Spontaneous resolution of new conglomerates in the series of 4-arenesulfonyliminocyclohex-2-en-1-ones

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Racemic mixtures **1a**–**f**, **2a**–**e** crystallise as conglomerates at room temperature and lead to spontaneous resolution; tosylimines **1e** and **2c** give homochiral crystals (space group *P*1), whereas similar benzenesulfonyloximes **3a**,**b** give heterochiral packings (space groups $P2_1/n$ and $P2_1/c$, respectively).

Conglomerate formation is a necessary condition both for spontaneous resolution of enantiomers and for resolution by crystallization from optically active solvents or by an entrainment procedure.[1] Conglomerate formation is of poor occurrence; up to 1979 only 250 conglomerates were reported, according to nowaday estimations the frequency of organic conglomerates does not exceed 10%,[1] so that a search for conglomerates comprises an essential challenge. Some previous studies[2] have shown that this proportion can fluctuate to a large extent in some particular series of organic compounds. Earlier we have found conglomerates among various classes of organic compounds using X-ray data,[3,4] resolution by crystallization from optically active solvents,[5,6] and engineering homochiral crystals.[7,8]

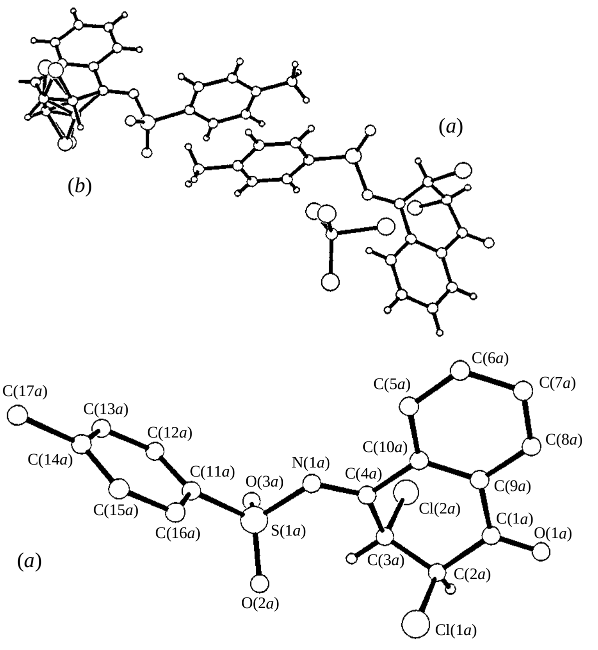


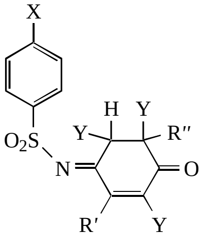
Figure 1 Crystal structure of **2c**. Above: two independent molecules of **2c** (*a* and *b*) and a molecule of the entrained CCl_4, in the molecule *b* a statistical disorder on two positions of the C(2*b*)C(3*b*) fragment is observed; below: the molecular structure of an independent molecule *a* of **2c**. Selected bond lengths (Å): S(1*a*)–N(1*a*) 1.672(4), Cl(1*a*)–C(2*a*) 1.800(6), Cl(2*a*)–C(3*a*) 1.843(7), O(1*a*)–C(1*a*) 1.205(7), N(1*a*)–C(4*a*) 1.287(7), C(1*a*)–C(9*a*) 1.478(8), C(1*a*)–C(2*a*) 1.517(8), C(2*a*)–C(3*a*) 1.462(9), C(3*a*)–C(4*a*) 1.513(8), C(4*a*)–C(10*a*) 1.482(7), C(9*a*)–C(10*a*) 1.390(8); selected dihedral angles (°): S(1*a*)–N(1*a*)–C(4*a*)–C(10*a*) 179.9(4), S(1*a*)–N(1*a*)–C(4*a*)–C(3*a*) 3.0(8), C(3*a*)–C(4*a*)–C(10*a*)–C(9*a*) 17.7(7), C(2*a*)–C(3*a*)–C(4*a*)–C(10*a*) 45.2(7), Cl(1*a*)–C(2*a*)–C(3*a*)–Cl(2*a*) 177.9(3).

Table 1 Conditions of crystallization and optical activity of the obtained compounds.

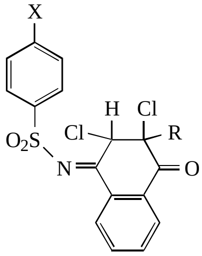
Compound	Solvent for the crystal growth	Number of crystals	Weight of each crystal/ mg	Optical activity of each crystal[a] $[\alpha]^{20}_{546}$/° (*c*, $CHCl_3$)	
1a	$CHCl_3$–*n*-heptane (1:1)	4	3.6–13.2	+2.7–9.3	(0.6–1.1)
		3	9.1–29.1	–4.0–7.0	(0.8–2.4)
1b	$CHCl_3$	2	10.7–30.4	+2.4–5.6	(0.9–2.5)
		1	11.1	–3.2	(0.9)
1c	$CHCl_3$–*n*-heptane (3:2)	1	26.6	+0.8	2.2)
		1	6.3	–3.8	(0.5)
1d	$CHCl_3$–*n*-heptane (1:1)	1	12.4	+4.8	(1.0)
		2	11.5–29.0	–2.9–3.1	(1.0–2.4)
1e	$CHCl_3$	3	2.7–12.2	+2.1–7.8	(0.2–0.9)
		1	12.2	+2.1	(0.9)[b]
		3	7.5–63.4	–2.8–6.4	(0.5–5.3)
1f	$CHCl_3$–*n*-heptane (3:2)	1	28.2	+12.3	(2.4)
		1	15.2	+2.4	(1.3)[c]
		1	56.1	–7.2	(4.7)
2a	$CHCl_3$–*n*-heptane (1:2)	2	20.5–26.4	+2.3–2.7	(1.7–2.2)
		1	14.0	–2.6	(1.2)
2b	$CHCl_3$–CCl_4 (1:1)	1	15.9	+8.7	(1.3)
		3	11.1–14.2	–7.2–9.6	(0.9–1.2)[d]
2c	CCl_4	2	11.5–12.6	+1.9–2.1	(1.0)
		2	1.3–2.5	+8.8–21.2	(0.1–0.2)[c]
		1	29.0	+0.8	(2.4)[e]
		1	53.5	–2.2	(4.4)
2d	$CHCl_3$–*n*-heptane (1:1)	1	12.6	+1.0	(1.1)
		1	11.5	–1.1	(1.0)
2e	$CHCl_3$–*n*-heptane (2:1)	2	3.3–13.1	+3.2–5.5	(0.3–1.1)
		1	7.5	–5.1	(1.0)
2c[f]	Me_2CO–*n*-hexane (1:5)	the entire precipitate	45.2	–1.3	(3.8)

[a] Optical rotation was measured on a Polamat A polarimeter. [b] In MeOH. [c] In Me_2CO. [d] Optical rotation remained unchanged after 1 week at 20 °C. [e] In EtOH. [f] **2c** (100 mg) was powdered, treated under a vacuum (1 Torr, 2 h) in order to remove the entrained CCl_4, and then crystallised from a mixture of the solvents with the addition of deficiency of CCl_4 (the ratio **2c**:CCl_4 = = 4:1).

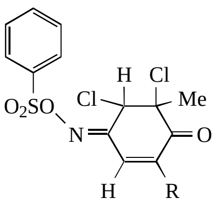
In this work, another intriguing instance of conglomerate formation has been found in the rather wide series of derivatives of 4-arenesulfonyliminocyclohex-2-en-1-ones **1**, **2**. Compounds of this class have been synthesised recently by the halogenation of corresponding *N*-arenesulfonyl-*p*-quinone imines or 4-arenesulfonylaminophenols.[9] Similar 4-arenesulfonyloximinocyclohex-2-en-1-ones such as **3** have been obtained by the chlorination of corresponding *O*-arenesulfonyl-*p*-quinone oximes.[10–12] We optimised the above methodology and thus rised the yields by 11–25% up to 75–86% (*cf.* ref. 12), improved the purity of **1b**,**c**,**f**, **2b**, **3a** (the analytically pure products were obtained after single crystallizations) and synthesised **1a**,**c**,**d**, **2a**,**d** and **3b** for the first time. All the products were characterised by spectroscopic data[†] and elemental analysis; the structures of **1e**, **2c** and **3a**,**b** were also confirmed by X-ray diffraction analysis (the data for **1e** and **3a**,**b** will be published later). Compounds **1** and **2** both in solution and in crystals exist solely in the form of *E*-isomers relative to the double cyclohexene bond. For compound **3** in solution *Z*- and *E*-isomers are observed, whereas only the *E*-isomer is detected in a crystal (*cf.* refs. 10–12). All the above compounds are stable and give well-formed, rather large-sized, transparent crystals. By testing the optical activity of individual crystals, (+)- and (–)-enantiomers of compounds **1** and **2** were isolated. This results in the identification of 11 new conglomerates (Table 1). Consistently, X-ray diffraction analysis performed on **1e** and **2c** demonstrated that single crystals contain homochiral molecules (space groups *P*1) (Figure 1).[‡] By contrast, structurally related *O*-benzenesulfonyloximes **3a**,**b** form centrosymmetric crystals and thus do not lead to any spontaneous resolution.



1a–f



2a–e



3a,**b**

a X = H, R′ = Me, R″ = Y = Cl
b X = H, R′ = R″ = Y = Cl
c X = H, R′ = R″ = Me, Y = Br
d X = R′ = Me, R″ = Y = Cl
e X = Me, R′ = R″ = Y = Cl
f X = Cl, R′ = R″ = Y = Cl

a X = H, R = H
b X = H, R = Cl
c X = Me, R = H
d X = Cl, R = H
e X = Cl, R = Cl

a R = Me
b R = Cl

Compound **2c** crystallises as a CCl_4 solvate with the 2:1 stoichiometry. This achiral solvent molecule could favour the crystallization in non-centrosymmetric space group and thus acts as a conglomerator.[13] Therefore, a predetermined optical enrichment of compound **2c** can be performed by crystallization in the presence of a half-mole quantity of CCl_4. In this case, the entire precipitate possessed optical activity whereas upon crystallization from CCl_4 only individual crystals were optically active, but the entire precipitate was a racemic conglomerate.

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[†] *Characteristics and spectroscopic data*. ^1H and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, in $CDCl_3$.

1a: yield 72%, mp 124–125 °C (AcOH). ^1H NMR, δ: 2.25 (s, 3H, 3-Me), 6.64 (s, 1H, 5-H), 7.62, 7.72 and 8.05 (m, 5H, Ph). IR, ν/cm^{-1}: 1725 (C=O), 1610, 1584 (C=N, C=C), 1338, 1170 (SO_2).

1b:[9] yield 78%, mp 137–138 °C (AcOH). ^1H NMR, δ: 6.69 (s, 1H, 5-H), 7.63, 7.74 and 8.07 (m, 5H, Ph). ^{13}C NMR {^1H}, δ: 58.2 [C(5)], 81.2 [C(6)], 127.8, 129.4, 134.5 and 138.2 (Ph), 138.6, 143.8 [C(2), C(3)], 160.3 [C(4)], 173.4 [C(1)].

1c: yield 86%, mp 155–156 °C (AcOH). ^1H NMR, δ: 2.19 (s, 3H, 6-Me), 2.28 (s, 3H, 3-Me), 6.48 (s, 1H, 5-H), 7.60, 7.70 and 8.05 (m, 5H, Ph). ^{13}C NMR {^1H}, δ: 20.12 (3-Me), 25.48 (6-Me), 46.59 [C(5)], 55.58 [C(6)], 127.55, 129.18, 133.91 and 139.32 (Ph), 133.95 [C(2)], 148.22 [C(3)], 167.10 [C(4)], 181.50 [C(1)]. IR, ν/cm^{-1}: 1710 (C=O), 1600 (C=N, C=C), 1320, 1169 (SO_2).

1d: yield 62%, mp 142–143 °C (AcOH). ^1H NMR, δ: 2.24 (s, 3H, 3-Me), 2.50 (s, 3H, Me), 6.66 (s, 1H, 5-H), 7.40 and 7.92 (dd, 4H, C_6H_4, ^3J 8.4 Hz). ^{13}C NMR {^1H}, δ: 17.02 (3-Me), 21.71 (Me), 58.64 [C(5)], 81.63 [C(6)], 127.82, 129.93, 145.52, and 146.46 (C_6H_4), 135.83 [C(2)], 145.52 [C(3)], 164.67 [C(4)], 174.83 [C(1)]. IR, ν/cm^{-1}: 1723 (C=O), 1595, 1570 (C=N, C=C), 1339, 1161 (SO_2).

1e:[9] yield 77%, mp 141–142 °C (AcOH). ^1H NMR, δ: 2.49 (s, 3H, Me), 6.71 (s, 1H, 5-H), 7.40 and 7.97 (dd, 4H, C_6H_4, ^3J 8.3 Hz). ^{13}C NMR {^1H}, δ: 21.77 (Me), 52.8 [C(5)], 81.40 [C(6)], 128.03, 130.05, 135.46, and 145.89 (C_6H_4), 138.70 and 143.96 [C(2), C(3)], 160.02 [C(4)], 173.52 [C(1)]. IR, ν/cm^{-1}: 1724 (C=O), 1610, 1555 (C=C, C=N), 1346, 1168 (SO_2).

1f:[9] yield 75%, mp 141–142 °C (AcOH). ^1H NMR, δ: 6.63 (s, 1H, 5-H), 7.60 and 8.00 (dd, C_6H_4, ^3J 8.7 Hz). IR, ν/cm^{-1}: 1723 (C=O), 1600, 1553 (C=C, C=N), 1350, 1170 (SO_2).

2a: yield 81%, mp 130–131 °C (CCl_4). ^1H NMR, δ: 4.76 (d, 1H, 2-H, ^3J 3.9 Hz), 6.55 (d, 1H, 3-H, ^3J 3.9 Hz), 7.61, 7.68 and 8.13 (m, 5H, Ph), 7.61 and 8.12 (m, 4H, 5,6,7,8-H).

2b:[9] yield 82%, mp 141–142 °C (AcOH). ^1H NMR, δ: 6.83 (s, 1H, 3-H), 7.61, 7.70 and 8.10 (m, 5H, Ph), 7.78 and 8.14 (m, 4H, 5,6,7,8-H). IR, ν/cm^{-1}: 1719 (C=O), 1612, 1583 (C=C, C=N), 1330, 1161 (SO_2).

2c:[9] yield 84%, mp 136–137 °C (CCl_4). ^1H NMR, δ: 2.48 (s, 3H, Me), 4.75 (d, 1H, 2-H, ^3J 3.6 Hz), 6.57 (d, 1H, 3-H, ^3J 3.6 Hz), 7.40 and 7.99 (dd, 4H, C_6H_4, ^3J 8.1 Hz), 7.75 and 8.13 (mm, 4H, 5,6,7,8-H). IR, ν/cm^{-1}: 1705 (C=O), 1612, 1587 (C=N, C=C), 1330, 1165 (SO_2).

2d: yield 86%, mp 138–139 °C (CCl_4). ^1H NMR, δ: 4.77 (d, 1H, 2-H, ^3J 3.3 Hz), 6.51 (d, 1H, 3-H, ^3J 3.6 Hz), 7.58 and 8.04 (m, 4H, C_6H_4, ^3J 8.7 Hz), 7.77 and 8.12 (m, 4H, 5,6,7,8-H).

2e:[9] yield 80%, mp 167–168 °C (AcOH). ^1H NMR, δ: 6.78 (s, 1H, 3-H), 7.60 and 8.05 (dd, 4H, C_6H_4, ^3J 8.7 Hz), 7.80 and 8.17 (m, 4H, 5,6,7,8-H). IR, ν/cm^{-1}: 1725 (C=O), 1620, 1589 (C=C, C=N), 1343, 1170 (SO_2).

3a:[12] yield 78%, mp 110 °C (AcOH); the ratio of isomers *E*/*Z* = 2.1. *E*-isomer: ^1H NMR, δ: 1.85 (s, 3H, 6-Me), 2.02 (d, 3H, 2-Me, ^4J 1.5 Hz), 5.47 (d, 1H, 3-H, ^4J 1.5 Hz), 6.76 (s, 1H, 5-H), 7.58, 7.71 and 8.01 (m, 5H, Ph). ^{13}C NMR {^1H}, δ: 16.74 (6-Me), 22.33 (2-Me), 53.18 [C(5)], 63.35 [C(6)], 122.67, 129.05, 129.25 and 130.03 (Ph), 134.56 and 140.54 [C(2), C(3)], 157.24 [C(4)], 188.80 [C(1)]. *Z*-isomer: 1.86 (s, 3H, 6-Me), 2.07 (d, 3H, 2-Me, ^4J 1.5 Hz), 4.89 (d, 1H, 3-H, ^4J 1.5 Hz), 7.27 (s, 1H, 5-H), 7.58, 7.71 and 8.01 (m, 5H, Ph). ^{13}C NMR {^1H}, δ: 16.98 (6-Me), 22.75 (2-Me), 61.71 [C(5)], 65.10 [C(6)], 122.67, 129.00, 129.24 and 130.03 (Ph), 134.44 and 141.74 [C(2), C(3)], 155.75 [C(4)], 188.60 [C(1)]. IR, ν/cm^{-1}: 1703 (C=O), 1630, 1590 (C=N, C=C), 1394, 1209 (SO_2).

3b: yield 73%, mp 143 °C (AcOH), the ratio of isomers in $CDCl_3$ *E*/*Z* = 4.0. *E*-isomer: ^1H NMR, δ: 1.90 (s, 3H, 6-Me), 5.49 (s, 1H, 3-H), 7.15 (s, 1H, 5-H), 7.59, 7.72 and 8.00 (m, 5H, Ph). *Z*-isomer: 1.90 (s, 3H, 6-Me), 5.48 (s, 1H, 3-H), 7.14 (s, 1H, 5-H), 7.59, 7.72 and 8.00 (m, 5H, Ph).

[‡] *Crystallographic data for* **2c** at 20 °C: $(C_{17}H_{13}NO_3SCl_2)_2 \cdot CCl_4$, triclinic, crystal size 0.36×0.39×0.48 mm, space group *P*1, $a = 12.959(5)$ Å, $b = 13.271(6)$ Å, $c = 13.951(7)$ Å, $\alpha = 63.03(4)°$, $\beta = 77.56(4)°$, $\gamma = 71.69(5)°$, $V = 2023$ Å^3, $Z = 2$, $d_{calc} = 1.508$ g cm^{-3}, μ(MoKα) = 0.706 mm^{-1}, $F(000) = 932$. The intensities of 7581 reflections were measured on an Enraf-Nonius CAD-4 diffractometer at 20 °C (λMoKα radiation, $\theta/2\theta$ scan, $12° < \theta < 23°$), and 6075 independent reflections were used in further calculations and refinement. The structure was solved by a direct method and refined using the full-matrix least-squares method against F^2 in the anisotropic–isotropic approximation. The refinement is converged to $wR_2 = 0.2148$ and GOF = 0.988 for all independent reflections [$R_1 = 0.0789$ is calculated against F for 6044 observed reflections with $I > 2\sigma(I)$]. The number of refined parameters is 514. All the calculations were performed using the SHELXS and SHELXL 93 programs. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun*., 2000, Issue 1. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/60.

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