Relationship between Chemical Selectivity and Melting Points of Reacting Molecules

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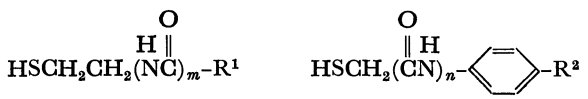
Synopsis. A relationship has been found to exist between the selectivity (the ratio of an unsymmetrical disulfide to symmetrical one) in the oxidation of a pair of associating thiols, 1-acyl-3-(2-sulfhydrylethyl)urea (**1**) and 1-(*p*-*N*,*N*-dimethylaminophenyl)-3-(sulfhydrylacetyl)urea, and the melting point of **1** in cases where **1** belongs to a homologous series.

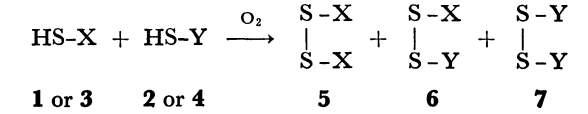
As a continuing study on a correlation of reaction behavior of molecules (*i.e.*, chemical selectivity) with their physicochemical properties,[1] this paper describes a relationship between the selectivity in the oxidation of a pair of associating thiols and the melting point of one of these two thiols.

Previously we have examined the oxidation of a pair of associating thiols (**1** and **2**) with O_2 in 80% (v/v) acetonitrile–20% water. The selectivity (R) in this oxidation was represented by the ratio of an unsymmetrical disulfide (**6**) to symmetrical one (**7**) (R=**6**/**7**).[2] The result is illustrated in Fig. 1. In the case of **1a** and **2**, maximal selectivity occurred at j=2.[2] In contrast, with **1b** and **2** alternation in the selectivity was clearly observed: R was 4.5, 0.28, 0.53, 0.29, and 0.40 for k=0, 1, 2, 3, and 4, respectively.[2] Further, with **1c** and **2**, maximal selectivity (R=16) occurred at x=2.



1a m=2; R^1=$(CH_2)_jCH(CH_3)_2$
1b m=2; R^1=$(CH_2)_kCH_2CH_2CH_3$
1c m=2; R^1=$(CH_2)_xC_6H_5$
3a m=1; R^1=$(CH_2)_jCH(CH_3)_2$
3c m=1; R^1=$(CH_2)_xC_6H_5$

2 n=2; R^2=$N(CH_3)_2$
4 n=1; R^2=H



1 or **3** **2** or **4** **5** **6** **7**

The data in Fig. 1 also indicate that the melting point of **1** depends sharply on the structure of R^1: **1a** or **1c** displayed maximal melting point at j=2 or x=2, respectively, while **1b** showed a striking alternation in melting points.[3] Therefore, Fig. 1 shows that the structure-selectivity profile for the oxidation of **1** and **2** is similar to the structure-melting point profile for **1**. It should be noted that this relationship between the selectivity and melting points does not hold for **1** having the para-substituted phenyl groups as R^1, which do not belong to a homologous series.

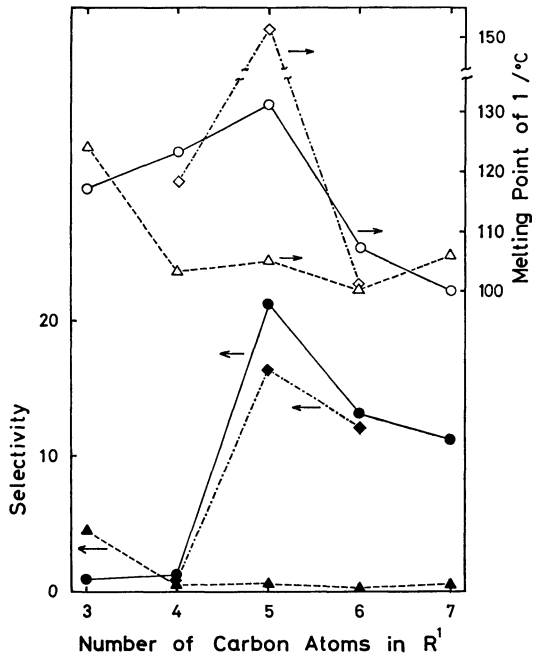


Fig. 1. Dependence of the selectivity (R=**6**/**7**), in the oxidation of a 1:1 mixture of **1** and **2** with oxygen, and of the melting point of **1** on the number of carbon atoms in R^1. With **1c** [R^1=$(CH_2)_xC_6H_5$] the number of carbon atoms in R^1 is counted as "x+3." ●, R for the oxidation of **1a** and **2**; ▲, R for the oxidation of **1b** and **2**; ◆, R for the oxidation of **1c** and **2**; ○, melting point of **1a**; △, melting point of **1b**; ◇, melting point of **1c**. Thiol **2** melted at 173 °C.

Control experiments using **1a** (or **3**) and **4** made it clear that the selectivity was insensitive to the structure of R^1 (Fig. 2): (i) in the case of **1a** and **4**, R showed a small maximum at j=1, (ii) with **3a** and **4**, R ranged only from 1.8 to 1.9, and (iii) with **3c** and **4**, R showed a small maximum at x=2. Moreover, it was found that the melting point of **3a** decreased progressively with the number of carbon atoms in R^1 and that **3c** displayed maximal melting point (66 °C) at x=2 (Fig. 2). These findings demonstrate that with **1a** (or **3**) and **4** the correlation described above does *not always* exist.[4]

^{1}H NMR results together with other experimental data revealed that **1a** (j=2) [or **1b** (k=2)] and **2** form weak complexes with each other as well as with themselves.[5] Furthermore, the degree of association (f)[6] for amide derivatives (**3** and **4**) proved to be much smaller than f for acylurea derivatives (**1** and **2**). This suggests that **1** and **2** associate strongly with themselves, while **3** and **4** associate very weakly with

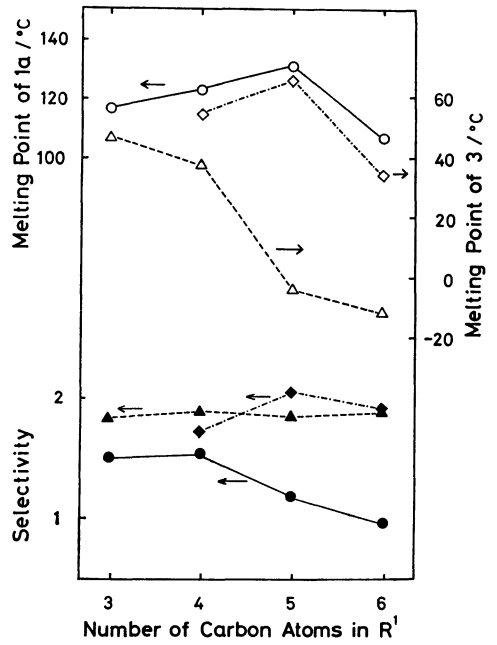


Fig. 2. Dependence of the selectivity (R=**6**/**7**), in the oxidation of a 1:1 mixture of **1a** (or **3**) and **4**, and of the melting points of **1a** and **3** on the number of carbon atoms in R^1. With **3c** [$R^1=(CH_2)_xC_6H_5$] the number of carbon atoms in R^1 is also counted as "x+3." ●, R for the oxidation of **1a** and **4**; ▲, R for the oxidation of **3a** and **4**; ◆, R for the oxidation of **3c** and **4**; ○, melting point of **1a**; △, melting point of **3a**; ◇, melting point of **3c**. Thiol **4** melted at 113 °C.

themselves and that **4** associates very weakly with **3**—or even with **1a** because of marked difference in f between **4** and **1a**.

All of the data presented here would suggest that chemical selectivity in the reaction of a pair of associating molecules can be correlated with the melting point of one of these two molecules in cases where one of these two molecules belongs to a homologous series.

Experimental

Materials. Thiols **1**, **2**, and **4** were prepared as described before.[5,7] Thiol **3** was synthesized according to the method previously reported.[8] Satisfactory spectroscopic data were used to support the assignment of all new compounds.

Oxidation of a Pair of Thiols. A 1:1 mixture of **1** and **2** [or of **1a** (or **3**) and **4**, 0.5 mmol each] was treated with oxygen at 35.0 °C in 12.5 ml of 80% (v/v) acetonitrile–20% water in the presence of a catalytic amount of Et_3N (0.05 mmol). When the oxidation was completed, the reaction mixture was evaporated to dryness. Yields of **6** and **7** were determined by the use of their absorption at 310 nm after separation by TLC in the oxidation of **1** and **2**,[9] and determined gravimetrically after separation by preparative TLC in the oxidation of **1a** (or **3**) and **4**.

Determination of Melting Points. Melting points of thiols (**1**—**4**) were obtained from the DTA (Differential Thermal Analysis) curves recorded with a Shimadzu DT-20B thermal analysis apparatus. The samples were finely powdered, diluted with fine-grained quartz wool in the specimen holder, and heated in a stream of nitrogen with a heating rate of 10 °C/min.

Determination of Degree of Association (f). The effective mole fraction of the solute was determined on a Hitachi Perkin-Elmer 115 molecular weight apparatus using a differential vapor pressure method at 36.0 °C and 0.01 M (1 M= 1 mol dm^{-3}) in benzene.[10]

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References

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2) T. Endo, A. Kuwahara, H. Tasai, T. Murata, M. Hashimoto, and T. Ishigami, *Nature*, **268**, 74 (1977).
3) It is rather a frequent phenomenon that there is a radical difference in the structure dependence of melting points between the homologs of the branched alkyl and straight-chain alkyl groups, as is the case with *N*-phenylcarboxamides ($R^3CONHC_6H_5$): maximal melting point occurs at the isobutyl group for $R^3=i\text{-}C_3H_7$ to $i\text{-}C_6H_{13}$, whereas alternation in melting points occurs for $R^3=n\text{-}C_3H_7$ to $n\text{-}C_6H_{13}$.
4) Intermolecular association is considered to aid to correlate chemical selectivity with melting points.
5) T. Endo, Y. Takeda, T. Orii, Y. Kaneko, and M. Kondo, *Chem. Lett.*, **1979**, 1455.
6) The value of f is obtained by dividing the stoichiometric mole fraction of the solute by the effective mole fraction of the solute. The f value for **3** and **4** was less than 1.05, and the f value for **1** and **2** ranged from 1.3 to 1.5.
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