Thermodynamic Stability of β-Chloro-, β-Phenylthio-, and β-Phenylamino-Substituted α,β- and β,γ-Unsaturated Ketones

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Synopsis. Acid-catalyzed chemical equilibration studies on the titled compounds have been carried out. The β,γ-isomers are highly favored at equilibrium in the cases of β-chloro- and β-phenylthio-substituted ketones. Hydrogen-bonding between carbonyl oxygen and sulfonium or amine proton stabilizes the α,β-unsaturated form.

The relative stabilities of the α,β- and β,γ-unsaturated carbonyl compounds have been studied extensively by Kon, Linstead, and co-workers.[1] The equilibration is strongly affected by substituents located on the three-carbon propenyl chain, and the following generalizations emerged: (1) If the γ-positions of unsaturated carbonyl compounds are unsubstituted, equilibria between α,β- and β,γ-unsaturated isomers very strongly favor the conjugated one. (2) Substitution of alkyl groups, particularly methyl, at the γ-position increases the stability of the β,γ-isomers. (3) Introduction of an alkyl group, particularly methyl, at the α-position favors the α,β-isomer. (4) In contrast, the equilibria are not sensitive to β-alkyl substitution. The point of acid-catalyzed equilibrium in 5-methyl-4- and -5-hepten-3-one was reported to be 58% α,β- and 42% β,γ-isomers.[2] We previously reported that chloro substitution at the β-position remarkably shifted the equilibrium toward the β,γ-unsaturated form in the triphenylphosphine–carbon tetrachloride-catalyzed equilibrium; this fact would not have been expected on the basis of earlier analyses.[3] Regarding the effect of heteroatom substituents at the β-position, Rhoads and co-workers[4] and Taskinen and Mukkala[5] have reported that the introduction of a methoxyl group at the β-position strongly shifts the equilibrium towards the β,γ-unsaturated isomers. In this paper we report on the contributions of chloro, thio, and amino groups as the β-heteroatom substituents on the acid-catalyzed equilibration of the propenyl ketone system.

Results and Discussion

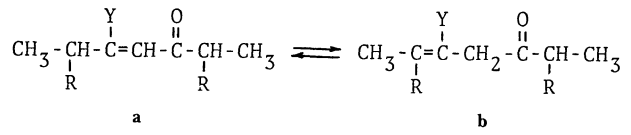
As the β-heteroatom-substituted propenyl ketone systems we employed 5-chloro-, 5-phenylthio-, and 5-phenylamino-4- or -5-hepten-3-one and their 2,6-dimethyl substituted homologues. These unsaturated ketones were isomerized using trifluoroacetic acid as the catalyst in chloroform-*d*. The progress of a given reaction was monitored by ^{1}H NMR spectroscopy. These isomers were easily distinguished by their spectra, the α,β-unsaturated isomers showing an α-vinyl proton at δ 5.1—6.5 and the β,γ-unsaturated isomers showing α-methylene protons at δ 3.2—3.6. The results are summarized in Table 1.

The points of equilibrium in β-chloro ketones **1a** and **1b** were 90 and 95% of the β,γ-unsaturated form (**1b**), respectively; these points were considerably nearer the β,γ-unsaturated end than the value (85% β,γ-) found with a triphenylphosphine–carbon tetrachloride catalyst. Since the point of equilibrium was too close to the β,γ-unsaturated end, γ-methyl substitution did not show any clear influence on the equilibrium (**2a** and **2b**).

Table 1. Tautomeric Equilibrations of β-Substituted α,β- and β,γ-Unsaturated Ketones

Run	Starting materials		Equilibration conditions			Equilibrium composition (a:b)
		Y	Cat./Subst.	Temp/°C	Time/h	
1	**1a**	Cl	1.08	50	64	10:90
2	**1b**	Cl	0.98	50	392	5:95
3	**2a**	Cl	0.98	50	338	8:92
4	**2b**	Cl	1.04	50	36	10:90
5	**3a**	PhS	1.06	rt[a]	335	88:12
6	**3b**	PhS	0.96	rt	359	88:12
7	**3a**	PhS	0.48	rt	480	84:16
8	**3b**	PhS	0.62	rt	480	82:18
9	**3a**	PhS	0.29	50	106	66:34
10	**3b**	PhS	0.25	50	323	65:35
11	**4a**	PhS	1.17	rt	50	19:81
12	**4b**	PhS	1.07	rt	50	18:82
13	**4a**	PhS	0.52	50	27	8:92
14	**4b**	PhS	0.50	50	45	4:96
15	**4a**	PhS	0.22	50	84	5:95
16	**4b**	PhS	0.28	50	84	4:96
17	**5a**	PhNH	1.13	50	—	100: 0
18	**6a**	PhNH	1.07	50	—	100: 0

a) Room temperature (20—25 °C).



a b

1. R = H, Y = Cl
2. R = CH_3, Y = Cl
3. R = H, Y = SC_6H_5
4. R = CH_3, Y = SC_6H_5
5. R = H, Y = NHC_6H_5
6. R = CH_3, Y = NHC_6H_5

Scheme 1.

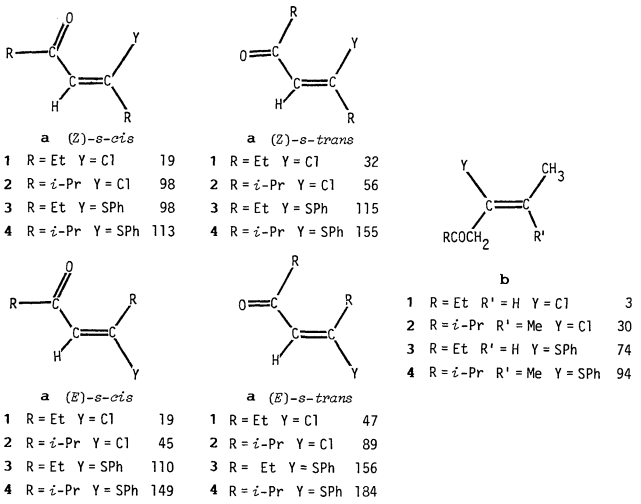


Fig. 1. MMP calculations for each isomer of **1**, **2**, **3**, and **4**. MMP steric energies are given in kJ mol^{-1}.

In considering these results we tried to calculate the molecular mechanic energies (MME) using the CHEM-X MMP program[6] for each conformation as a qualitative indicator of the stabilities. The lowest energy for each conformation is depicted in Fig. 1.

In the (*E*)-*s*-trans conformation of an α,β-unsaturated ketone, a large steric repulsion between the methyl groups adjacent to the olefinic linkage and the acyl group is expected. Such steric repulsion would be rather small in the (*Z*)-*s*-cis conformation, but repulsive cis dipole–dipole interaction between the two polar functions, chlorine and carbonyl, was expected to be quite large. These steric and dipole–dipole interactions are relieved in the β,γ-unsaturated isomer. Thus, the β,γ-unsaturated isomer is favored in the equilibrium. The MME data of each conformation also support these considerations.

In the case of β-phenylthio-substituted unsaturated ketones, the amount of acid catalyst strongly influenced the point of equilibrium (Runs 5—10 and 11—16). The equilibrium between the α,β- and β,γ-unsaturated compounds shifted toward the conjugated isomer by increasing the amount of trifluoroacetic acid (Fig 2). Regarding the ^1H NMR spectrum of a mixture of the β-phenylthio ketone and trifluoroacetic acid, a new absorption signal appeared around δ 8.8, in addition to the signals of the substrates and the catalyst; it then

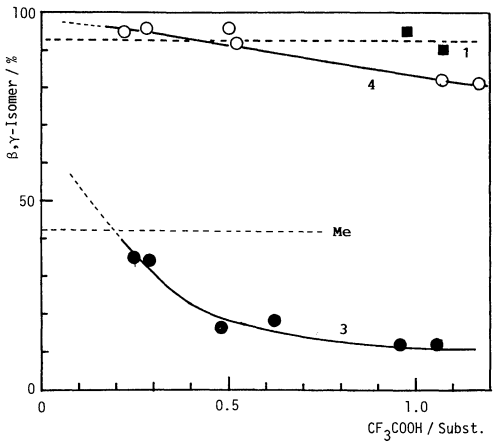


Fig. 2. The dependence of equilibrium of β-phenylthio-substituted unsaturated ketones, **3** and **4**, on the amount of acid catalyst. Dotted lines **1** and **Me** indicate the equilibrium points of the β-chloro- and β-methyl-substituted analogs of **3**, 5-chloro-4-(-5-)hepten-3-one and 5-methyl-4-(-5-)hepten-3-one,[2] respectively.

gradually shifted toward a lower magnetic field during the progress of the reaction. These phenomena could not be observed in the case of the chloro ketones. This new absorption signal was expected to be due to a sulfonium proton generated by protonation to the sulfide. Therefore, the relative thermodynamic stabilities of β-phenylthio ketones can be obtained by extrapolating the curves of Fig. 2 to the point of no catalyst. These values also clearly indicate that phenylthio substitution at the β-position strongly favors the β,γ-isomer. The MME data also became suitably oriented so as to stabilize the β,γ-unsaturated isomer. However, the MME data could not elucidate that the introduction of a methyl group into the γ-position strongly shifts the equilibrium towards the β,γ-unsaturated isomer. It may be mainly due to an inductive or hyperconjugation effect of the methyl group, as known.[1]

In contrast, protonation to the thioether sulfur would occur in an acidic media; it removes the dipole–dipole repulsion of the (*Z*)-*s*-cis conformation of α,β-isomer, while the hydrogen bonding between the carbonyl oxygen and the sulfonium proton increases the stability of the α,β-unsaturated isomer. Although it is also possible to use the protonated β,γ-unsaturated isomer to bring about hydrogen bonding, its exo-olefinic six-membered cyclic structure would be expected to be less stable than the endo-olefinic six-membered cyclic structure of the hydrogen-bonded α,β-unsaturated isomer. As a result, the equilibrium point shifts toward the α,β-unsaturated isomer by increasing the amount of acid catalyst.

β-Phenylamino-substituted ketone indicated quite a different behavior from the chloro- and the phenylthio-substituted ketones regarding its equilibrium. Although the point of equilibrium could not be determined from both sides of the α,β- and β,γ-unsaturated isomers, because only the α,β-unsaturated ketone

could be obtained, isomerization did not occur at all. This indicates that the α,β-unsaturated isomer is quite stable in this case.[7] Since the ^{1}H NMR absorption of amine protons of **5a** and **6a** was observed at δ 12—13, and their IR carbonyl absorptions shifted from 1680 cm^{-1} of the usual ketones to around 1600 cm^{-1}, the formation of hydrogen bonding between the carbonyl oxygen and the amine proton was expected. Thus, these compounds would be stabilized in α,β-unsaturated forms.

These studies show that the heteroatom substituents at the β-position strongly shift the equilibrium of the propenyl ketone system toward the unconjugated isomer, except when hydrogen bonding is available between the carbonyl and heteroatom moieties. In the latter case, the conjugated form becomes the predominant isomer.

Experimental

^{1}H NMR spectra were taken on JEOL PMX-60 and on Hitachi R-600 spectrometers in $CDCl_3$ with TMS as an internal standard. The substrates, (*E*)-**1a**, **1b**, (*E*)-**2a**, **2b**, (*E*)-**3a**, **3b**, (*E*)-**4a**, **4b**, (*Z*)-**5a**, and (*Z*)-**6a**, were prepared in previous studies, and the spectral data of these substrates and their isomers were also given.[3,8]

A Typical Procedure for Equilibration. To a solution of 94.5 mg (0.430 mmol) of (*E*)-**3a** in 0.4 ml of $CDCl_3$ was added a solution of 51.8 mg (0.454 mmol) of trifluoroacetic acid in 0.4 ml of $CDCl_3$; the mixture in an NMR tube was kept at room temperature (20—25 °C) and its ^{1}H NMR spectra were taken at regular intervals. The ratio of **3a** and **3b** was determined by peak integrals of the 4-CH= proton signal at δ 5.60 for (*E*)-**3a** and δ 6.34 for (*Z*)-**3a**, and 4-CH_2 proton signal at δ 3.30 for (*E*)-**3b** and δ 3.25 for (*Z*)-**3b**. Peak integrals of phenyl proton at δ 7.48 for **3a** and δ 7.27 for **3b** were supplimentarily used for the calculation. When the isomer ratio did not change further, the mixture was estimated as being equilibrated. During the course of equilibration, no peaks other than the expected equilibrium components could be detected. The results are summarized in Table 1.

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6) Molecular mechanic energies were calculated using Chem-X MMP program, Chemical Design Ltd.

7) A solution of 4-diethylamino-2,6-dimethyl-4- and -5-hepten-3-one (isomer ratio 50:50) in $CDCl_3$ prepared by the addition of an equivalent amount of diethylamine to 2,6-dimethyl-4,5-heptadien-3-one, was similarly equilibrated in the presence of an equivalent amount of trifluoroacetic acid. After 4 h duration, the originally presented ^{1}H NMR signals at δ 5.00 (vinyl proton of (*E*)-α,β-unsaturated isomer) and δ 3.15 (4-CH_2 proton of β,γ-unsaturated isomer) was completely disappeared, and a more simple series of the signals was resulted (δ 1.17 (d, 6H), 1.21 (d, 6H), 1.39 (t, 6H), 2.61 (sept, 1H), 2.85 (sept, 1H), 3.81 (q, 4H), 5.54 (s, 1H)). The product is most plausibly expected to be (*Z*)-4-diethylamino-2,6-dimethyl-4-hepten-3-one. This result indicates that the protonated β-amino-α,β-unsaturated ketone is favored in the acid-catalyzed equilibration.

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