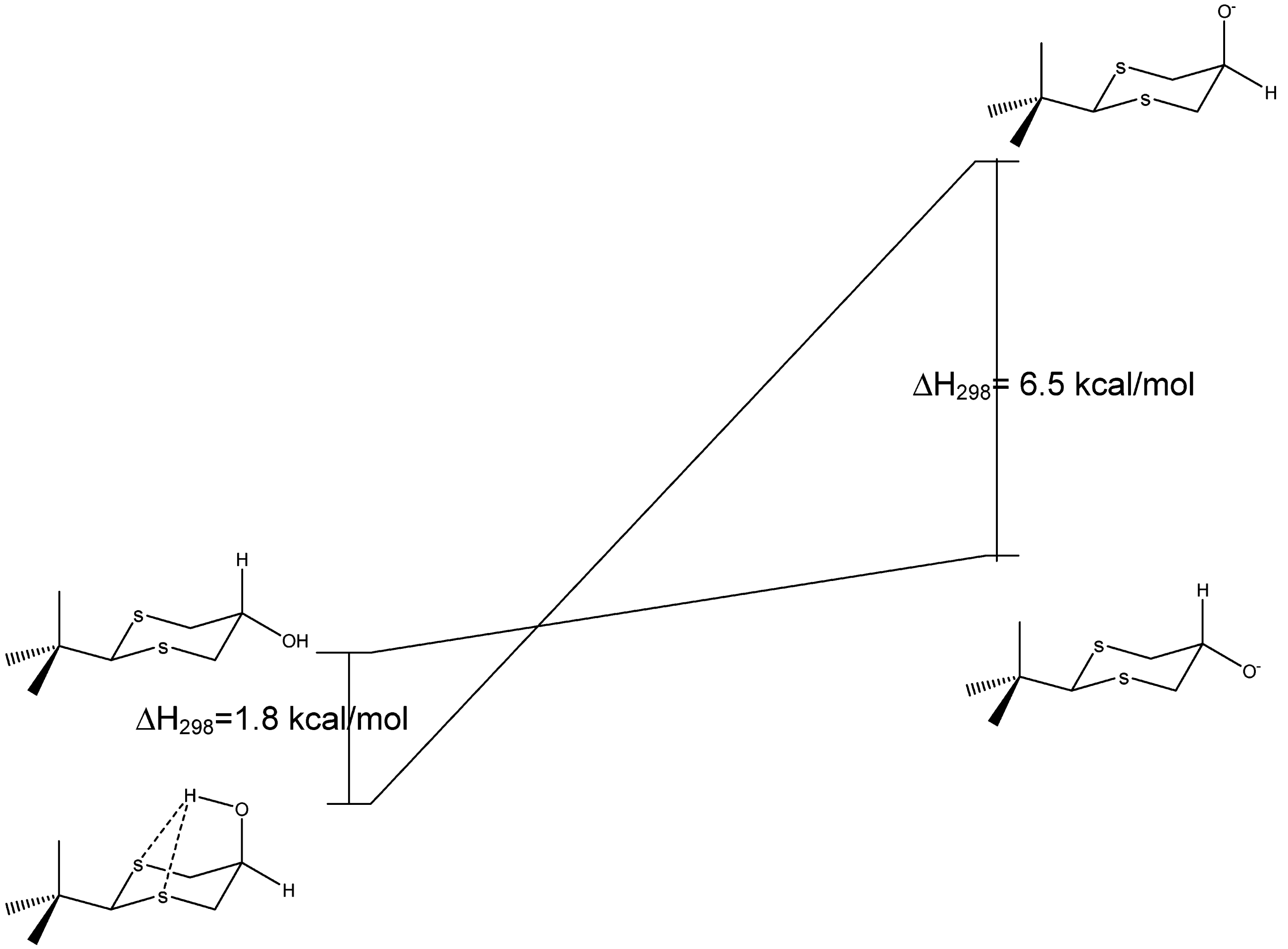


Figure 5. Relative enthalpies of *cis*- and *trans*-2-*tert*-butyl-1,3-dithian-5-ol and corresponding alkoxides.

TABLE 3: Total Energies,[a] E(0K) and H(293K) of Relevant Species Calculated by Theory,[b] as Well as Calculated (Isodesmic) and Experimental Values of ΔG_{acid} for *cis*- and *trans*-2-*tert*-Butyl-1,3-dithian-5-ol

species	E(0K)	H(298K)	ΔH (kcal/mol)	ΔG_{acid}(exp) (kcal/mol)	ΔG_{acid}(calcd) (kcal/mol)
cis-2-*tert*-butyl-1,3-dithian-5-ol	−1186.040200	−1186.026165	−12.83258	354.9 ± 1.2	365.1
trans-2-*tert*-butyl-1,3-dithian-5-ol	−1186.037792	−1186.023365	−21.04041	350.8 ± 4.9	356.2
cis-2-*tert*-butyl-1,3-dithian-5-oxide	−1185.458030	−1185.444173			
trans-2-*tert*-butyl-1,3-dithian-5-oxide	−1185.468422	−1185.454453			
CH_3OH	−115.716552	−115.712247		374.6 ± 2.1[c]	
CH_3O^-	−115.113661	−115.109805			

[a] Energies and enthalpies are in hartrees and were calculated at the B3LYP/6-311+G(2d,p)+ZPVE level of theory. [b] Reference 32. [c] Reference 29.

corresponding *trans*-isomer by approximately one kcal/mol (ΔG_{acid} = 365.1 ± 0.1 and 366.2 ±0.2 kcal/mol for *trans*-2-methylcyclohexanol and *trans*-4-methylcyclohexanol, respectively). The authors attribute the origin of the enhanced acidity of the axial (*cis*-)alcohols to a hyperconjugative stabilization in the corresponding alkoxides.[20,31]

The unusually low gas-phase acidity of **1** relative to **2** is believed to be a result of an unfavorable electrostatic repulsion between the negatively charged axial oxygen in the corresponding alkoxide and the ring sulfur lone pairs. For the alkoxide corresponding to compound **1**, this unfavorable repulsion is further enhanced by its geometrical nature. The long C−S bonds and small C−S−C angle cause the ring to be significantly puckered,[32] thus augmenting the electrostatic repulsion between the axial negative oxygen and the two ring sulfur atoms (Figure 4). This hypothesis is further supported by density functional theory B3LPY/6-311+G(2p,d)+ZPVE), which predicts the alkoxide corresponding to **2** to be more stable than that corresponding to **1** by 6.5 kcal/mol ($\Delta\Delta G_{acid}$ = 8.9 kcal/mol). Moreover, the hyperconjugative stabilization present in *cis*-4-methylcyclohexanol should not be present in **1**, because there are no axial hydrogen atoms at positions 1 and 3 relative to the axial hydroxyl group. In fact, **1** is predicted to be more stable than **2** by 1.8 kcal/mol (Figure 5). This stability may be due to a favorable electrostatic interaction between the ring sulfur lone pairs and the axial hydroxyl group in **1** (the geometry that represents the global energy minimum), an interaction not present in **2**. It is evident that the difference in acidity of the two diastereomeric alcohols is unusually large, in agreement with the large difference between the ΔG_{acid} values of **1** and **2** measured by the Cooks kinetic method and those predicted by density functional theory (Table 3).

Conclusions

The gas-phase acidities of cis and trans-2-*tert*-butyl-1,3-dithian-5-ol (**1** and **2**, respectively) have been measured using the Cooks kinetic method and acid−base bracketing. The ΔG_{acid} values of 354.9 ± 1.2 and 350.2 ± 2.8 kcal/mol for **1** and **2**, respectively, reflect a difference in gas-phase acidity that is unexpectedly large for two species who differ solely in the stereochemistry about a single carbon atom. However, the low gas-phase acidity of **1** relative to **2** is readily rationalized in terms of repulsive electrostatic interaction between the negatively charged oxygen and the ring sulfur lone pairs in the conjugate base of **1**. No evidence was found for stabilization due to hyperconjugation of the axial alkoxide of **1** relative to the alkoxide obtained by deprotonation of **2**. Finally, although the determination of ΔG_{acid} for **1**, and especially, **2**, by kinetic method exhibited a rather poor precision, it is evident that the method can be exquisitely sensitive to the stereochemistry around the center bearing the charge moiety (the negatively charged oxygen atoms in the case of **1** and **2**).

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