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The Role of Molecular Shape Similarity in Specific Molecular Recognition

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For the oxidation of associating thiols [(1) and (2)] and the formation of a 1:1 crystalline complex between acylurea derivatives [(6) and (7)] it has been shown that a similarity in geometrical shape of interacting groups is responsible for specific molecular recognition.

From studies of structure-activity relationships for pheromones,¹ excitatory transmitters,² drugs,³ etc. it is now accepted that biological activity and recognition are closely related to specific noncovalent interactions of bioactive substances with their specific receptors on cell membranes. In order to elucidate the factors controlling *in vivo* specific recognition, we have examined the effect of the spatial relationship between the recognition sites in reacting molecules on the discrimination both in solution and in the solid state.

We have previously reported the dependence of selectivity in the oxidation of the pair of thiols [(1) and (2a)] on their structures in 80% (v/v) acetonitrile-20% water at 35.0 °C;^{4,5} the selectivity (r) (a measure of the degree of molecular recognition) is represented by the logarithmeric ratio of the yield of the unsymmetrical disulphide (4) to twice that of the symmetrical disulphide (3) { $r = \ln[(4)/2(3)]$ }. When R¹ was a series of branched alkyl groups⁴ ([CH₂]_mCHMe₂, m = 0—4) or phenylalkyl groups⁵ ([CH₂]_nPh, n = 1—3), the selectivity reached a sharp maximum at m = 2 (r = 2.4) and n = 2 (r =2.1), respectively. The selectivity in the oxidation of the thiols, (1) and (2b), was examined[†] in order to elucidate the relationship between selectivity[‡] and shape similarity. The selectivity for $Z = CHMe_2$ (r = 1.2) has proved to be the same as that for $Z = NO_2$ (r = 1.2). Additionally, the *r* value of -0.86 for $Z = Me^6$ is similar to that of -1.0 for Z = Cl. This clearly indicates that the CHMe₂ and NO₂ groups, both having a branched structure similar to the NMe₂ group of (1), give higher selectivity than sphere-like groups (Me and Cl).

It has been shown, regarding the nature of the oxidation, that (i) thiols (1) and (2) associate strongly in benzene via two $NH \cdots O$ intermolecular hydrogen bonds⁶ between the inner

[†] The acylurea derivatives (1), (2), (6), and (7) were readily prepared as described previously.⁶ Satisfactory spectroscopic data were obtained for all new compounds.

[‡] The two thiols [(1) and (2), 0.50 mmol each] were treated with O_2 in the presence of Et₃N (0.05 mmol) at 35.0 °C in 12.5 ml of 80% (v/v) acetonitrile-20% water until the oxidation was complete. The yields of (3) and (4) were determined as described previously.⁶



(2)
$$\mathbf{a}$$
; $\mathbf{R'} = [CH_2]_m CHMe_2$ and $[CH_2]_n Ph$

$$HS - X + HS - Y \xrightarrow{O_2} | + | + | + | (1) (2) (3) (4)$$

-N(H)C(:O)- units in the -C(:O)N(H)C(:O)N(H)- group to form tetramers (reaction intermediates) such as (5) (Figure 1) as well as dimers, (ii) the S-S bonds are formed between the two proximate HS groups in the tetramers,⁶ and (iii) the product ratio in this type of oxidation is kinetically controlled;^{4,6} r values reflect the shape similarity between the C₆H₄NMe₂ and R¹ groups [the recognition sites of (1) and (2)].§

In order to correlate the observed selectivity with the structures of the tetramers, attempts were made to prepare crystalline complexes between (1) and (2). However, no complexes were obtained whose crystals were suitable for X-ray analysis. Further studies were carried out with the acylurea derivatives

§ The observed selectivity is difficult to explain by hydrophobic interaction. This is because the order of π values for the substituents Z (*i.e.* CHMe₂ > Cl > Me > NO₂) in (2b) differs sharply from that of the corresponding r values, the π value being a measure of hydrophobicity (T. Fujita, J. Iwasa, and C. Hansch, J. Am. Chem. Soc., 1964, **86**, 5175). See also ref. 6.



Figure 1. Association scheme in a typical tetramer (5). The hydrogen bonds (---) in the dimers and the noncovalent weak interactions $(\cdot \cdot \cdot \cdot)$ responsible for the stabilisation of the tetramers are shown. The symbols X and Y represent $C_0H_4NMe_2$ and R^3 , respectively.

[(6) and (7)][†] each having two substituents structurally related to the recognition site of (1): (i) a nonpolar group (\mathbb{R}^2 or \mathbb{R}^3) instead of the HS[CH₂]₁ or 2 group and (ii) C₆H₄NMe₂ or C₆H₄NO₂ which are similar in shape to each other. Compounds (6) and (7) (0.50 mmol each) were dissolved in acetonitrile, and this solution was allowed to evaporate slowly at room temperature. The resulting crystal was identified as the 1:1 complex (8) by the following criteria: (i) a sharp melting point, different from those of (6) and (7) and (ii) the presence of (6) and (7) in 1:1 molar ratio in the u.v. absorption spectrum of a dilute acetonitrile solution of the crystal.

Figure 2 shows the structure dependence of this new type of crystalline 1:1 complex formation on various combinations





Figure 2. Crystalline 1: 1 molecular complex formation for various combinations of \mathbb{R}^2 and \mathbb{R}^3 . Complex formation is indicated by + and the colour of the complexes is given: bp, brownish purple; rp, reddish purple; o, orange; rb, reddish brown; py, pale yellow; p, purple; dp, dark purple; db, dark brown; y, yellow; pb, pale brown. As the components (6) and (7) are colourless or pale yellow crystals, the very characteristic colour of (8) confirms the crystalline complex formation. The — indicates that no complex was formed. With $\mathbb{R}^2 = \mathbb{R}^3 = p-\text{MeC}_6H_4$ and $\mathbb{R}^3 = p-\text{ClC}_6H_4$, the complex formation was carried out in N,N-dimethylformamide owing to the very low solubilities of the corresponding components (6) and (7) in acetonitrile.

of R^2 and R^3 . The groups $Me_2CH[CH_2]_2$ and $Me_2N[CH_2]_2$ as R^3 , both with a branched structure, give (8) with approximately the same probability when paired with a variety of groups; this is also the case with the pair of *p*-substituted phenyl groups, *p*-MeC₆H₄ and *p*-ClC₆H₄. Moreover, among the nine possible combinations where R^2 is a cyclohexylalkyl group (C₆H₁₁[CH₂]₀₋₂) and R^3 is a phenylalkyl group (Ph[CH₂]₀₋₂), only two have been found to afford (8) each having two spatially similar groups with the same number of carbon atoms: the pairs C₆H₁₁-Ph and C₆H₁₁[CH₂]₂-Ph[CH₂]₂.

If the shape similarity effect is responsible for the specific recognition described above, a pair of groups with similar geometrical shape would be expected to be brought close together. Indeed, this is true for NMe₂ and CHMe₂ groups (part of C₆H₄NMe₂ and Me₂CH[CH₂]₂), as demonstrated by X-ray analysis (Figure 3) of 1:1 complex (**8a**) (R² = Ph[CH₂]₂ and R³ = Me₂CH[CH₂]₂, m.p. 171.0—172.5 °C) (crystals grown from acetonitrile).¶ It is interesting to note that the use of Me₂CH[CH₂]₂ as R¹ in the oxidation of (1) and (2) produced the highest selectivity so far studied⁴⁻⁶ at 35.0 °C in 80% (v/v) acetonitrile-20% water.

On the basis of the results reported here, we propose that the three-dimensional shape similarity between groups in reacting molecules is responsible for more specific and precise molecular recognition than would otherwise be achieved. This hypothesis would be applicable to discrimination between molecules which differ in the structure of nonpolar groups, and would be of biological significance (*e.g.* Pr¹, Bu¹, and PhCH₂ employed as amino acid side chains).

¶ Crystal data for (8a): $C_{31}H_{38}N_6O_6$, M = 590.69, triclinic, space group $P\overline{1}$, a = 11.036(2), b = 18.466(3), c = 8.123(1) Å, $\alpha = 96.62(2)$, $\beta = 100.99(1)$, $\gamma = 74.79(2)^\circ$, U = 1564.3(4) Å³, Z = 2, $D_e = 1.254$ g cm⁻³. The structure was solved by direct methods and refined anisotropically to R = 0.094. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication. A recent structure determination of complex (8b) (R² = Me₂CH[CH₂]₂ and R³ = Ph[CH₂]₂, m.p. 145.5— 147.5 °C) has also demonstrated close proximity between R² and R³, the combination of R² and R³ being reversed in (8a) and (8b).



Figure 3. Stereoscopic view of a tetramer composed of two hydrogen-bonded (8a) units. The thin lines indicate hydrogen bonds in (8a). Similarly-shaped groups, *p*-(dimethylamino)-phenyl and isopentyl, are in close contact.

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