Influence of the Chalcogenocarbonyl Group on the Structure of Heterocyclic Analogues of β-Tricarbonyl Compounds. Synthesis and Structural Features of Schiff Bases Derived from 3-Formyl-4-thio(seleno)coumarin

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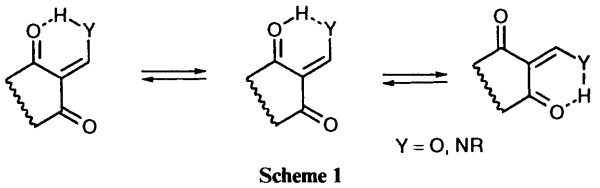
The equilibrium between *Z* and *E* isomers of Schiff bases derived from 3-formyl-4-thio(seleno)coumarin **1**, **2** resulting from the hindered rotation around the exocyclic carbon–carbon bond in the stable ketoamine tautomeric form has been studied by means of IR and 1D and 2D (NOESY) ^{1}H NMR spectroscopy and *ab initio* and semiempirical calculations. The ratio between the *Z* and *E* forms in solution was found to lie in the range 3.5:1–5.8:1 (X=S) and 2.4:1–3.1:1 (X=Se). The activation energy for $Z \rightleftharpoons E$ interconversion was estimated for **1a** and **2a** using dynamic ^{1}H NMR spectroscopy to be 45.7 and 35.3 kJ mol^{-1}, respectively. The process was found to be catalysed by trifluoroacetic acid. The relative stability of both tautomeric and conformational isomers calculated theoretically at MP2/6-31G* level for the model molecules of 3-methylimino-4-hydroxy(thio,seleno)-2-pyrone is in good agreement with experimental data. Estimated activation barriers for the rotational mechanism are higher than experimentally obtained which may indicate a contribution from acid-promoted reaction pathways.

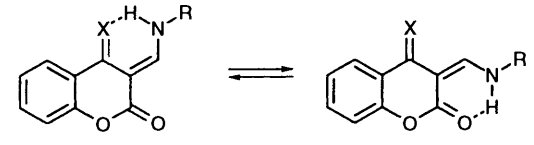
The structure of aromatic and heteroaromatic analogues of β-tricarbonyl compounds has been a subject of interest[1–3] with respect to their predominant tautomeric form and the relative preference of two conformational isomers (*Z* and *E* with regard to the exocyclic carbon–carbon bond) stabilized by an intramolecular hydrogen bond. In principle, these may exist in dynamic equilibrium as it is depicted in Scheme 1.



Scheme 1

In the case of corresponding Schiff bases (Y = NR), the keto amino form is usually preferred to the hydroxy imino form and transformations occur between conformational isomers, whereas in the case of Y = O the situation is also complicated by prototropic tautomerism. The latter interconversion is fast on the NMR timescale and the former is slow. The combination of donor centres involved in the six-membered hydrogen-bonded rings formed appears to be important in determining the relative stability of both the tautomeric and geometrical isomers. This has, so far, been limited to O,O,O- and O,N,O-groups of atoms. In order to study the influence of substitution of one of the carbonyl groups with a chalcogenocarbonyl group we prepared and investigated the compounds of S,N,O- and Se,N,O-types: Schiff bases of 3-formyl-4-thio(seleno)coumarin **1**, **2**. These show considerably different structural features indicating a more even distribution of the *Z* and *E* forms and a lower rotational barrier.

Novel 4-thio(seleno) derivatives of 3-formylcoumarin described herein may be useful starting materials for the synthesis of [3,4]-condensed coumarins incorporating sulfur- and selenium-containing heterocyclic rings of potential biological activity. Related 4-hydroxy-, chloro-, amino- and azido-coumarins have recently been reported[4] in cyclization reactions to afford polyheterocycles with fused benzodiazepine, oxazole, thiazole, pyrazole and quinoline rings.



a R = CH_3
b R = Pr^i
c R = Bu^t
d R = CH_2Ph
e R = $C_6H_4CH_3$-*p*
f R = $C_6H_2(CH_3)_3$-2,4,6

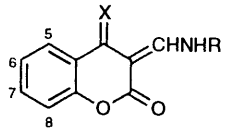
Experimental

Instrumentation.—^{1}H NMR spectra were recorded in deuteriochloroform (Aldrich) on 250 MHz Bruker AC FT and 500 MHz Varian Unity spectrometers equipped with a standard temperature controller; chemical shifts are reported relative to Me_4Si as an internal reference. Electronic impact mass spectra (70 eV) were obtained on a Varian MAT 311 spectrometer, IR spectra on a Perkin-Elmer 580 spectrometer. Activation energies for the interconversion were estimated by modelling the temperature-variable ^{1}H NMR spectra using a program for the full lineshape analysis.[5]

Calculations.—*Ab initio* calculations were done using the GAUSSIAN 92 program package[6] using standard methods.[7] The Se basis was taken from Lehn *et al.*[8] while the 6-31G* basis was used for all other atoms. Geometries were optimized at the HF level, followed by single-point MP2 calculations. The authenticity of the transition states were checked by frequency calculations at the HF/3-21G level for the X = O systems. The solvent effects were estimated by the reaction-field method.[9] PM3 calculations were done using the MOPAC program.[10]

General Procedure for the Synthesis of **1**, **2**.—To a solution of NaSH or NaSeH (6 mmol)[11] in absolute ethanol (20 cm^3) was added 4-chloro-3-formylcoumarin (4 mmol)[4c] and the reaction

Table 1 The ^1H NMR chemical shifts of **1**, **2** in $CDCl_3$ at ambient temperature and *Z*:*E* ratios



R	X	NH	CHNH	C(5)H[a]	C(7)H	C(6)H, C(8)H	R	$N_{Z:E}$
CH_3[b]	S	14.62 11.03	8.79 (d, ^3J 14.7) 9.34 (d, ^3J 14.6)	8.51 (d, ^3J 8.1) 8.65 (d, ^3J 8.1)	7.54 (t, ^3J 7.8) 7.50–7.68 (m)	7.19–7.29 (m)	3.43 (d, ^3J 5.1) 3.46 (d, ^3J 5.1)	3.5:1
Pr^i	S	14.88 11.07	8.82 (d, ^3J 14.8) 9.41 (d, ^3J 14.8)	8.55 (d, ^3J 7.8) 8.65 (d, ^3J 8.2)	7.50–7.68 (m)	7.19–7.39 (m)	3.92 (septet, CH) 1.49, 1.62 (dd, ^3J 6.6, $2CH_3$)	3.5:1
Bu^t[c]	S	15.22 11.39	8.87 (d, ^3J 15.1) 9.51 (d, ^3J 15.4)	8.53 (d, ^3J 8.0) 8.66 (d, ^3J 8.0)	7.50–7.68 (m)	7.20–7.38 (m)	1.54 (s)	5.8:1
$C_6H_4CH_3$-*p*	S	16.56 12.68	9.22 (d, ^3J 14.4) 9.73 (d, ^3J 14.7)	8.53 (d, ^3J 8.1) 8.65 (d, ^3J 8.1)	7.51–7.69 (m)	7.20–7.37 (m, +tolyl-H)	2.40 (s, CH_3)	5.1:1
$C_6H_2(CH_3)_3$-2,4,6	S	15.86 12.21	8.84 (d, ^3J 14.4) 9.41 (d, ^3J 14.8)	8.56 (d, ^3J 8.0) 8.66 (d, ^3J 8.0)	7.48–7.64 (m)	7.19–7.30 (m)	6.96 (s, *m*-H) 2.35 (s, 2 *o*-CH_3) 2.33 (s, *p*-CH_3)	5.2:1
CH_3[c]	Se	15.15 11.35	8.91 (d, ^3J 14.5) 9.35 (d, ^3J 14.5)	8.52 (d, ^3J 8.0) 8.71 (d, ^3J 8.0)	7.54–7.65 (m)	7.16–7.39 (m)	3.42 (s, *p*-CH_3) 3.445 (s, ^3J 5.0)	3.1:1
CH_2Ph	Se	15.60 11.55	9.07 (br d) 9.49 (br d)	8.55 (br s) 8.69 (br s)	7.15–7.64 [m, C(6)–C(8)H, +CH_2Ph]		4.79 (s, CH_2)	3.0:1
$C_6H_4CH_3$-*p*	Se	14.89 12.92	9.44 (d, ^3J 14.6) 9.83 (d, ^3J 14.6)	8.58 (d, ^3J 8.0) 8.75 (d, ^3J 8.0)	7.23–7.74 [m, C(6)–C(8)H, +tolyl-H]		2.40 (s, CH_3)	2.4:1

[a] ^4J = 1.5 Hz. [b] At 0 °C. [c] At −30 °C.

mixture was heated with stirring at 60 °C for 2 h under a nitrogen atmosphere. Insoluble materials were filtered off and the appropriate amine (3.5 mmol) was added to the filtrate. After being refluxed for 0.5 h, the solution was neutralized by addition of acetic acid (6 mmol) in ethanol (5 cm^3). Cooling resulted in the formation of a bulky precipitate of the required **1**, **2**. Recrystallization from tetrachloroethane gave analytically pure **1**, **2** in 60–70% yields. Characterization data are given below, the ^1H NMR chemical shifts are collected in Table 1.

3-*Methylaminomethylene*-4-*thioxo*-3,4-*dihydro*-1-*benzopyran*-2-*one* **1a**. M.p. 210 °C (Found: C, 60.4; H, 4.2; N, 6.4. $C_{11}H_9NO_2S$ requires C, 60.3; H, 4.1; N, 6.4); ν_{max}(KBr)/cm^{-1} 1703, 1671 (CO), 1636 and 1605 (enamine); ν_{max}($CHCl_3$)/cm^{-1} 1703, 1673 (CO), 1634 and 1606 (enamine); *m*/*z* 219 (M^+, 100%) and 204 ($M^+ - CH_3$, 19).

3-*Isopropylaminomethylene*-4-*thioxo*-3,4-*dihydro*-1-*benzopyran*-2-*one* **1b**. M.p. 96 °C (Found: C, 63.3; H, 5.2; N, 5.8. $C_{13}H_{13}NO_2S$ requires: C, 63.1; H, 5.3; N, 5.7); ν_{max}(KBr)/cm^{-1} 1708, 1703 (CO), 1631 and 1605 (enamine); ν_{max}($CHCl_3$)/cm^{-1} 1698, 1693 (CO), 1623 and 1607 (enamine); *m*/*z* 247 (M^+, 100%) and 204 ($M^+ - C_3H_7$, 64).

3-tert-*Butylaminomethylene*-4-*thioxo*-3,4-*dihydro*-1-*benzopyran*-2-*one* **1c**. M.p. 111 °C (Found: 64.4; H, 5.5; N, 5.2. $C_{14}H_{15}NO_2S$ requires: C, 64.3; H, 5.8; N, 5.4); ν_{max}(KBr)/cm^{-1} 1698, 1693 (CO), 1626 and 1604 (enamine); ν_{max}($CHCl_3$)/cm^{-1} 1699, 1672 (CO), 1625 and 1606 (enamine); *m*/*z* 261 (M^+, 45%) and 204 ($M^+ - C_4H_9$, 100).

3-(p-*Tolylaminomethylene*)-4-*thioxo*-3,4-*dihydro*-1-*benzopyran*-2-*one* **1e**. M.p. 160 °C (Found: C, 69.4; H, 4.3; N, 4.9. $C_{17}H_{13}NO_2S$ requires: C, 69.1; H, 4.4; N, 4.7; ν_{max}(KBr)/cm^{-1} 1706, 1669 (CO), 1623 and 1603 (enamine); ν_{max}($CHCl_3$)/cm^{-1} 1703, 1669 (CO), 1622 and 1605 (enamine); *m*/*z* 295 (M^+, 100%) and 204 ($M^+ - C_6H_4CH_3$, 36).

3-(2,4,6-*Trimethylphenylaminomethylene*)-4-*thioxo*-3,4-*dihydro*-1-*benzopyran*-2-*one* **1f**. M.p. 158 °C (Found: C, 70.2; H, 5.4; N, 4.6. $C_{19}H_{17}NO_2S$ requires: C, 70.6; H, 5.3; N, 4.3); ν_{max}(KBr)/cm^{-1} 1704, 1669 (CO), 1618 and 1604 (enamine); ν_{max}($CHCl_3$)/cm^{-1} 1703, 1698 (CO), 1616 and 1606 (enamine); *m*/*z* 323 (M^+, 25%) and 204 [$M^+ - C_6H_2(CH_3)_3$, 100].

3-*Methylaminomethylene*-4-*selenoxo*-3,4-*dihydro*-1-*benzopyran*-2-*one* **2a**. M.p. > 300 °C (Found: C, 49.8; H, 3.5; N, 5.1. $C_{11}H_9NO_2Se$ requires: C, 49.6; H, 3.4; N, 5.3); ν_{max}(KBr)/cm^{-1} 1699, 1664 (CO), 1638 and 1601 (enamine); ν_{max}($CHCl_3$)/cm^{-1} 1665, 1636 (CO), 1601 and 1581 (enamine); *m*/*z* 267 (M^+, 100%).

3-*Benzylaminomethylene*-4-*selenoxo*-3,4-*dihydro*-1-*benzopyran*-2-*one* **2d**. M.p. 181 °C (Found: C, 63.2; H, 4.0; N, 4.2. $C_{17}H_{13}NO_2Se$ requires: C, 63.0; H, 4.0; N, 4.3); ν_{max}(KBr)/cm^{-1} 1698, 1631 (CO), 1602 and 1582 (enamine); ν_{max}($CHCl_3$)/cm^{-1} 1701, 1670 (CO), 1624 and 1604 (enamine); *m*/*z* 348 (M^+, 38%) and 252 ($M^+ - CH_2Ph$, 22).

3-(p-*Tolylaminomethylene*)-4-*selenoxo*-3,4-*dihydro*-1-*benzopyran*-2-*one* **2e**. M.p. 246 °C (Found: C, 63.25; H, 4.1; N, 4.0. $C_{17}H_{13}NO_2Se$ requires: C, 63.0; H, 4.0; N, 4.3); ν_{max}(KBr)/cm^{-1} 1712, 1666 (CO), 1621, 1600 and 1584 (enamine); ν_{max}($CHCl_3$)/cm^{-1} 1703, 1665 (CO), 1621 and 1602 (enamine); *m*/*z* 343 (M^+, 50%) and 252 ($M^+ - C_6H_4CH_3$, 100).

Results and Discussion

^1H NMR chemical shifts for **1**, **2** recorded in $CDCl_3$ at 25 °C are shown in Table 1. The spectral pattern displays a double set of signals of unequal intensity with broadening of minor resonances in some cases. This could be interpreted as the occurrence of an equilibrium mixture of *Z* and *E* isomers interconverting at intermediate rates on the NMR timescale. Recently reported[12] oxygen analogues of **1**, **2**, 3-ureidomethylene coumarins, *N*-(methylene-4-oxocoumarinyl) carbamates and *N*-substituted α-amino acids containing the 4-hydroxycoumarin moiety also display a mixture of *Z* and *E* isomers in solution. Similar structural features have been deduced from the

NMR spectra of enamines derived from 3-formyl-4-hydroxycoumarin[13] but a kinetic study has not been performed.

Ethylenic proton signals in **1**, **2** appear as doublets with spin–spin couplings of 14.2–15.4 Hz consistent with localization of the labile proton on the nitrogen atom in the amino thione-(selone) tautomeric form. NH resonances were observed as downfield shifted broadened signals at 11.0–13.0 and 14.6–16.6 ppm which vanished upon deuteriation, characteristic of a strong intramolecular hydrogen bond. The ethylenic proton spin–spin coupling $^3J(CH\,NH)$ also disappeared upon deuteron exchange. The major resonances in the spectra appeared at higher field compared with the minor ones (except for those for the NH group) and could be assigned to the *Z*-isomer, taking into account the data related to Schiff bases from 3-acetyl-6-methylpyran-2,4-dione.[3,14] For these compounds, the ^{1}H NMR spectra are dominated by the signals of *Z*-isomer which was found[14] to be stable in the solid state by X-ray diffraction whereas the minor resonances corresponding to the *E*-isomer are shifted downfield, except those of the NH group, displaying larger chemical shifts (by 2–2.5 ppm). In the case of **1**, **2**, the larger NH group chemical shifts of the *Z*-form may also be expected from the well-documented fact[15] that for heterocyclic enamines the NH ··· S proton signals are more shielded than NH ··· O. This may be an additional contribution leading to further signal separation by 3.5–4 ppm for **1**, **2** [S(Se),N,O-type] compared with the pyrandiones (O,N,O-type).

IR spectra of **1**, **2** recorded in chloroform (see the Experimental section) also confirm the presence of *Z*- and *E*-forms in solution: two stretching vibrations related to the $C{=}O_{ester}$ carbonyl group were observed in the range 1630–1710 cm^{-1}. Similar spectral features were also revealed in the solid state thus indicating the retention of both isomers in this case.

Populations of the isomers in solution were estimated from the integral intensity of CH–N signals in the ^{1}H NMR spectra and are presented in Table 1. *Z*:*E* ratios, $N_{Z:E}$, were found to lie in the range 3.5:1–5.8:1 (78–85% *Z* isomer) for **1** (X = S) and 2.4:1–3.1:1 (71–76% *Z* isomer) for **2** (X = Se). These values are substantially lower than those reported[3] for structurally similar (X = O) Schiff bases from 3-acetyl-6-methylpyran-2,4-dione which exhibited $N_{Z:E}$ values varying from 23:1 to 60:1. For pyrandiones, the measurable amounts of the minor rotamer were found only at −50 °C in chloroform whereas at room temperature these were not detected owing to the low signal intensities in the NMR spectra. This fact indicates that the value of equilibrium entropy $\Delta S°$ is small and its contribution to $\Delta G°$ is almost negligible. It is consistent with our observations that the ratio is nearly independent of the temperature variations. If the pyrandione model is correct for comparison, the amount of *Z* form decreases in the order O ≫ S > Se; however, this form is preferred in all cases.

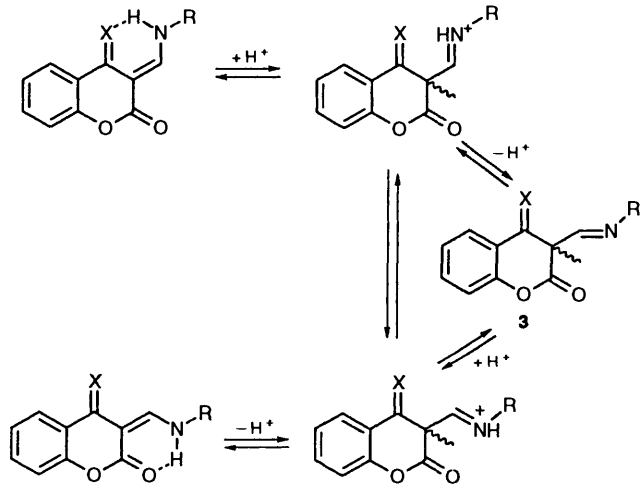
It is reasonable to account for the energy difference between the *Z* and *E* forms as being determined by the difference in the strength of corresponding hydrogen bonds $NH \cdots X_{keto}$ and $NH \cdots O_{ester}$ upon the changes of X. Chemical shifts of the NH group are a commonly used probe in the characterization of hydrogen bonds and it is usually assumed that δ_{NH} increases as the hydrogen bond strengthens. However, no regular changes in δ_{NH} for either of the forms were revealed when comparing O-, S- and Se-containing compounds which exhibited corresponding chemical shifts in the range 11–13 (*E*) and 14–16.6 ppm (*Z*). The different values of δ_{NH} are mainly derived from the substituents R at the imino group being larger for both of the forms in the case of R = Ar compared with those with R = Alk. The influence of R is also seen in $N_{Z:E}$ variations. For X = S, this ratio increases by about 50% for alkyl compared with the aryl substituents while for X = Se the trend is the opposite and the difference is less.

For compounds **1c**, **2a** and **2d**, ^{1}H NMR spectra at room temperature revealed noticeably broadened resonances associated with the rates of $Z \rightleftharpoons E$ interconversion which were intermediate on the NMR timescale.

In order to obtain additional evidence for the occurrence of an exchange pattern between *Z* and *E* isomers the NOESY ^{1}H NMR spectra of **1a** and **2a** were recorded. The NOESY experiment generates off-diagonal cross-peaks between nuclei coupled by dipole–dipole interaction or chemical exchange. For molecules of medium size with short correlation times, NOE cross-peaks are in the opposite phase to that of the diagonal peaks whereas in the case of chemical exchange these appear with the same phase.[16] Using a mixing time τ_m of 50 ms at 298 K the off-diagonal peaks of the same phase as the relevant diagonal peaks related to the exchange between CH–N and C(5)H protons, respectively, were observed, indicating the presence of chemical exchange within the timescale of τ_m.

Activation parameters and the rate constants for $Z \rightleftharpoons E$ interconversion in **1**, **2** were evaluated for two representative compounds **1a** and **2a** using dynamic ^{1}H NMR spectroscopy. The process was followed by observing the temperature-variable spectra of the NCH_3 group which consisted, at the low exchange rate limit, of two doublets separated by 15 Hz (**1a**) and 12.5 Hz (**2a**) at 500 MHz. The rate constants at different temperatures were obtained by a computer-assisted lineshape simulation taking into account varied *k* values and comparison of the calculated and experimental spectra. The activation energies $\Delta E_a^{\ddagger}$ were obtained using the Arrhenius equation to be 45.7 ± 2.4 (k_{298} = 12 ± 1.2 s^{-1}) (**1a**) and 35.3 ± 0.8 kJ mol^{-1} (k_{298} = 87 ± 9 s^{-1}) (**2a**). The energy difference between the *Z* and *E* forms was estimated to be 2.8 (**1a**) and 1.9 kJ mol^{-1} (**2a**). Thus the thermodynamic contribution of 0.9 kJ mol^{-1} to the increase of the activation barrier on going from Se to S (10.4 kJ mol^{-1}) is small.

We found that the samples dissolved in commercially available deuteriochloroform (used as delivered) for dynamic ^{1}H NMR experiments provided well reproducible kinetic results and neither passing the solvent through anhydrous K_2CO_3 nor keeping it over molecular sieves slows down the interconversion. However, noticeably broadened resonances were produced by adding trace amounts of CF_3COOH to the solution. It may be assumed that activation of the $Z \rightleftharpoons E$ interconversion occurs because of the protonation of the CO, CX[17a] or NH group[17b] resulting in weakening of the double-bond character of the exocyclic carbon–carbon bond. Alternatively, it may be caused by acid-catalysed formation of the intermediate **3** in a plausible mechanism shown in Scheme 2, as reported[18] in the case of quinaldyl ketones. These exist predominantly in the NH form which participates in a rapid



Scheme 2

Table 2 Calculated relative energies (kJ mol^{-1}) of the plausible tautomeric and rotameric forms depicted in Scheme 3 and the transition states for their interconversion

	X = O			X = S			X = Se		
Compound	HF	MP2	$\Delta\Delta E_{solv}$ (ε = 40)	HF	MP2	$\Delta\Delta E_{solv}$ (ε = 40)	HF	MP2	$\Delta\Delta E_{solv}$ (ε = 40)
GS/X-1	0	0	0	0	0	0	0	0	0
GS/X-2	2.1	3.3	1.3	−3.3	1.3	−2.1	16.7	23.0	−1.7
GS/X-3	43.1	24.3	1.3	60.2	49.4	1.3	54.0	48.1	0.4
GS/X-4	92.5	90.8	2.5	99.2	90.4	1.7	124.3	116.7	0.8
TS/X-1	140.2	149.0	−11.3	99.2	117.6	−8.8	102.5	105.0	−2.1
TS/X-2	71.5	30.5	1.7	86.6	45.6	2.5	71.5	36.4	2.1

Table 3 Selected bond lengths (Å), valence and torsion angles (°) calculated for the isomers depicted in Scheme 3 and transition states for their interconversions

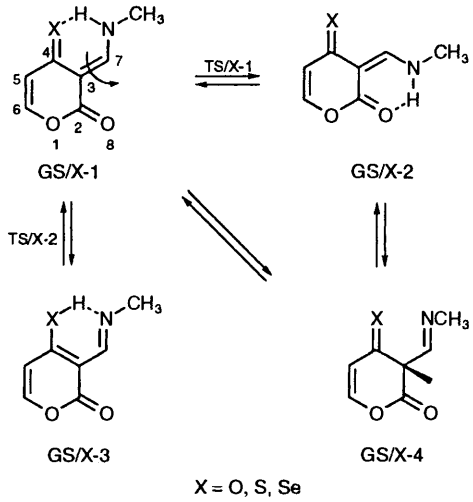
	d(C–X)	d(C–N)	d(N–H)	d(X–H)/d(O–H)[a]	d(C–C_{exo})	<X–H–N/<N–C–C–C(X)[b]
GS/O-1	1.215	1.309	1.002	1.974	1.382	129.7
GS/O-2	1.206	1.310	1.001	2.012	1.381	237.9
GS/O-3	1.305	1.260	1.820	0.970	1.462	143.5
GS/O-4	1.190	1.244	—	—	1.506	115.5
TS/O-1	1.218	1.274	1.002	—	1.460	86.1
TS/O-2	1.267	1.276	1.291	1.176	1.432	152.3
GS/S-1	1.676	1.299	1.005	2.290	1.400	135.7
GS/S-2	1.665	1.302	1.002	1.949	1.396	128.7
GS/S-3	1.750	1.255	2.007	1.327	1.478	136.7
GS/S-4	1.620	1.244	—	—	1.508	118.7
TS/S-1	1.696	1.272	1.002	—	1.469	89.5
TS/S-2	1.730	1.265	1.401	1.516	1.455	151.8
GS/Se-1	1.776	1.298	1.007	2.300	1.404	137.1
GS/Se-2	1.764	1.301	1.002	1.962	1.399	128.4
GS/Se-3	1.861	1.254	2.063	1.472	1.478	128.9
GS/Se-4	1.707	1.242	—	—	1.514	139.9
TS/Se-1	1.815	1.281	1.002	—	1.468	95.9
TS/Se-2	1.836	1.264	1.445	1.605	1.459	147.9

[a] d(O–H) for GS/X-2. [b] <N–C–C–C(X) for TS/X-1 and GS/X-4.

equilibrium with the CH isomer by addition of a catalytic amount of acid. The energy of species such as **3** estimated theoretically agrees with the above suggestion (see below).

Calculations.—The relative energies of tautomeric forms and geometrical isomers as well as the barriers to N → X (X = O, S, Se) hydrogen transfer and rotation around the exocyclic C=C bond were estimated by *ab initio* calculations with the 6-31G* basis at HF and MP2 levels referring to the model molecules of 3-methylimino-4-hydroxy(thio, seleno)-2-pyrone with possible isomers depicted in Scheme 3. The data obtained are represented in Table 2. Selected geometrical parameters are listed in Table 3. Those for the GS/O-1 isomer are consistent with X-ray diffraction data.[14] The solvent effects were taken into account by means of the reaction field approach where the solvent is modelled as a homogeneous polarizable medium.[9] The entropy contribution was estimated for X=O.

The selected level of *ab initio* calculation appears to provide satisfactory results for a description of prototropic tautomerism in **1**, **2**. Discrepancies between the results obtained for tautomeric heterocyclic compounds by different semiempirical computational methods have recently been reviewed[19] and only the modern parametrizations such as AM1 and PM3 have been shown to be appropriate. For **1**, **2**, the tautomeric keto amino form was found to be preferred to the hydroxy imino form for all the donor atoms X = O, S, Se in accordance with experimental results. The latter form is destabilized by 24.3, 49.4 and 48.1 kJ mol^{-1}, respectively. The increased stability of the keto amine form for X = S, Se compared with X = O is consistent with the experimental results on the study of



Scheme 3

tautomeric equilibrium in β-aminopropenones(thiones, selones) indicating a shift of the equilibrium towards a keto amine form in the case of X = S, Se.[20] Activation energies of a hydrogen transfer considered as a [1,5]-proton shift were calculated to be 30.5 (X = O), 45.6 (X = S) and 36.4 kJ mol^{-1} (X = Se).

Calculations correctly predicted the higher stability of *Z*-isomers, however, the increase in the energy gap between *Z* and *E* forms found to be S (1.3 kJ mol^{-1}) < O (3.3) < Se (23.0) does not correspond to that obtained from NMR data

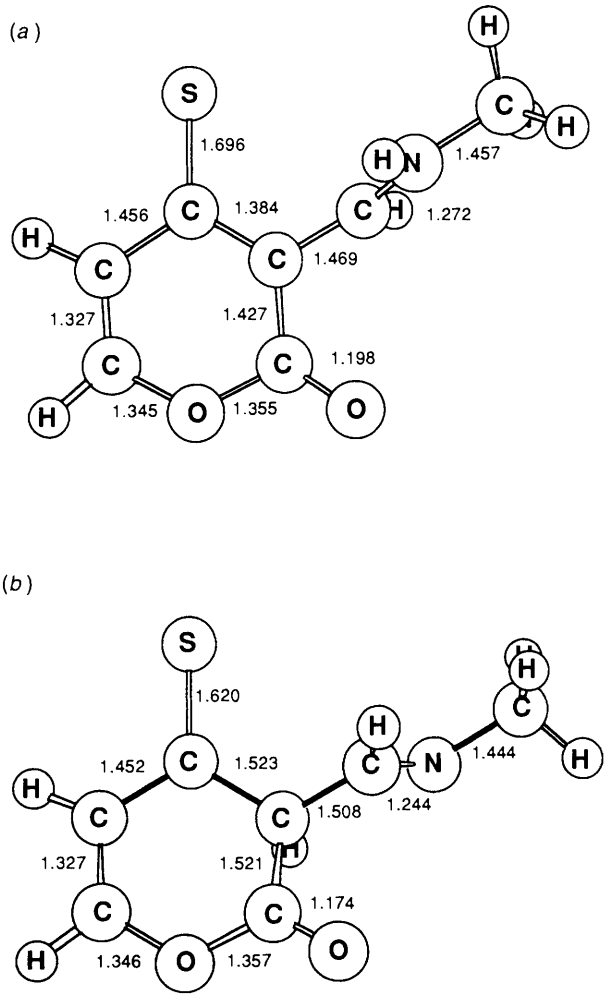


Fig. 1 MP2/6-31G* optimized structures of (*a*) TS/S-1 and (*b*) GS/S-4 with selected bond distances (Å)

Table 4 π-Bond orders for GS/X-1 according to PM3 calculations

Bond	X = O	X = S	X = Se
C(5)C(6)	0.84	0.80	0.79
C(4)C(5)	0.08	0.14	0.15
C(3)C(4)	0.13	0.29	0.34
C(2)C(3)	0.11	0.10	0.10
C(2)O(8)	0.85	0.85	0.85
C(3)C(7)	0.46	0.35	0.32
C(4)X	0.80	0.52	0.42
C(7)N	0.48	0.59	0.62

Se < S < O. This disagreement refers to X = Se displaying a markedly higher energy for the *E* form. Despite the fact that the estimated solvent effects (ε = 40) are small and do not exceed 2.1 kJ mol^{-1}, in view of the low *Z*:*E*-energy separation comparable to these values for X = O, S the position of equilibrium may be strongly affected by solvent.

The activation barriers to rotation around the exocyclic C=C bond were found to be X = Se (105.5 kJ mol^{-1}) < S (117.6) < O (149.0), in increasing order consistent with experimental data. The calculated structure for TS/S-1 transition state is shown in Fig. 1. For all the three cases, X = O, S, Se, the enamine moiety is oriented almost perpendicularly with respect to the pyranone ring so that the torsion angle N–C–C–C(X) is close to 90° (Table 3).

The electronic factors of the substituents adjacent to the C=C bond is known to be responsible for the height of the rotation barrier. σ- and π-electron-withdrawing groups decrease its double-bond character and thus facilitate interconversion whereas the electron-donating groups result in more hindered rotation. To rationalize the contribution related to the effects of π-delocalization induced by variations of X we calculated the corresponding π-bond orders in the model molecule GS/X-1 using semiempirical PM3 method. The data are given in Table 4. π-Bond orders of C(3)=C(7) increase in the order X = Se (0.32) < S (0.35) < O (0.46) following the enhancement of calculated barriers and showing the influence of the better electron-accepting properties of the carbonyl group compared with chalcogenocarbonyl group. It is noteworthy that the C(6)C(5)C(4)C(3)C(7)XN fragment displays pronounced conjugation and correlated changes in π-bond orders of the involved single and double bonds whereas the bond order of lactone carbonyl group C(2)O(8) is invariably 0.85.

With reference to the magnitude of calculated barriers, these are about 70 kJ mol^{-1} larger than those obtained from dynamic NMR spectroscopy. Since the experimental data indicate that the interconversion could be acid-promoted, we have also estimated the energy of the third plausible tautomeric form GS/X-4 (Fig. 1) where the labile proton is bound to a carbon atom. This form is usually less favoured in the case of Schiff bases but can be found in measurable amounts for β-diketones and arylimines of β-keto esters. The calculated relative energies of 90.8 (X = O), 90.4 (X = S) and 116.7 kJ mol^{-1} (X = Se) are 58.1 (X = O), 27.2 kJ mol^{-1} (X = S) lower and 11.7 kJ mol^{-1} (X = Se) higher than that of the transition state TS/X-1 in terms of rotation. Therefore the alternative interconversion pathway involving the GS/X-4 intermediate seems to be very likely, particularly for X = O, S.

Finally, the vibrational corrections for enthalpy and entropy contributions to the relative energies of the TS/O-1 and GS/O-2 states were estimated at the HF/3-21G level. These are insignificant: $\Delta\Delta H^{\ddagger} = -4.64$, $-T\Delta\Delta S^{\ddagger} = 0.05$ kJ mol^{-1} (T = 300 K); $\Delta\Delta H^{\circ} = 0.25$, $-T\Delta\Delta S^{\circ} = 0.13$ kJ mol^{-1} (T = 300 K).

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References

1 T. Yamaguchi, K. Saito, T. Tsujimoto and H. Yuki, *J. Heterocycl. Chem.*, 1976, **13**, 533; *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1161.
2 K. Saito and T. Yamaguchi, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1605.
3 S.-F. Tan, K.-P. Ang, H. L. Jayachandran, A. J. Jones and W. R. Begg, *J. Chem. Soc., Perkin Trans. 2*, 1982, 513.
4 (*a*) D. Heber, *Arch. Pharm. (Weinheim)*, 1987, **320**, 595; (*b*) R. Djudjič and M. Trkovnik, *Monatsh. Chem.*, 1991, **122**, 77; (*c*) T. Steinführer, A. Hantschmann, M. Pietsch and M. Weißenfels, *Liebigs Ann. Chem.*, 1992, 23; (*d*) I. Ivanov, S. K. Karagiosov and M. F. Simeonov, *Liebigs Ann. Chem.*, 1992, 203.
5 D. S. Stephenson and G. Binch, DNMR5, *An Iterative Nuclear Magnetic Resonance Program for Unsaturated Exchange-Broadened Bandshapes*, *QCPE Bull.*, 1989, **8**, 365.
6 M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Anders, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart and J. A. Pople, GAUSSIAN 92, Gaussian Inc., Pittsburg PA, 1992.
7 W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986.
8 J.-M. Lehn, G. Wipff and J. Demuynck, *Helv. Chim. Acta*, 1977, **60**, 1239.
9 M. W. Wong, M. J. Frisch and K. B. Wiberg, *J. Am. Chem. Soc.*, 1991, **113**, 4776.
10 J. J. P. Stewart, MOPAC v6.0, *QCPE Bull.*, 1990, **10**, 86.

11 D. L. Klayman and T. S. Griffin, *J. Am. Chem. Soc.*, 1973, **95**, 1979.
12 (*a*) R. Sakellariou, V. Speziale and M. Hamdi, *Synth. Commun.*, 1990, **20**, 3443; (*b*) V. S. Speziale, R. Sakellariou and M. Hamdi, *Synthesis*, 1992, 921; (*c*) M. Hamdi, R. Sakellariou and V. Speziale, *J. Heterocycl. Chem.*, 1992, **29**, 1817.
13 (*a*) P. Ollinger, O. S. Wolfbeis and H. Junek, *Monatsch. Chem.*, 1975, **106**, 963; (*b*) O. S. Wolfbeis and A. Knierzinger, *J. Heterocycl. Chem.*, 1980, **17**, 225.
14 G. Xiao, D. van der Helm, R. C. Hider and P. S. Dobbin, *Acta Crystallogr., Sect. C*, 1993, **49**, 980.
15 V. P. Litvinov, A. F. Vaisburg and V. Yu. Mortikov, *Sulfur Rep.*, 1992, 321.
16 J. A. Bovey, J. Jelinski and P. A. Murau, *Nuclear Magnetic Resonance Spectroscopy*, 2nd edn., Academic Press, New York, 1988.
17 (*a*) W. Schroth and G. W. Fischer, *Chem. Ber.*, 1969, **102**, 575; (*b*) V. A. Bakhmutov and V. A. Burmistrov, *Org. Magn. Reson.*, 1979, **12**, 185.
18 D. L. Dotson and H.-H. Lo, *J. Heterocycl. Chem.*, 1992, **29**, 1361.
19 A. R. Katritzky, M. Karelson and P. Harris, *Heterocycles*, 1991, **32**, 329.
20 A. D. Garnovskii, A. L. Nivorozhkin and V. I. Minkin, *Coord. Chem. Rev.*, 1993, **126**, 1.

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