DL-**2h**, mp 122–124 °C (lit.[14] mp 127 °C).

The ester DL-**2h** can be saponified to DL-phenylalanine as follows. Sodium hydroxide (6 N, 4.5 mL, 27 mmol, 3 equiv) was added to 2.00 g (8.71 mmol) of DL-**2h** and the mixture was stirred at room temperature for 2 h. The pH of the solution was adjusted to the isoelectric point with 1 N HCl to obtain 1.17 g (81%) of crystalline DL-phenylalanine, mp 268–271 °C dec (lit.[15] mp 271–273 °C dec).

The Schiff base DL-**3h** can be converted directly to the amino acid by refluxing a mixture of DL-**3h** (4.00 g, 11.2 mmol) in 20 mL of 6 N HCl under argon for 6 h. The solution was cooled and washed several times with ether, and the layers were separated. Water and excess HCl were removed from the aqueous layer, distilled water was added, and the aqueous solution was taken to the isoelectric point with aqueous NaOH to yield 1.69 g (91%) of DL-phenylalanine, mp 250–251 °C dec (commercial sample, U.S. Biochemical Corp., mp 258–259 °C dec; mmp 248–249 °C dec).

All three hydrolysis products described above showed one spot on TLC which was identical with an authentic sample.

Optical Rotation Studies. The starting L-phenylalanine ethyl ester hydrochloride (L-**4a**) used in this study was prepared from L-phenylalanine (Aldrich) by the method of Brenner and Huber.[13a] Two grams of L-**4a** was hydrolyzed to the amino acid L-**5a** as described above. Five grams of the amino ester hydrochloride L-**4a** was converted to the Schiff base L-**3h** by the general transimination procedure. Part (2.0 g) of this Schiff base (L-**3h**) was hydrolyzed back to L-phenylalanine ethyl ester hydrochloride (L-**4b**) and another portion (2.0 g) of L-**3h** was hydrolyzed directly to L-phenylalanine (L-**5b**) according to the procedures described previously. All four products were recrystallized (ethanol/ether for the esters L-**4a** and L-**4b** and water/ethanol for the amino acids L-**5a** and L-**5b**) and dried in a vacuum oven [60 °C (1 mmHg)]. Three solutions (~2g/100 mL) of each product were prepared, and the optical rotation of each solution was measured 3 times at a constant temperature of 25 °C. The resulting optical rotations and literature references are listed below. The various reactions as well as the average rotations are presented in Scheme I.

L-**4a**: $[\alpha]^{25}_{\mathrm{D}}$ +35.90°, +35.05°, +35.88°; average $[\alpha]^{25}_{\mathrm{D}}$ +35.6 ± 0.5° (*c* 2, EtOH); lit.[16] $[\alpha]^{20}_{\mathrm{D}}$ +33.5° (EtOH).

L-**4b**: $[\alpha]^{25}_{\mathrm{D}}$ +35.57°, +35.13°, 35.55°; average $[\alpha]^{25}_{\mathrm{D}}$ +35.4 ± 0.2° (*c* 2, EtOH).

L-**5a**: $[\alpha]^{25}_{\mathrm{D}}$ −6.70°, −5.95°, 6.14°; average $[\alpha]^{25}_{\mathrm{D}}$ −6.3 ± 0.4° (*c* 2, 1 N HCl); lit.[17] $[\alpha]^{25}_{\mathrm{D}}$ −4.47° (*c* 1–2, 5 N HCl); lit.[18] $[\alpha]_{\mathrm{D}}$ −7.4° (5 N HCl).

L-**5b**: $[\alpha]^{25}_{\mathrm{D}}$ −6.38°, −6.44°, −6.88°; average $[\alpha]^{25}_{\mathrm{D}}$ −6.6 ± 0.3° (*c* 2, 1 N HCl).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. This work was also supported in part by grants from the Research Corporation, Eli Lilly and Co. and the National Institutes of Health. We thank the North Atlantic Treaty Organization for a Research Grant that has helped support an ongoing collaboration with the laboratory of Professor L. Ghosez at the Université Catholique de Louvain in Louvain-la-Neuve, Belgium. We also thank Professor P. W. Rabideau, W. Bruder, J. Goedde, J. Pfeil, and Dr. D. B. Rusterholz for their assistance and Dr. G. Tarzia for helpful discussions.

Registry No. 1, 1013-88-3; **2a**·HCl, 5680-79-5; **2b**·HCl, 623-33-6; **2c** tosylate, 81477-92-1; **2d** tosylate, 5042-82-0; **2e**·HCl, 27532-96-3; **2f**·HCl, 6011-14-9; DL-**2g**·HCl, 617-27-6; DL-**2h**·HCl, 3182-93-2; L-**2h**·HCl, 3182-93-2; DL-**2i**·HCl, 72651-17-3; DL-**2j**·HCl, 4089-07-0; DL-**2k**·HCl, 40611-00-5; L-**2l**·HCl, 26988-71-6; L-**2m**·HCl, 22888-60-4; **2n**·HCl, 15028-41-8; **2o**·HCl, 2776-60-5; **2p**·HCl, 13031-60-2; **3a**, 81167-39-7; **3b**, 69555-14-2; **3c**, 81477-91-0; **3d**, 81477-93-2; **3e**, 81477-94-3; **3f**, 70591-20-7; DL-**3g**, 69555-16-4; DL-**3h**, 69555-18-6; L-**3h**, 81477-95-4; DL-**3i**, 81477-96-5; L-**3j**, 81477-97-6; DL-**3k**, 81477-98-7; L-**3l**, 81167-36-4; L-**3m**, 81477-99-8; **3n**, 81478-00-4; **3o**, 81478-01-5; **3p**, 81478-02-6; L-**4a**, 3182-93-2; L-**5a**, 17585-69-2.

---

[14] Curtius, T.; Müller, E. *Ber Dtsch. Chem. Ges.* **1904**, *37*, 1261–79.

[15] Marvel, C. S. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, pp 705–8.

[16] "Dictionary of Organic Compounds", 4th ed.; Oxford University Press: New York, **1965**; p 2668.

[17] "Data for Biochemical Research", 2nd ed.; Dawson, R. M. C., Elliott, D. C., Elliott, W. H., Jones, K. M., Eds; Oxford University Press: New York, 1969; p 51.

[18] Greenstein, J. P.; Winitz, M. "Chemistry of the Amino Acids"; Wiley: New York, 1961; p 2156.

Anomalous Hydrogen-Deuterium Exchange of Cyclic β-Keto Sulfides[1]

Jacob J. Guth, Rosalind L. Gross, and Frederick W. Carson*

Department of Chemistry, The American University,
Washington, DC 20016

Received July 24, 1981

The effect of divalent sulfur in enhancing the acidity of protons attached to an adjacent carbon atom has been known for over 40 years.[2] The size of this influence is typically more than 3 orders of magnitude.[3] The work reported here was stimulated by the observation of an apparent anomaly: the protons at C4 display a higher kinetic acidity than those at C2 in 3-thiolanone (4) when hydrogen–deuterium exchange is catalyzed by pyridine. The purpose of this study was to measure and compare the rates of hydrogen–deuterium exchange of 4 and a series of related ketones. An objective was to determine whether the kinetic acidity at C4 is enhanced or that at C2 is suppressed in 4. The former was found to be true.

Experimental Section

General Methods. Melting points are uncorrected. A Varian Model A-60 NMR spectrometer equipped with a Model V-6040 variable-temperature controller was used to obtain analytical 60-MHz ^{1}H NMR spectra of various compounds and to follow the kinetics of deuteration reactions. Chemical shifts are reported with respect to Me_4Si as internal reference. Constant temperature baths were used to control the temperature of samples involved in the longer studies to within ±0.1 °C. Both temperature control systems were adjusted by use of thermometers calibrated against a thermometer that had been tested at the National Bureau of Standards.

Substrates. Commerical 3-pentanone (1) and cyclopentanone (2) were purified by distillation, bp 101–103 °C (lit.[4] bp 102 °C) and bp 130–131 °C (lit.[5] bp 129 °C), respectively.

1-(Methylthio)-2-propanone (3) contained substantial byproducts as evidenced by ^{1}H NMR analysis when prepared by the method of Cain and Cunneen.[6] The following synthesis eliminated that problem. Metallic sodium (34.5 g, 1.50 mol) was dissolved in 700 mL of anhydrous EtOH under nitrogen. Methanethiol (72 g, 1.5 mol) was added slowly and the mixture was allowed to stand for 1 h. This solution was added dropwise with stirring to bromoacetone[7] (206 g, 1.5 mol) in 200 mL of anhydrous EtOH at a rate sufficient to keep the reaction mixture boiling gently under reflux. The mixture was heated to maintain boiling an additional 20 min and was then poured into 200 mL

---

[1] This paper is based, in part, on the M.S. Thesis of R. L. Gross and the Ph.D. Dissertation of J. J. Guth.

[2] Gilman, H.; Webb, F. *J. Am. Chem. Soc.* **1940**, *62*, 897.

[3] Bordwell, F. G.; Van Der Puy, M.; Vanier, N. R., *J. Org. Chem.* **1976**, *41*, 1885.

[4] Timmermans, J.; Hennaut-Roland, M. *J. Chim. Phys.* **1932**, *29*, 548.

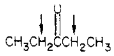
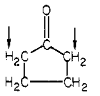
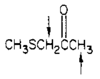
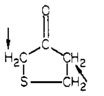
[5] Noller, C. R.; Adams, R. *J. Am. Chem. Soc.* **1926**, *48*, 1080.

[6] Cain, M. H.; Cunneen, J. I. *J. Chem. Soc.* **1962**, 2959.

[7] Levene, P. A. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 88.

0022-3263/82/1947-2666$01.25/0

Table I. Normalized Relative Kinetic Acidities of Cyclic and Acyclic Ketones

compd	position deuterated	normalized rel kinetic acidity[a] series I[b]	normalized rel kinetic acidity[a] series II[c]
1  $CH_3CH_2C(=O)CH_2CH_3$	C2, C4	1.00 ± 0.09	1.0 ± 0.1
2 	C2, C5	6.3 ± 0.2	9. ± 1.
3  $CH_3SCH_2C(=O)CH_3$	C1	3700 ± 300	2900 ± 400
	C3	27. ± 2.	16. ± 1.
4 	C2	1600 ± 700	2100 ± 200
	C4	5400 ± 600	1100 ± 300

[a] Pseudo-first-order rate constants in series I and second-order rate constants in series II were normalized by dividing each rate constant by the number of exchangeable hydrogens at the site being observed. Normalized relative kinetic acidities were calculated by dividing each normalized rate constant by that of 1, the standard for comparison. [b] Pseudo-first-order rate constants for hydrogen–deuterium exchange of samples containing 15% substrate, 25% pyridine, 40% Me_2SO-d_6, and 20% D_2O by weight at 39.5 ± 0.5 °C were obtained as described in the Experimental Section. The pseudo-first-order rate constant measured for 1 was $(1.2 \pm 0.1) \times 10^{-8}$ s^{-1}. [c] Pseudo-first-order rate constants for hydrogen–deuterium exchange of samples containing 0.3–0.5 M substrate buffered with 0.125 M sodium carbonate and 0.125 M sodium metaborate in a solvent consisting of 1:9 v/v Me_2SO-d_6/D_2O at 25.0 ± 0.5 °C were obtained as described in the Experimental Section. Second-order rate constants were calculated by dividing each pseudo-first-order rate constant by the appropriate deuteroxide ion concentration. The second-order rate constant for deuteration of 1 was 0.046 ± 0.005 L mol^{-1} s^{-1}.

of water, which was extracted 5 times with 150-mL portions of ether. The combined ether extracts were extracted with 100 mL of brine, the solvent was removed under vacuum, and the residue was dried with Na_2SO_4. Vacuum distillation gave 15 g (0.10 mol, 6.6%) of 3 as a light-yellow liquid: bp 58–64 °C (2.7 kPa) (lit.[6] bp 153 °C); ^1H NMR (neat) δ 1.80 (s, SCH_3), 2.00 (s, $COCH_3$), 3.05 (s, CH_2).

3-Thiolanone (4) was prepared according to the Buiter[8] modification of the Karrer and Schmid[9] synthesis and was purified by vacuum distillation, bp 50–54 °C (0.4 kPa) [lit.[9] bp 68.5–71.0 °C (1.6 kPa)]; ^1H NMR ($CDCl_3$) δ 2.43–2.77 (m, $COCH_2$), 2.90–3.20 (m, SCH_2), 3.23 (s, SCH_2CO).

Solvents and Buffers for Kinetic Studies. Research Grade deuterated solvents and reagents were purchased from Stohler Isotope Chemicals, Rutherford, NJ, and were used for kinetic studies without further purification. Pyridine was distilled from barium oxide and the fraction boiling at 116 °C (lit.[10] bp 115.2 °C) was used as the base in series I of the kinetic studies of hydrogen–deuterium exchange.

Sodium metaborate and sodium carbonate used to prepare buffers for kinetic measurements in series II were dried as follows. Each was warmed in a flask evacuated to 0.1 Pa for a few minutes with a heat gun. After the system was opened to atmospheric pressure and allowed to cool, sufficient D_2O was added to just dissolve the solid. Then the container was resealed, cooled with liquid nitrogen, and evacuated to 0.1 Pa. The solvent was allowed to evaporate by warming the flask slowly and then heating to dryness with a heat gun. D_2O solutions prepared with these compounds were adjusted to pD values giving conveniently measured rates of hydrogen–deuterium exchange with 38% DCl, employing a Fisher Accumet Model 520 digital pH/ion meter standardized against nondeuterated buffers. PD values were calculated as pD = apparent pH + 0.4.[11]

Final solvent compositions are given in the footnotes to Table I.

Kinetic Studies. Samples were kept in capped 5-mm NMR tubes. Series I samples were maintained at 39.5 ± 0.5 °C, and the temperature was 25.0 ± 0.5 °C in series II. ^1H NMR spectra were recorded at regular intervals over a period of at least 1 half-life.

Data Treatment. Integrated peak areas were used to calculate the fractional deuteration, $(S)/(S)_0$, at each enolizable site. Plots of $\ln (S)_0/(S)$ vs. time were linear. Linear regression analysis was used to obtain the slope of each line, corresponding to a pseudo-first-order rate constant for exchange of a particular type of labile hydrogen with solvent deuterium.

Results

Results of kinetic studies of deuteration of a series of related cyclic and acyclic ketones are compared to those of 1 as a standard in Table I.

Discussion

From Table I it can be seen that C1 of 3 exchanges its hydrogens for deuterium about 3000 times faster than 1 under the conditions used for both series I and II measurements. This value incorporates a statistical correction factor for the greater number of exchangeable hydrogens in 1. Thus, adjacent sulfur powerfully enhances the kinetic acidity of an enolizable group by similar amounts whether the weak base pyridine is used as a catalyst, as in series I, or the strong base deuteroxide is the catalyst in a highly aqueous medium, as in series II. Such an acidification of C–H bonds adjacent to divalent sulfur is to be expected, although the origin of the effect has been the subject of controversy. Recent theoretical and experimental studies have discounted d-orbital participation as an important stabilizing factor. Hyperconjugation and polarizability of the C–S σ bond at the carbanionic site are thought to account for stereochemical and regiochemical aspects of bond acidification, respectively.[12] However, Bordwell and co-workers believe that a conjugative interaction between a phenylthio group and a neighboring carbanion is important in compounds that they studied.[13]

In view of the expected powerful enhancement of the acidity of protons on carbon atoms adjacent to sulfur, it was surprising to find that the pyridine-catalyzed hydrogen–deuterium exchange of 4 was faster at C4 than at C2 in initial observations. Indeed, this result contradicted expectations based upon the fact that acetylation of the enolate of 4 results in 85% substitution at C2 and only 15% substitution at C4,[14] although the differences might arise from kinetic vs. thermodynamic control. Therefore, a systematic series of kinetic studies of hydrogen–deuterium exchange of 4 and related ketones was initiated. It was expected that the results would distinguish between the possibilities of an unusual suppression of the kinetic acidity at C2 or an enhancement at C4 of 4.

The results displayed in Table I demonstrate conclusively that 4 displays enhanced kinetic acidity at C4. The

---

(8) Buiter, F. A.; Sperna, J. H.; Wynberg, H. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1160.

(9) Karrer, P.; Schmid, H. *Helv. Chim. Acta* **1944**, *27*, 116.

(10) McCullough, J. P.; Douslin, D. R.; Messerly, J. F.; Hossenlopp, I. A.; Kincheloe, T. C.; Waddington, G. *J. Am. Chem. Soc.* **1957**, *79*, 4289.

(11) Bender, M. L. *J. Am. Chem. Soc.* **1964**, *86*, 3680.

(12) Borden, W. T.; Davidson, E. R.; Andersen, N. H.; Denniston, A. D.; Epiotis, N. D. *J. Am. Chem. Soc.* **1978**, *100*, 1604 and references cited therein.

(13) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Drucker, G. E.; Gerhold, J.; McCollum, G. J.; Van Der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 326.

(14) Buchi, G.; Degen, P.; Gautschi, F.; Willhalm, B. *J. Org. Chem.* **1971**, *36*, 199.

normalized relative kinetic acidity at C2 of 4 is within the expected range, about one-half that at C1 of 3 and around 2000 times greater than that of C2 and C4 of 1, the standard for comparison. On the other hand, exchange at C4 of 4 can be seen to be more than 3 orders of magnitude faster than that of acyclic 1 and even about 2 powers of 10 greater than that of cyclic 2. The origin of this extraordinary enhancement cannot be assessed unequivocally. The relative exchange rates may or may not parallel equilibrium acidities in these compounds. If they do, then such factors as the gauche effect,[15] s character of the C–H bonds (hybridization),[16] angle strain (I strain), eclipsing (torsional) interactions between vicinal hydrogens, and inductive effects all should be considered.[17] However, these inherent properties often are outweighed by solvation effects[18] and complications may arise from internal return and ion pairing.[19] In view of these uncertainties, attention will be focused on just two features of these systems: torsion and a "1,4-effect".

Contributions of torsion, angle strain, and hybridization of the C–H bonds are difficult to separate in most carbocyclic compounds. Enol or enolate formation in 2 would relieve eclipsing between hydrogens at C2 and C3, but this would be counterbalanced by an increase in eclipsing strain between hydrogens at C3, C4, and C5 due to the attendant conformational restrictions accompanying the change in hybridization at C2. In contrast, 4 affords a system in which eclipsing interactions are present only at C4 and C5. They would promote exchange at C4 since carbanion or enol formation would relieve most of the eclipsing strain. A measure of the energy associated with such torsional interactions may be obtained by comparing the heats of formation of 2-thiolene (12.76 kcal/mol), which has four eclipsed protons, and 3-thiolene (11.31 kcal/mol),[20] which has no eclipsed protons. These data would lead to the prediction of an increased rate of exchange at C4 of 4 arising from four eclipsed protons not paralleled at C2, with no eclipsed protons, if the transition state for isotopic exchange resembles an enol or enolate. Torsional strain comparable to the 1.45 kcal/mol stability difference between the model compounds could account for about 1 order of magnitude of the enhanced kinetic acidity seen at C4 of 4.

An unusual feature brought out in Table I is the fact that exchange at C3 of 3 is 16–27 times faster than that of 1, indicating the existence of a 1,4-interaction between the sulfur atom and the C4 position of 4. A similar high kinetic acidity at C3 of 1-methoxy-2-propanone has been observed in the laboratories of both Hine[21] and Bothner-By.[22] The origin of this "1,4-effect" is unknown and preliminary results indicate that it is even larger in cyclic than in acyclic systems.[23]

In summary, the results reported here demonstrate that the kinetic acidity of C–H bonds at C4 of 4 is about 1000–5000 times higher than those at C2 and C4 of 1. Two factors which reasonably could contribute to this enhanced kinetic acidity are torsional strain between vicinal hydrogens and a 1,4-effect of the heteroatom of unknown origin, each of which might contribute an order of magnitude to the rate enhancement. However, lack of knowledge of the structure of the transition state in these exchanges makes these suggestions speculative. It is predicted that, in general, five-membered-ring heterocyclic enols or enolates having sp^2 hybridization at C3 and C4 and sp^3 hybridization at C2 and C5 will be formed ten to 100 times faster than the corresponding isomers having sp^2 hybridization at C2 and C3 and sp^3 hybridization at C4 and C5. Further studies to test this hypothesis are in progress.

Acknowledgment. Partial support of this work through a grant from the Brown-Hazen Fund of the Research Corporation is acknowledged with gratitude. Additional assistance was provided by a Faculty Summer Research Grant to F.W.C. and a Graduate Student Research Fund grant to J.J.G. from The American University.

Registry No. 1, 96-22-0; 2, 120-92-3; 3, 14109-72-9; 4, 1003-04-9; methanethiol, 74-93-1; bromoacetone, 598-31-2.

---

[15] Epiotis, N. D.; Yates, R. L.; Bernardi, F.; Wolfe, S. *J. Am. Chem. Soc.* **1976**, *98*, 5435 and references cited therein.

[16] Schechter, H.; Cullis, M. J.; Dessy, R. E.; Okuzumi, Y.; Chen, A. *J. Am. Chem. Soc.* **1962**, *84*, 2905.

[17] Abad, G. A.; Jindal, S. P.; Tidwell, T. T. *J. Am. Chem. Soc.* **1973**, *95*, 6326.

[18] Pross, A.; DeFrees, D. J.; Levi, B. A.; Pollack, S. K.; Radom, L.; Hehre, W. J. *J. Org. Chem.* **1981**, *46*, 1693.

[19] Bordwell, F. G.; Matthews, W. S.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 442.

[20] Davies, J. V.; Sunner, S. *Acta Chem. Scand.* **1962**, *16*, 1870.

[21] Hine, J.; Hampton, K. G.; Menon, B. C. *J. Am. Chem. Soc.* **1967**, *89*, 2664.

[22] Bothner-By, A. A.; Sun, C. *J. Org. Chem.* **1967**, *32*, 492.

[23] J. J. Guth, unpublished observations.

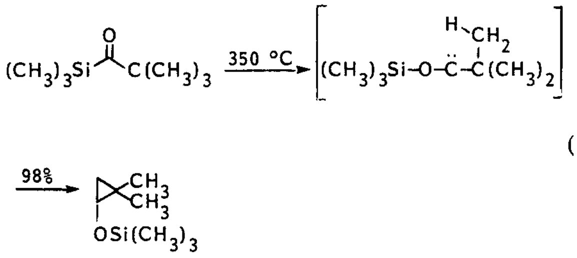
Thermal and Photochemical Rearrangement of (*o*-Tolylcarbonyl)trimethylsilane. A 1,5-Shift of a Trimethylsilyl Group from Oxygen to Carbon

Chuan Shih and John S. Swenton*

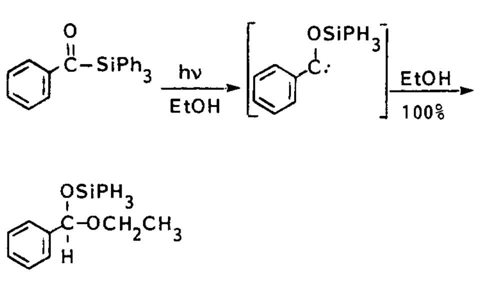
Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received December 11, 1981

The pioneering studies of Brook and co-workers have established that siloxycarbenes are available in high yield from acylsilanes by either thermal[1] or photochemical activation[2,3] as illustrated below (eq 1 and 2). Of special interest to us was the high-yield insertion of the thermally generated siloxycarbene into carbon–hydrogen bonds. If



(1)



(2)

---

[1] Bassindale, A. R.; Brook A. G.; Harris, J. *J. Organomet. Chem.* **1975**, *90*, C6–C8.

[2] Duff, J. M.; Brook, A. G. *Can. J. Chem.* **1973**, *51*, 2869–2883.

[3] For recent mechanistic studies, see: Bourgue, R. A.; Daus, P. D.; Dalton, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 697–699, 699–700.