Kinetic Stability as Monomeric Forms of 2-Alkyl-5,6-dihydro-3-thioacetyl-2*H*-naphtho[1,2-*b*]thiopyrans

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Synopsis. 2-Alkyl-5,6-dihydro-3-thioacetyl-2*H*-naphtho-[1,2-*b*]thiopyrans (**2**) exist stably in the form of monomers at room temperature, whereas unsubstituented ones at the 2-position are apt to dimerize. Based on the X-ray analysis of (**2g**), UV spectral study of (**2**), and on semi-empirical calculations, this difference of the stability could be rationalized mainly by steric reason around the heterodiene C=C–C=S system.

We previously reported the synthesis and reactions of thiochalcones and 2-(arylmethylene)tetralin-1-thiones.[1,2] Such α,β-unsaturated thioketones exist as dimers and are regenerated by heating to be trapped as heterodienes by reacting with a variety of dienophiles in the hetero-Diels–Alder reaction.[2] Recently, we have reported the synthesis of highly conjugated $\alpha,\beta:\gamma,\delta$-unsaturated thioketones, viz., 2-aryl- and 2-alkyl-5,6-dihydro-3-thioacyl-2*H*-naphtho[1,2-*b*]thiopyrans **1**,[3] which exist stably in the monomeric forms at room temperature. They also underwent the hetero-Diels–Alder reaction, in which the C=C–C=S system behaved as a heterodiene.[4] Their contrastive properties to those of thiochalcones and the related thioketones gave us an impetus to study more examples to prove their causes of stability and behavior.

So far, stably isolated monomeric α,β-unsaturated thioketones may be roughly classified into three groups in terms of the following main stabilizing factors. The first one consists of *exo*-cyclic thioketones such as 2-cycloalkene-1-thiones, which do not undergo the Diels–Alder reaction as heterodienes because of the rigid *s-trans* conformations.[5] The second consists of heteroatom stabilizing α,β-unsaturated thioketones such as enamino thioketones, which are electronically stabilized by a resonance effect of the heteroatom.[6] Representatives of the third group are 3-(arylmethylene)-bornane-2-thiones, in which the thiocarbonyl group is sterically blocked by neighboring bulky groups, thus being stabilized kinetically.[7] By comparison of the structures of **1**[4] with those of the above examples,[6,7] two considerable factors may be envisaged in stabilizing **1** as monomers. One is the resonance effects of the R^1 group and of the 2*H*-thiopyran-sulfur through the conjugation on the thiocarbonyl group. The other is the steric reason due to steric repulsion between the R^1 and R^2 groups to prevent it in taking the *s-cis* conformation necessary for dimerization. To clarify the reason for the stabilization/dimerization, we have investigated the resonance and/or the steric effect using more examples of the derivatives with R^1 and R^2.

As for the thioketones with an alkyl group in R^1, the thioketones **2c**—**g** having a substituent (Me, Et, Pr, *i*-Pr, or *t*-Bu) in R^2 were obtained stably as monomers, while with $R^2=H$, the thioketones **2a**,**b** are insufficiently stable for isolation, the dimers **3a**,**b** being obtained (Scheme 1). If the thioketones **2** were stabilized largely enough by the resonance effect through the 2*H*-thiopyran, they would have existed stably as monomers with any variation of the R^2 group, even for $R^2=H$. These facts suggest that the resonance effect through the 2*H*-thiopyran[8] does not sufficiently stabilize the thioketones **2** to allow isolation in their monomeric forms. On the other hand, the aromatic thioketones **1** ($R^1=Ph$) could be isolated considerably stably as monomers even when $R^2=H$,[4] suggesting the significant contribution to stabilization by the resonance through the aromatic group (R^1).

Turner et al. have reported a good example of the steric effect which determines a *s-cis*/*s-trans* conformation of the oxabutadiene system in 1-acetyl-2-methylcyclohexene. In this ketone, the *s-cis* conformation predominates due to the steric repulsion between the two methyl groups in the *s-trans* form[9] (Fig. 1). In our cases, such as steric repulsion between R^1 and R^2 may also play an important role in the conformation associated with the kinetic stability of the thioketones.

In this context, we first investigated the reactivity of **2**/**3** as heterodienes (C=C–C=S) by varying the substituent R^2 with Me, Et, Pr, *i*-Pr, *t*-Bu group in the Diels–Alder reaction with norbornadiene in refluxing benzene: the thioketones **2c**—**e**($R^2=$Me, Et, *n*-Pr) did react as heterodiene counterparts to give the cycloadducts **4c**—**e**, whereas **2f**,**g** having a bulkier group in R^2 (*i*-Pr, *t*-Bu) did not react under the same reaction conditions.[10] These results suggest that the *s-cis* conformations in **2f**,**g** is much more inhibited by the bulkier subsituent (*i*-Pr, *t*-Bu) and that the *s-trans* form pre-

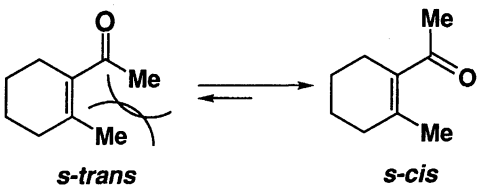
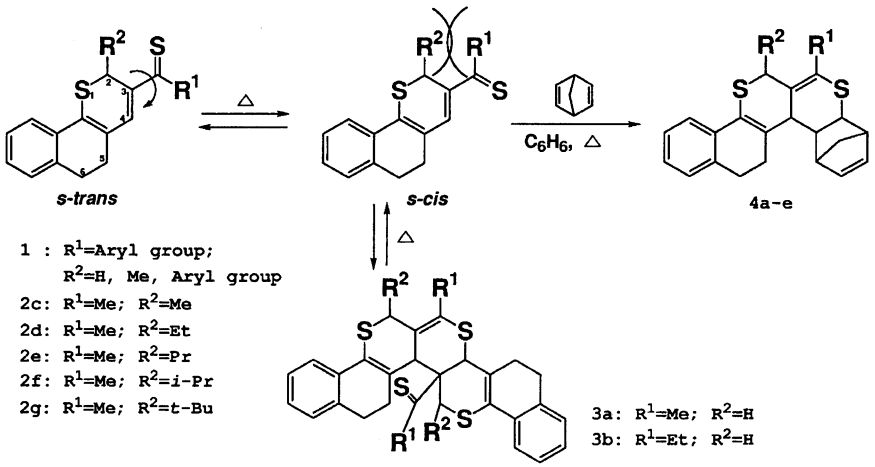


Fig. 1. Conformation of 1-acetyl-2-methylcyclohexene.



Scheme 1.

dominates. This suggestion was confirmed by the X-ray analysis of **2g**[11] (Fig. 2). The C=C–C=S moiety takes the slightly twisted *s-trans* conformation. For the other thioketones **2c**—**f**, the same was deduced by comparing their UV spectra with that of **2g**, in which characteristic bands of the $\pi \rightarrow \pi^*$ transition due to the thiocarbonyl group in the conjugation, were observed at the almost same wavelength (489—498 nm) (Table 1).

Furthermore, we calculated the stable conformations of **2a**, **2c**, and **2g** with respect to the rotation around the single bond of the C=C–C=S moiety[12] using the AM1 method with the MOPAC[13] on the basis of the data obtained by X-ray analysis. As shown in Fig. 3, two energy minima were observed at nearly *s-cis* and

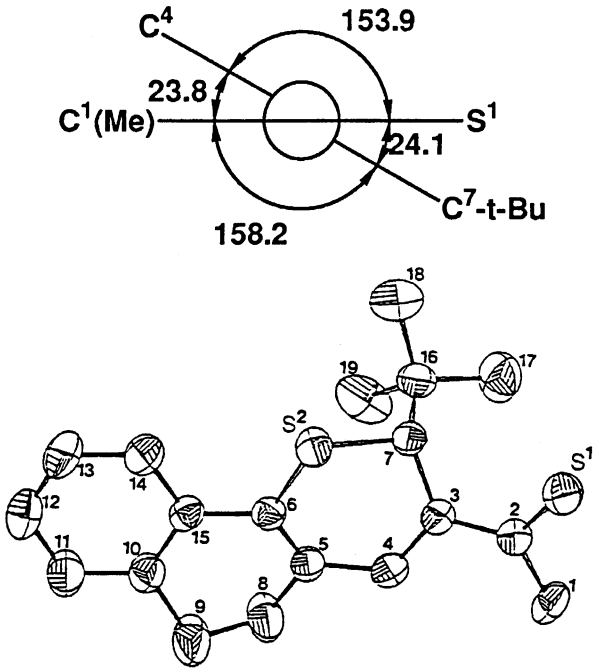


Fig. 2. Newman's projection of C^2–C^3 and ORTEP view of the thioketone **2g**.

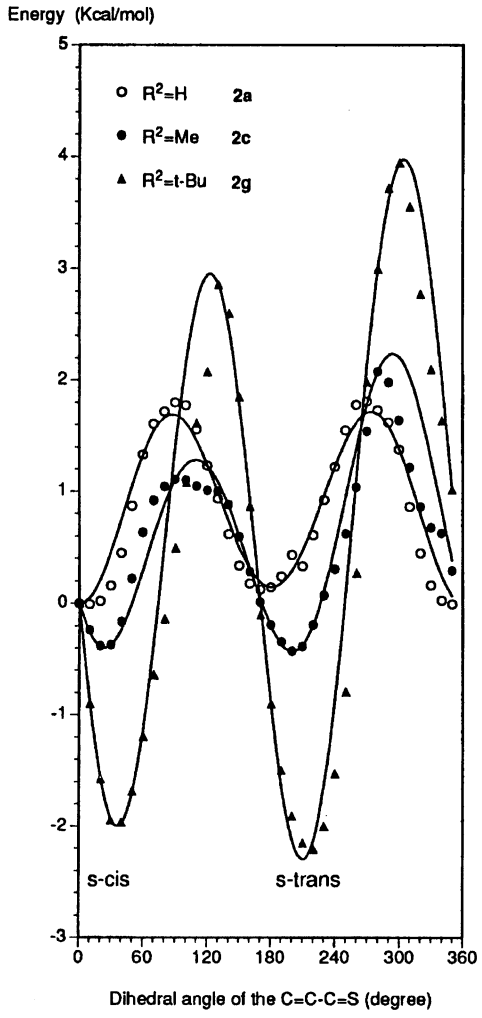


Fig. 3. Heats of formation as a function of dihedral angle.

s-trans conformations in each case. The preferred lowest energy corresponds to the twisted *s-trans* conformations for **2c** (dihedral angle; +202 degree) and **2g** (+217 degree), whereas that of **2a** is nearly in the *s-cis* conformation (−8 degree). These results show that the

Table 1. Preparation and Properties of the Thioketones **2** and **3**

Thioketone[a]	R^1	R^2	Form	Yield %	Mp °C	UV nm (log ε)
3a	CH_3	H	Dimer	40	103—104	—
3b	C_2H_5	H	Dimer	61	54—56	—
2c	CH_3	CH_3	Monomer	41	53—54	489 (3.89)
2d	CH_3	C_2H_5	Monomer	46	55—56	492 (3.92)
2e	CH_3	C_3H_7	Monomer	75	39—40	492 (3.90)
2f	CH_3	*i*-C_3H_7	Monomer	84	58—59	493 (3.87)
2g	CH_3	*t*-C_4H_9	Monomer	75	106—107	498 (3.98)

a) The thioketones were prepared by the reaction of the corresponding ketones with Lawesson's reagent.

thioketones preferring the twisted *s-trans* conformation can exist stably in the monomeric forms, whereas the ones in the *s-cis* conformation are apt to dimerize. This is consistent with the experimental results.

In conclusion, we have shown that α,β-unsaturated thioketones can be stabilized as monomers by the kinetic conformational factors due to steric repulsion without loss of their reactivity.

Experimental

All melting points were uncorrected. ^1H and ^{13}C NMR (DEPT; Distortionless Enhancement by Polarization Transfer) spectra were determined on a JEOL FX-100 or EX-270 spectrometer in $CDCl_3$ solvent. TMS was used as internal standard. IR and UV spectra were measured with Hitachi 270-30 and 320. Mass spectra (*m/z*; %) were measured on a Hitachi mass spectrometer RMU-7M (70 eV) or M-80 with a data processing system M-003. Elemental analyses were preformed using a Yanagimoto Model MT-3 CHN corder. Preparation of **2** and **3** (Table 1) and cycloaddition of **2** with 2,5-norbornadiene were carried out by the similar manner to the previous reports.[3,4]

5,6-Dihydro-3-thioacetyl-2*H*-naphtho[1,2-*b*]thiopyran Dimer (3a): Red solid; MS 258 ($M^+/2$; 100), 225 (47), 199 (34); ^1H NMR δ=2.09—2.85 (12H, m), 2.94 (3H, s), 3.39—3.92 (3H, m), 4.08—4.22 (2H, m), 7.02—7.60 (8H, m); ^{13}C NMR δ=20.5 (CH_3), 27.2 (CH_2), 28.05 (CH_2), 28.1 (CH_2), 28.2 (CH_2), 28.6 (CH_2), 28.8 (CH_2), 35.7 (CH_3), 48.2 (CH), 54.8 (CH), 59.3 (C), 230.2 (C=S). Found: C, 69.57; H, 5.21%. Calcd for $C_{30}H_{28}S_4$: C, 69.72; H, 5.46%.

5,6-Dihydro-3-thiopropionyl-2*H*-naphtho[1,2-*b*]thiopyran Dimer (3b): Red solid; MS 272 ($M^+/2$; 94), 257 (100), 239 (75); ^1H NMR δ=1.04 (3H, t, *J*=7.3 Hz), 1.21 (3H, t, *J*=7.6 Hz), 2.11—2.88 (13H, m), 3.35—3.48 (1H, m), 3.65—3.87 (2H, m), 4.18—4.22 (2H, m), 7.16—7.60 (8H, m); ^{13}C NMR δ=9.3 (CH_3), 14.4 (CH_3), 26.3 (CH_2), 28.1 (CH_2), 28.1 (CH_2), 28.6 (CH_2), 28.9 (CH_2), 29.7 (CH_2), 31.7 (CH_2), 40.1 (CH_2), 47.0 (CH), 50.2 (CH), 63.9 (C), 237.7 (C=S). Found: C, 70.51; H, 6.16%. Calcd for $C_{32}H_{32}S_4$: C, 70.54; H, 5.92%.

5,6-Dihydro-2-methyl-3-thioacetyl-2*H*-naphtho[1,2-*b*]thiopyran (2c): Red solid; MS 272 (M^+; 25), 239 (35), 213 (100); ^1H NMR δ=1.21 (3H, d, *J*=6.9 Hz), 2.21—2.91 (4H, m), 2.95 (3H, s), 5.13 (1H, q, *J*=6.9 Hz), 7.02—7.30 (4H, m), 7.62—7.82 (1H, m); ^{13}C NMR δ=20.0 (CH_3), 28.3 (CH_2), 28.8 (CH_2), 34.2 (CH), 35.8 (CH_3), 230.0 (C=S). Found: C, 70.59; H, 5.73%. Calcd for $C_{16}H_{16}S_2$: C, 70.54; H, 5.91%.

2-Ethyl-5,6-dihydro-3-thioacetyl-2*H*-naphtho[1,2-*b*]thiopyran (2d): Red solid; MS 286 (M^+; 29), 257 (36), 241 (55), 227 (55); ^1H NMR δ=0.93 (3H, d, *J*=7.3 Hz), 1.45—1.61 (2H, m), 2.42—2.91 (4H, m), 2.96 (3H, s), 4.94 (1H, dd, *J*=5.0 and 9.2 Hz), 7.11—7.32 (4H, m), 7.68—7.71 (1H, m); ^{13}C NMR δ=10.4 (CH_3), 25.2 (CH_2), 28.3 (CH_2), 28.8 (CH_2), 35.9 (CH_3), 41.6 (CH), 230.5 (C=S). Found: C, 71.45; H, 6.11%. Calcd for $C_{17}H_{18}S_2$: C, 71.27; H, 6.33%.

5,6-Dihydro-2-propyl-3-thioacetyl-2*H*-naphtho[1,2-*b*]thiopyran (2e): Dark red solid; MS 300 (M^+; 15), 267 (32), 257 (22), 241 (100); ^1H NMR δ=0.85 (3H, t, *J*=6.9 Hz), 1.26—1.58 (4H, m), 2.47—2.91 (4H, m), 2.95 (3H, s), 5.06 (1H, dd, *J*=4.3 and 9.6 Hz), 7.03—7.28 (3H, m), 7.32 (1H, s), 7.65—7.70 (1H, m); ^{13}C NMR δ=13.6 (CH_3), 18.7 (CH_2), 28.3 (CH_2), 28.8 (CH_2), 34.2 (CH_2), 35.9 (CH), 39.4 (CH_3), 230.3 (C=S). Found: C, 71.64; H, 6.91%. Calcd for $C_{18}H_{20}S_2$: C, 71.95; H, 6.71%.

5,6-Dihydro-2-isopropyl-3-thioacetyl-2*H*-naphtho-[1,2-*b*]thiopyran (2f): Dark purple solid; MS 300 (M^+; 27), 268 (44), 257 (100); ^1H NMR δ=0.83 (3H, d, *J*=6.6 Hz), 0.97 (3H, d, *J*=6.9 Hz), 1.81—1.99 (1H, m), 2.65—2.92 (4H, m), 2.99 (3H, s), 5.02 (1H, d, *J*=7.6 Hz), 7.10—7.39 (4H, m), 7.66—7.73 (1H, m); ^{13}C NMR δ=19.0 (CH_3), 19.2 (CH_3), 28.2 (CH_2), 28.7 (CH_2), 31.3 (CH), 36.1 (CH_3), 45.4 (CH), 231.8 (C=S). Found: C, 71.86; H, 6.58%. Calcd for $C_{18}H_{20}S_2$: C, 71.95; H, 6.71%.

2-*t*-Butyl-5,6-dihydro-3-thioacetyl-2*H*-naphtho[1,2-*b*]thiopyran (2g): Dark purple cubes recrystallized from benzene/hexane; MS 314 (M^+; 9), 257 (100); ^1H NMR δ=0.87 (9H, s), 2.42—2.90 (4H, m), 3.01 (3H, s), 5.25 (1H, s), 7.14—7.17 (1H, m), 7.23—7.29 (2H, m), 7.44 (1H, s), 7.73 (1H, dd, *J*=3.7 and 5.3 Hz); ^{13}C NMR δ=26.4 ($3CH_3$), 28.2 (CH_2), 28.8 (CH_2), 36.4 (CH_3), 39.4 (C), 47.4 (CH), 233.7 (C=S). Found; C, 72.81; H, 7.32%. Calcd for $C_{19}H_{22}S_2$: C, 72.56; H, 7.05%.

9,12,12a,12b,13,14-Hexahydro-6,7-dimethyl-9,12-menthano-6*H*,8a*H*-5,8-dithiabenzo[*c*]chrysene (4c): Yield 35%; mp 205—207 °C; MS 364 (M^+; 74), 298 (96), 283 (48), 272 (87), 265 (100); ^1H NMR δ=1.28 (3H, d, *J*=6.9 Hz), 1.62 (1H, d, *J*=8.5 Hz), 1.99 (3H, s), 2.10—2.21 (1H, m), 2.42—3.14 (9H, m), 3.94 (1H, q, *J*=6.9 Hz), 6.07—6.13 (2H, m), 7.17—7.25 (3H, m), 7.65 (1H, d, *J*=7.2 Hz). Found: C, 75.46; H, 6.64%. Calcd for $C_{23}H_{24}S_2$: C, 75.77; H, 6.64%.

6-Ethyl-9,12,12a,12b,13,14-hexahydro-7-methyl-

9,12-menthano-6*H*,8a*H*-5,8-dithiabenzo[*c*]chrysene (4d): Yield 36%; mp 67—69 °C; MS 378 (M^+; 59), 349 (12), 312 (79), 297 (16), 286 (56), 253 (100); ^{1}H NMR δ=0.93 (3H, t, J=7.3 Hz), 1.41—1.82 (4H, m), 1.99 (3H, d, J=1.3 Hz), 2.15—2.27 (1H, m), 2.37—3.16 (8H, m), 3.65 (1H, d, J=6.9 Hz), 6.07—6.15 (2H, m), 7.03—7.37 (3H, m), 7.59 (1H, d, J=7.6 Hz); ^{13}C NMR δ=12.6 (CH_3), 20.7 (CH_3), 26.8 (CH_2), 28.0 (CH_2), 31.8 (CH_2), 43.0 (CH_2), 46.5 (CH), 46.9 (CH), 47.7 (CH), 49.7 (CH), 50.5 (CH), 53.8 (CH). Found: C, 75.95; H, 7.01%. Calcd for $C_{24}H_{26}S_2$: C, 76.14; H, 6.92%.

9,12,12a,12b,13,14-Hexahydro-7-methyl-9,12-menthano-6-propyl-6*H*,8a*H*-5,8-dithiabenzo[*c*]chrysene (4e): Yield 56%; mp 68—70 °C; MS 392 (M^+; 59), 349 (9), 326 (72), 311 (15), 293 (75), 283 (53), 267 (100), 257 (53); ^{1}H NMR δ=0.83 (3H, t, J=6.3 Hz), 1.26—1.63 (6H, m), 1.99 (3H, d, J=1.7 Hz), 2.15—2.24 (1H, m), 2.44—3.63 (3H, m), 2.77—2.84 (2H, m), 2.95—3.15 (3H, m), 3.74 (1H, dd, J=4.9 and 9.5 Hz), 6.09—6.13 (2H, m), 7.15—7.26 (3H, m), 7.70 (1H, d, J=7.3 Hz); ^{13}C NMR δ=13.5 (CH_3), 20.7 (CH_3), 20.8 (CH_2), 28.0 (CH_2), 31.8 (CH_2), 35.7 (CH_2), 43.0 (CH_2), 44.4 (CH), 46.5 (CH), 47.7 (CH), 49.7 (CH), 50.6 (CH), 53.8 (CH). Found: C, 76.71; H, 7.19%. Calcd for $C_{25}H_{28}S_2$: C, 76.48; H, 7.19%.

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$$V(\phi) = \frac{1}{2}V_1(1-\cos\phi) + \frac{1}{2}V_2(1-\cos 2\phi) + \frac{1}{2}V_3(1-\cos 3\phi) + V_1'\sin\phi + V_2'\sin 2\phi. \quad (1)$$

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