

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 logarithmic 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]_{*m*}CHMe₂, $m = 0-4$) or phenylalkyl groups⁵ ([CH₂]_{*n*}Ph, $n = 1-3$), 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 = CHMe₂ ($r = 1.2$) has proved to be the same as that for Z = NO₂ ($r = 1.2$). Additionally, the r value of -0.86 for Z = Me⁶ 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 ··· 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 O₂ 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

of R^2 and R^3 . The groups $\text{Me}_2\text{CH}[\text{CH}_2]_2$ and $\text{Me}_2\text{N}[\text{CH}_2]_2$ 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*- MeC_6H_4 and *p*- ClC_6H_4 . Moreover, among the nine possible combinations where R^2 is a cyclohexylalkyl group ($\text{C}_6\text{H}_{11}[\text{CH}_2]_{0-2}$) and R^3 is a phenylalkyl group ($\text{Ph}[\text{CH}_2]_{0-2}$), only two have been found to afford (8) each having two spatially similar groups with the same number of carbon atoms: the pairs $\text{C}_6\text{H}_{11}\text{-Ph}$ and $\text{C}_6\text{H}_{11}[\text{CH}_2]_2\text{-Ph}[\text{CH}_2]_2$.

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 NMe_2 and CHMe_2 groups (part of $\text{C}_6\text{H}_4\text{NMe}_2$ and $\text{Me}_2\text{CH}[\text{CH}_2]_2$), as demonstrated by *X*-ray analysis (Figure 3) of 1:1 complex (8a) ($R^2 = \text{Ph}[\text{CH}_2]_2$ and $R^3 = \text{Me}_2\text{CH}[\text{CH}_2]_2$, m.p. 171.0–172.5 °C) (crystals grown from acetonitrile).[¶] It is interesting to note that the use of $\text{Me}_2\text{CH}[\text{CH}_2]_2$ as R^1 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.* Pr^1 , Bu^1 , and PhCH_2 employed as amino acid side chains).

[¶] Crystal data for (8a): $\text{C}_{31}\text{H}_{38}\text{N}_6\text{O}_6$, $M = 590.69$, triclinic, space group $P\bar{1}$, $a = 11.036(2)$, $b = 18.466(3)$, $c = 8.123(1)$ Å, $\alpha = 96.62(2)$, $\beta = 100.99(1)$, $\gamma = 74.79(2)^\circ$, $U = 1564.3(4)$ Å³, $Z = 2$, $D_c = 1.254$ 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) ($R^2 = \text{Me}_2\text{CH}[\text{CH}_2]_2$ and $R^3 = \text{Ph}[\text{CH}_2]_2$, m.p. 145.5–147.5 °C) has also demonstrated close proximity between R^2 and R^3 , the combination of R^2 and R^3 being reversed in (8a) and (8b).

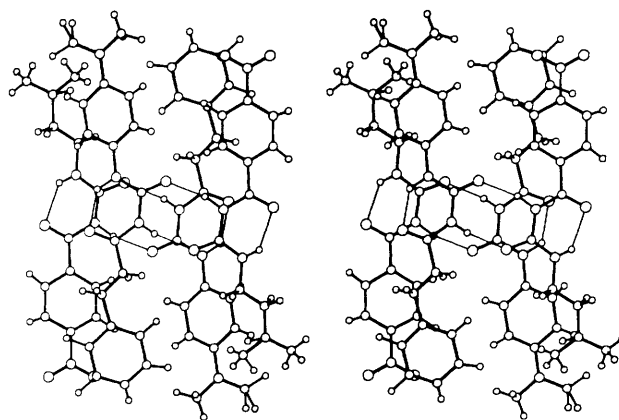


Figure 3. Stereoscopic view of a tetramer composed of two hydrogen-bonded (8a) units. The thin lines indicate hydrogen bonds in (8a). Similarly-shaped groups, *p*-(dimethylamino)-phenyl and isopentyl, are in close contact.

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