Stirring was continued for another 30 minutes and the precipitates were collected, dried, and recrystallized from ethanol or other suitable solvents.

General Procedure B.—Some of the dyes were prepared by condensation of the acylacetanylide with *p*-nitroso-N,N-dialkylaniline in the same fashion as the procedure of De Hoffmann, *et al.*[11] This procedure was suitable for the components that were unreactive toward oxidized *p*-amino-N,N-dialkylaniline although very cautious purification of the product was necessary in order to avoid contamination with azomethine N-oxide.

Compound **24** did not crystallize from the reaction mixture and was purified by repeated thin layer chromatography on silica gel using 1:4 methanol–benzene mixture. The acetone extract was directly used for the measurement.

Table III lists the melting points and nitrogen analyses of the dyes. Further structural confirmation was given by comparison of the infrared spectra with that of authentic **23** reported by Brown, *et al.*[9]

Most of the benzoylacetanilides were already reported by these authors, and unreported members were prepared in an analogous way.

Registry No.—**1,** 4754-85-2; **2,** 19650-46-5; **3,** 19650-47-6; **4,** 19755-72-7; **5,** 19779-37-4; **6,** 19755-73-8; **7,** 19755-74-9; **8,** 19755-79-4; **9,** 19755-80-7; **10,** 19650-48-7; **11,** 19755-82-9; **12,** 19755-83-0; **13,** 19755-84-1; **14,** 19755-85-2; **15,** 19779-38-5; **16,** 19650-49-8; **17,** 19755-87-4; **18,** 19755-88-5; **19,** 19755-89-6; **20,** 19759-05-8; **21,** 19759-06-9; **22,** 4754-88-5.

TABLE III

MELTING POINTS, SYNTHETIC PROCEDURES, AND ANALYSES OF DYES

Compd no.	Mp, °C	Synthetic procedure	N analysis, %	
			Calcd	Found
1	209	A	10.52	10.38
2	162	A	9.78	10.07
3	192	A	9.66	9.72
4	118	A	8.99	9.14
5	147	A	8.79	8.63
6	149	A	9.78	9.72
7	157	B	9.48	9.51
8	183	B	9.84	9.82
9	203	A	13.52	13.90
10	131	A	9.78	9.53
11	162	A	10.16	10.09
12	182	A	10.16	10.03
13	220	A	10.06	10.17
14	114	A	9.66	9.43
15	139	A	12.61	12.27
16	144	A	9.74	9.79
17	171	A	10.16	10.10
18	207	A	10.06	10.16
19	182	A	9.66	9.55
20	180	B	9.44	9.52
21	119	A	11.07	11.03
22	155	A	10.11	10.19

Acknowledgment.—The author wishes to thank Professor Y. Yukawa and Dr. Victor P. Vitullo for helpful discussions and comments. The author also extends his gratitude to Dr. K. Hirayama for advice in preparing the manuscript.

(11) E. De Hoffmann and A. Bruylants, *Bull. Soc. Chim. Belg.*, **74**, 609 (1965).

The Conformational Preferences of Sulfur and Oxygen in Hemithioketals[1]

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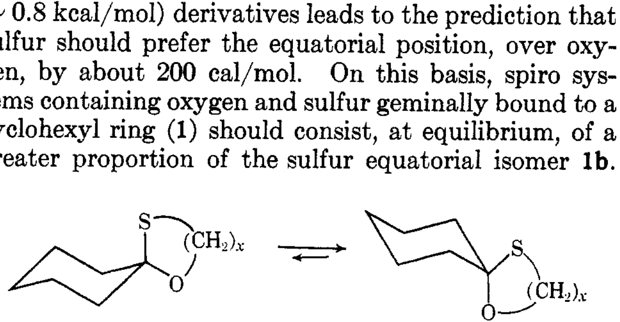
Both second-order catalytic rate constants and isomer ratios at equilibrium for boron trifluoride catalyzed interconversion of the equatorial oxygen and sulfur ethylene hemithioketals of 3,3,5-trimethylcyclohexanone are independent of catalyst concentration in the range of 0.016–0.095 M BF_3. Thus no catalyst complex with the hemithioketal forms to a significant extent and the equilibrium constant of 0.285 ± 0.005 favoring the equatorial oxygen species is a true measure of conformational preference in the hemithioketal.

The early conformational analysis studies of divalent sulfur attached to cyclohexyl systems were performed by Chiurdoglu and coworkers.[3] Subsequent studies by Eliel and coworkers,[4,5] using nuclear magnetic resonance suggested the opposite; values of 0.8 kcal/mol for SC_6H_5, 0.7 kcal/mol for SCH_3, and 0.9 kcal/mol for SH were found. Thus, the authors concluded that the nature of the substituent on sulfur (C_6H_5, CH_3, or H) appeared to have little effect on its conformational preference, which was for the equatorial position. Earlier studies on oxygen derivatives had given similar results.

A comparison of the conformational preferences of oxygen ($-\Delta G_{av} \sim 0.6$ kcal/mol) and sulfur ($-\Delta G_{av} \sim 0.8$ kcal/mol) derivatives leads to the prediction that sulfur should prefer the equatorial position, over oxygen, by about 200 cal/mol. On this basis, spiro systems containing oxygen and sulfur geminally bound to a cyclohexyl ring (**1**) should consist, at equilibrium, of a greater proportion of the sulfur equatorial isomer **1b**.



1a **1b**

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(1) This research was supported by the University of Kansas Research Fund. Further details may be found in M.S. Thesis in Medicinal Chemistry of H.-K. Lee, The University of Kansas, 1967.

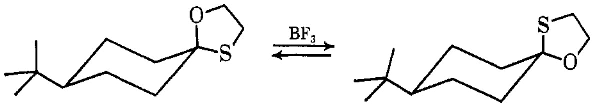
(2) Holders of Research Career Development Awards of the National Cancer Institute (M.P.M.) 1K3-CA-10,739 and the National Institute of General Medical Sciences (R.L.S.) 1-K4-GM-10,913.

(3) G. Chiurdoglu, J. Reisse, and M. VanderStichelen Rogier, *Chem. Ind.* (London), 1874 (1961). Interpretation of the infrared and Raman spectra of cyclohexanethiol resulted in the assignment of a conformational free-energy difference ($-\Delta G \equiv G_{ax} - G_{eq}$) of −0.4 kcal/mole to the SH group, a remarkable preference for the axial position.

(4) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(5) (a) E. L. Eliel and M. H. Gianni, *Tetrahedron Letters*, 97 (1962); (b) E. L. Eliel and B. P. Thill, *Chem. Ind.* (London), 88 (1963).

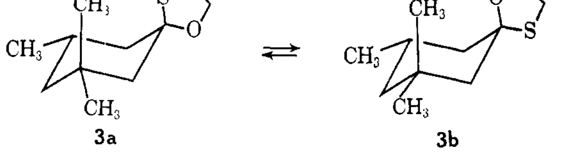
This assumes no strain or compression of the cyclohexyl ring imposed by the oxythio ring. Conformational equilibration of such compounds with five-membered heterocyclic rings ($x = 2$ in **1**) has, in fact, shown oxygen to be preferred over sulfur in the equatorial position. Eliel and coworkers[6] equilibrated the ethylene hemithioketals of 4-*t*-butylcyclohexanone (**2**) and found 58% of **2b** at equilibrium ($-\Delta G = 0.4$ kcal/mol for sulfur if $-\Delta G \cong 0.6$ kcal/mol is assumed for oxygen), if a catalytic quantity of boron trifluoride etherate was employed, whereas equal amounts of **2a** and **2b** resulted from use of excess catalyst. Additional studies[7] with boron trifluoride etherate catalyst at 34° in ether revealed the equilibrium mixtures of the ethylene hemithioketals of 3-methylcyclohexanone, 3,3,3-trimethylcyclohexanone, and 3-*t*-butylcyclohexanone to consist of 76–79% of the equatorial oxygen isomer ($-\Delta G \cong -0.2$ kcal/mole for sulfur relative to 0.6 kcal/mole for oxygen). At 80° (*p*-toluenesulfonic acid catalyst in benzene), the equatorial oxygen isomer constituted 80% of the equilibrium mixture for these compounds.



2a **2b**

In contrast to the above results, the trimethylene hemithioketal of 4-*t*-butylcyclohexanone yields, after equilibration, with boron trifluoride etherate catalyst at 34° in ether, 55% of the equatorial sulfur isomer[8] ($-\Delta G \cong 0.8$ kcal/mole for sulfur relative to 0.6 for oxygen), comparing favorably with the conformational free-energy values for sulfur derived from nmr studies. The conclusion was drawn that the six-membered ring of the trimethylene hemithioketal produced a strain-free system, which reflected the true conformational free-energy differences for sulfur and oxygen. The five-membered ring of the ethylene hemithioketal, however, bends the axial ring member away from the interfering 3-axial substituents; the outward displacement of the sulfur exceeds that for the oxygen, for the same angle deformation, because the carbon–sulfur bond is longer ("leverage effect[8]"). Thus the sulfur comes relatively to prefer the axial position.

It is nevertheless possible that the apparent preference of oxygen for the equatorial position in the ethylene hemithioketals might result from extensive complexation with the catalyst.[9] To establish whether this is so, we decided to examine the kinetics and apparent equilibrium isomer composition of the ethylene hemithioketals of 3,3,5-trimethylcyclohexanone (**3**) in ether, as a function of catalyst concentration.



3a **3b**

Results

Kinetics.—The conversion of pure **3a** into the equilibrium mixture of **3a** and **3b** in ether solution at 34.6°, as followed by glpc analysis, proceeded according to a simple first-order kinetic law within any given run, yielding the rate constants shown in Table I for various concentrations of boron trifluoride catalyst. These data are accurately described by eq 1, showing the reactions to be first order in catalyst throughout this concentration range. The small intercept presumably corresponds to an uncatalyzed reaction or to catalysis by adventitious impurities.

TABLE I

RATE AND EQUILIBRIUM CONSTANTS FOR CONFORMATIONAL EQUILIBRATION OF 0.159 M **3** IN ETHER AT 34.6 ± 0.1°, CATALYZED BY BORON TRIFLUORIDE

$[BF_3]$, M	[**3**]/$[BF_3]$	k_{obsd}, hr^{-1}	K_{app}
0.016	10.0	0.063	0.288
0.032	5.0	0.139	0.276
0.048	3.3	0.198	0.284
0.064	2.5	0.246	0.289
0.079	2.0	0.337	0.291
0.095	1.7	0.347	0.290

$$k_{obsd}\ (\text{sec}^{-1}) = (4.2 \pm 3.9) \times 10^{-6} + (1.03 \pm 0.06) \times 10^{-3}[BF_3] \quad (1)$$

Equilibrium.—The apparent conformational equilibrium constant, $K_{app} = [\mathbf{3b}/\mathbf{3a}]$, is shown in Table I as a function of boron trifluoride concentration. A least-squares fit of these data (as a linear function) yields eq 2, showing K_{app} to be, within experimental error, independent of catalyst concentration. The true equilibrium constant is thus $K_c = 0.285 \pm 0.005$.

$$K_{app} = (0.285 \pm 0.005) + (0.001 \pm 0.008)[BF_3] \quad (2)$$

From this value, which is equal to the ratio of forward and reverse rate constants and the catalytic constant (eq 1) for boron trifluoride, which equals their sum, we calculate $k_{for} = (2.3 \pm 0.8) \times 10^{-4}\ M^{-1}\ \text{sec}^{-1}$ and $k_{rev} = (8.0 \pm 0.5) \times 10^{-4}\ M^{-1}\ \text{sec}^{-1}$.

Discussion

It is in principle possible that either **3a** or **3b** could complex with boron trifluoride and that the latter could bind either to sulfur or to oxygen. All of these possibilities may be considered by defining four complex-formation constants K_a^o, K_a^s, K_b^o and K_b^s where the subscript identifies the isomer (**3a** or **3b**) and the superscript the binding site. The apparent equilibrium constant is then given, in the most general form, by eq 3. Our observation is that K_{app} does not change as the boron trifluoride concentration is varied. This means that either (a) all the complexation constants in eq 3 are small enough to contribute negligibly to K_{app} (*i.e.*, no complexes form under these conditions), (b) all the complexation constants are equal in eq 3 (*i.e.*, all com-

$$K_{app} = K_c \frac{1 + K_b^{\circ}\ [BF_3] + K_b^{\circ}\ [BF_3]}{1 + K_a^{s}\ [BF_3] + K_a^{s}\ [BF_3]} \quad (3)$$

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[6] (a) E. L. Eliel and L. A. Pilato, *Tetrahedron Letters*, 103 (1962); (b) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Am. Chem. Soc.*, **84**, 2377 (1962).

[7] M. P. Mertes, *J. Org. Chem.*, **28**, 2320 (1963).

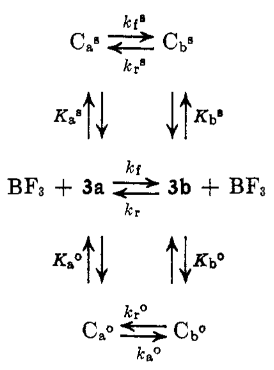
[8] (a) E. L. Eliel, E. W. Della, and M. Rogić, *ibid.*, **30**, 855 (1965); (b) a similar argument for the oxirane ring has been made by R. G. Carlson and N. S. Behn, *Chem. Commun.*, 339 (1968).

[9] (a) E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957); (b) E. L. Eliel and M. Renick, *ibid.*, **82**, 1367 (1960).

plexes are of equal stability), or (c) some complexation constants may be negligible and others equal (*e.g.*, K_a^s and K_b^s might be negligible if the Lewis acid prefers oxygen to sulfur, while K_a° and K_b° might be equal if the presence of the BF_3 causes no change in the conformational preference of oxygen).

The simple first-order dependence of the rate of equilibration on boron trifluoride gives less ambiguous information about complexation. Scheme I shows a highly general mechanistic formulation for boron trifluoride catalyzed interconversion of **3a** and **3b**, either directly (*via* the k_f and k_r route) or through the various possible complexes, denoted by C_a^s, C_a°, C_b^s, and C_b° with the superscript again indicating the site of binding and the subscript indicating the isomer involved. For this scheme the observed, pseudo-first-order rate constants are given by eq 4. No assumption is made as to whether complexes are reactive or unreactive; unreactive complexes will simply have zero rate constants associated with them. But if *any* of the complexation equilibria were nonnegligible, the $[BF_3]$ term in the denominator of eq 4 would lead to a less than first-order dependence on boron trifluoride. Such is not found, which unambiguously excludes significant complexation under these conditions.

Scheme I



$$k_{\text{obsd}} = [BF_3] \times \left\{ \frac{k_f^s K_a^s + k_f^\circ K_a^\circ + k_f}{1 + (K_a^s + K_a^\circ)[BF_3]} + \frac{k_r^s K_b^s + k_r^\circ K_b^\circ + k_r}{1 + (K_b^s + K_b^\circ)[BF_3]} \right\} \quad (4)$$

From $K_c = 0.285 \pm 0.005$, we calculate $\Delta G^\circ = G_{3b} - G_{3a} = 0.77 \pm 0.1$ kcal/mole, corresponding to a value of $-\Delta G$ for sulfur of -0.2 kcal/mole relative to 0.6 for oxygen in the five-membered hemithioketal ring of cyclohexanones. We conclude that no effect of catalyst is responsible for this preference of oxygen over sulfur for the equatorial position.

Experimental Section

The ethylene hemithioketal of 3,3,5-trimethylcyclohexanone was prepared as described[7] and the isomers were separated on alumina by elution with petroleum ether (30–60°). The nmr ($CDCl_3$) of the first isomer collected showed triplets centered at δ 3.00 (axial $S{-}CH_2$) and 4.17 (equatorial $O{-}CH_2$). The second isomer showed the corresponding triplets at δ 3.05 (equatorial $S{-}CH_2$) and 4.12 (axial $O{-}CH_2$); corresponding shifts are reported for similar systems.[6]

Equilibrations and Kinetic Studies.—Solutions (0.159 *M*) of either pure isomer or a mixture of isomers of the ethylene hemithioketal of 3,3,5-trimethylcyclohexanone containing freshly distilled boron trifluoride etherate in varying concentrations (0.016, 0.032, 0.048, 0.064, 0.079, and 0.095 *M*) were maintained at 34.6 ± 0.1° by immersion in a constant temperature bath. Portions for analysis (1.5 ml) were withdrawn and immediately shaken with 1 ml of 0.1 *N* sodium hydroxide. Gas chromatographic analysis using 10% diethylene glycol adipate on Firebrick gave optimum separation of the isomers. The peak areas were estimated using a disk integrator and assuming equal sensitivities for the two isomers. Rate constants were obtained from semilogarithmic plots of fraction of reaction *vs.* time.

Registry No.—**3a,** 19765-68-5; **3b,** 19765-69-6.