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PHENYL AND CYCLOHEXYL GROUPS AS SIMILARLY-SHAPED SUBSTITUENTS PRODUCING VERY SIMILAR CHEMICAL SELECTIVITY IN OXIDATION OF ASSOCIATING THIOLS

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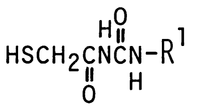
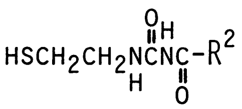
The selectivity in oxidation of a pair of associating thiols, one with R^2 as a substituent, was examined in aqueous acetonitrile. The selectivity for acyclic alkyl groups (R^2) differed entirely from that for the cyclohexyl and phenyl groups (R^2) at 35.0 °C. The pattern of temperature dependence of the selectivity for the two similarly-shaped cyclic groups (*i.e.*, cyclohexyl and phenyl groups) was very similar to each other.

We have been studying the factors controlling chemical selectivity using model compounds which can associate with each other,[1)] and report here the first example that the chemical selectivity for cyclohexyl and phenyl groups (similarly-shaped cyclic substituents) in one of the reacting molecules is very similar to each other, but differs entirely from that for acyclic groups. The model reaction used is oxidation of a pair of associating thiols (1 and 2).[2,3)] The selectivity (r) is represented by the logarithmic ratio of the yield of the unsymmetrical



$HSCH_2C(=O)NHC(=O)NH\text{-}R^1$



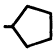
$HSCH_2CH_2NHC(=O)NHC(=O)\text{-}R^2$

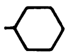
1a $R^1 = (CH_2)_4Me$

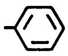
1b $R^1 = (CH_2)_2CHMe_2$

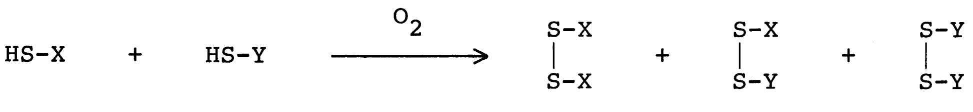
2a $R^2 = (CH_2)_mMe$

2b $R^2 = (CH_2)_3CHMe_2$

2c $R^2 =$ 

2d $R^2 =$ 

2e $R^2 =$ 



$$HS\text{-}X + HS\text{-}Y \xrightarrow{O_2} \begin{array}{c} S\text{-}X \\ | \\ S\text{-}X \end{array} + \begin{array}{c} S\text{-}X \\ | \\ S\text{-}Y \end{array} + \begin{array}{c} S\text{-}Y \\ | \\ S\text{-}Y \end{array}$$

1 2 3 4 5

disulfide (4) to twice that of the symmetrical disulfide (3) $\{r = \ln([4]/(2\,[3]))\}$.

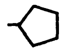
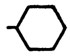
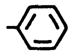
Table 1 lists the selectivity (r) as a function of the structures of R^1 and R^2 in H_2O – MeCN [mole fraction of H_2O (x_w) = 0.42] at 35.0 °C. The r values for acyclic alkyl groups as R^2 become large positive, whereas those for six-membered-ring (cyclic) groups [*i.e.*, cyclohexyl (c-C_6H_{11}) and phenyl (Ph) groups] as R^2 become large negative, regardless of the structures of R^1.[4,5)]

The correlation of geometrical shape of R^2 with the selectivity ($R^1 = n$-C_5H_{11}) was further investigated at various temperatures for $R^2 = i$-C_6H_{13}, c-C_6H_{11}, and Ph groups, all of which have the same number of carbon atoms (Fig. 1). The selectivity for $R^2 = c$-C_6H_{11} has proved to bear striking resemblance to that for R^2 = Ph over the temperature range 0 – 70 °C: the selectivity for the two cyclic groups both increases progressively with increasing temperature.[6)] In contrast, r values for $R^2 = i$-C_6H_{13} differ entirely from those for $R^2 = c$-C_6H_{11} and Ph.

The following observation indicates the significance of intermolecular association[7,9)] in controlling chemical reactions previously demonstrated:[1a)] r values for $R^2 = i$-C_6H_{13}, c-C_6H_{11}, and Ph (Fig. 1) all approach zero (the statistically expected value) under conditions unfavorable for hydrogen bonding, that is, at a higher temperature (70 °C).

Initial rates (v_0) —— average rates until 5% consumption of thiols ——

Table 1. Structure dependence of the selectivity (r) in oxidation of 1 and 2 at 35.0 °C in H_2O – MeCN (x_w = 0.42)

R^2	r[a)]	
	$R^1 = n$-C_5H_{11}	$R^1 = i$-C_5H_{11}
n-C_4H_9	3.60 ± 0.13	3.91 ± 0.03
n-C_5H_{11}	4.11 ± 0.16	3.68 ± 0.12
n-C_6H_{13}	3.68 ± 0.05	2.45 ± 0.07
i-C_6H_{13}	3.97 ± 0.05	2.44 ± 0.06
	-2.82 ± 0.09	2.30 ± 0.03
	-3.36 ± 0.07	-1.78 ± 0.08
	-3.51 ± 0.10	-2.30 ± 0.03

a) Errors given are the standard deviations. The r values are reproducible in two or more experiments within the errors shown in this table.

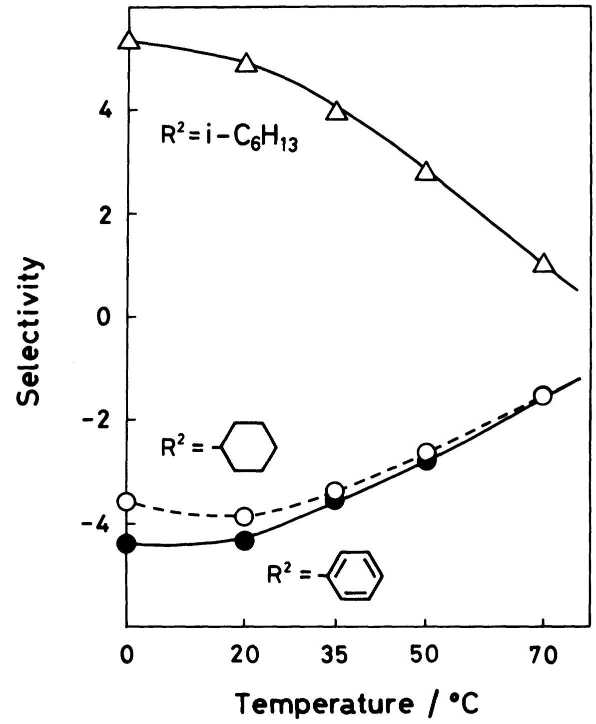


Fig. 1. Temperature dependence of the selectivity (r) in oxidation of 1a and 2 in H_2O – MeCN (x_w = 0.42). △ , 1a and 2b; ○ , 1a and 2d; ● , 1a and 2e. Errors (the standard deviations) for r values range from ± 0.12 to ± 0.14 ($r \geqslant 5$), from ± 0.03 to ± 0.10 ($5 > |r| \geqslant 3$), and from ± 0.01 to ± 0.08 ($3 > |r|$). The r values are reproducible in two or more experiments within the errors described above.

for thiol **1** [*ca.* $(7-9)\times10^{-7}$ mol l^{-1} s^{-1}] are about sixty times larger than those for thiol **2** [*ca.* $(1.2-1.5)\times10^{-8}$ mol l^{-1} s^{-1}] in H_2O − MeCN ($x_w = 0.42$) at 35.0 °C.[10] The observed large differences in reactivity between thiols **1** and **2** are not responsible for the selectivity data (Table 1), since the *r* shows positive as well as negative values.[11] Moreover, the solubility differences between thiols **1** and **2** cannot explain the selectivity, because all the reactions described here are homogeneous at temperatures higher than 35 °C.

The observed selectivity cannot be understood by the following effects. First, electronic effect of R^2 fails to account for the data in Table 1, because the order of σ_p values[12] for R^2 [−0.01 (Ph), −0.02 (c-C_5H_9), −0.15 (n-C_5H_{11}), *ca.* −0.15 (n- and i-C_6H_{13}),[13] −0.16 (n-C_4H_9), and −0.22 (c-C_6H_{11})] differs sharply from that of the corresponding *r* values at 35.0 °C (Table 1). Second, steric effect —— a measure of which is the υ[14] —— is not responsible for the selectivity, since there exists no appreciable relationship between the υ values for R^2 and the corresponding *r* values (Table 1). Third, hydrophobic effect cannot explain the selectivity data. This is because no close relationship exists between π values for R^2 [1.96 (Ph), 2.51 (c-C_6H_{11}), 2.14 (c-C_5H_9), 2.0 (n-C_4H_9), 3.0 (n-C_6H_{13}), *ca.* 2.8 (i-C_6H_{13}),[15] and 2.5 (n-C_5H_{11})][12,16] and the corresponding *r* values (Table 1), the π being a measure of hydrophobicity.

It is recognized that a cyclohexyl group resembles a phenyl group in geometrical shape.[17] From the experimental results and discussions presented here, it seems reasonable to conclude that geometrical shape resemblance between the cyclohexyl and phenyl groups is responsible for the close similarity between the selectivity for these two groups. This conclusion is consistent with the similarity recognition hypothesis.[18]

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References

1) a) T. Endo, A. Kuwahara, H. Tasai, T. Murata, M. Hashimoto, and T. Ishigami, *Nature*, 268, 74 (1977); b) T. Endo, Y. Takeda, T. Orii, T. Murata, M. Sakai, N. Nakagawa, and K. Nikki, *Chem. Lett.*, 1980, 1291; c) T. Endo, A. Okubo, Y. Kaneko, M. Uehara, H. Tasai, A. Sato, K. Nikki, N. Nakagawa, and S. Kamei, *Bull. Chem. Soc. Jpn.*, 55, 2224 (1982).

2) Thiols **1** and **2** were readily prepared as described previously.[1c] All new compounds had satisfactory analytical and spectroscopic data.

3) Thiols **1** and **2** (0.50 mmol each) in 12.5 ml of the solvent were treated with O_2 in the presence of triethylamine (0.05 mmol) in constant-temperature bath until the oxidation was complete. The yields of **3** and **4** were determined by HPLC using LiChrosorb CN.

4) The *r* value for $R^2 = c$-C_6H_{11} differs from that for $R^2 = c$-C_5H_9, particularly when $R^1 = i$-C_5H_{11}, but closely resembles that for $R^2 = $ Ph.

5) In enantiomer-differentiating acylation of racemic 1-phenylethylamine by (*S*)-$(REtCHCO)_2O$ in aqueous dioxane, it has been reported that the pattern of the dependence of the selectivity on solvent composition for $R = c$-C_6H_{11} is similar to that for R = Ph, although there exist considerable differences between the selectivity for $R = c$-C_6H_{11} and Ph [Y. Hiraki and A. Tai, *Bull. Chem. Soc. Jpn.*, 57, 1570 (1984)].

6) Also in $H_2O-EtOH$ ($x_w = 0.75$), the temperature–selectivity profiles for R^2 = c-C_6H_{11} are similar to those for R^2 = Ph (R^1 = n-C_5H_{11}).

7) Thiols **1** and **2** have been shown to associate strongly with each other as well as with themselves in benzene *via* two NH···O intermolecular hydrogen bonds between the inner -NHCO- units in the -CONHCONH- group to form a number of tetramers (reaction intermediates) as well as dimers [T. Endo, Y. Takeda, T. Orii, Y. Kaneko, and M. Kondo, *Chem. Lett.*, 1979, 1455]. In addition, the selectivity has been suggested to depend on the relative concentration of the tetramers.8)

8) T. Endo, M. Hashimoto, T. Orii, and M. M. Ito, *Bull. Chem. Soc. Jpn.*, 57, 1562 (1984).

9) Self-association constants (K) for dimerization of thiols determined by ^1H NMR (270 MHz) at 36 °C in benzene-d_6 are 87 ± 9, 183 ± 4, 99 ± 2, and 79 ± 3 M^{-1} for **1a**, **2b**, **2d**, and **2e**, respectively.

10) The thiol (**1** or **2**, 1.00×10^{-4} mol) was dissolved in 10.00 ml of the reaction solvent. The solution was stirred under an oxygen atmosphere for at least 4 h in a well-stirred water bath thermostated to ± 0.1 °C before the reaction was initiated by addition of Et_3N (1.0×10^{-5} mol) to the solution. At appropriate time intervals, a 0.50 ml portion of the reaction mixture was quenched in 5 ml of a 1:9 mixture of 3 M hydrochloric acid with MeCN. The amount of remaining thiols in the quenched solution was determined by titration with the 0.001 M iodine solution.8)

11) If the selectivity depends on the reactivity differences between **1** and **2**, r values should become negative, regardless of the structures of R^1 and R^2.

12) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, 16, 1207 (1973).

13) Since σ_p values for the C_2H_5, i-C_3H_7, n-C_4H_9, and n-C_5H_{11} groups are -0.15, -0.15, -0.16, and -0.15, respectively,12) σ_p values for the n- and i-C_6H_{13} groups are assumed to be *ca.* -0.15.

14) The υ values are 0.57 (or 2.15), 0.87, 0.71, 0.68, 0.73, 0.68, and 0.68 for the Ph, c-C_6H_{11}, c-C_5H_9, n-C_4H_9, n-C_6H_{13}, i-C_6H_{13}, and n-C_5H_{11} groups, respectively, these groups being arranged in order of increasing r values (R^1 = n-C_5H_{11}) at 35.0 °C when used as R^2 (Table 1) [M. Charton, "The Upsilon Steric Parameter——Definition and Determination," in "Steric Effects in Drug Design," ed by M. Charton and I. Motoc, Springer, Berlin (1983), p. 57; see also M. Charton, *J. Am. Chem. Soc.*, 97, 1552 (1975)].

15) The π value for the i-C_6H_{13} group is assumed to be *ca.* 2.8.16)

16) C. Hansch, A. R. Steward, J. Iwasa, and E. W. Deutsch, *Mol. Pharmacol.*, 1, 205 (1965).

17) There is a considerable difference in geometrical shape between cyclohexyl and cyclopentyl groups.

18) T. Endo, H. Tasai, K. Miyazawa, M. Endo, K. Kato, A. Uchida, Y. Ohashi, and Y. Sasada, *J. Chem. Soc., Chem. Commun.*, 1983, 636.

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