Microbial Stereo-differentiating Reduction of Carbonyl Compounds; Proposed Quadrant Rule[1]

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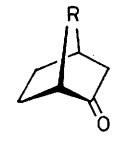
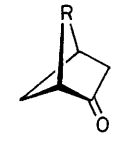
Summary The stereochemistry of the alcohols obtained from microbial reduction (*Curvularia lunata* and *Rhodotorula rubra*) of the cyclic ketones (**1**)—(**8**) with a wide variation in molecular framework has led to the formulation of a quadrant rule which provides information on the absolute configuration of the substrate ketone.

AMONG the various cyclic ketones whose metabolites have been investigated to elucidate stereoselectivity in microbial reduction, few have the carbonyl groups constrained in the non-chair form of a cyclohexane ring. This prompted us to examine the stereochemistry of microbial reduction products of the cage ketones (**1**)—(**8**) by *C. lunata* and *R. rubra*.

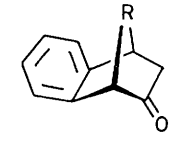
These results, together with our previous experiments[2] on microbial reduction of gyrochiral C_2-ketones whose carbonyl axes are located on the C_2-axes, can be summarized in a quadrant rule which can predict the stereochemistry of the reduction products, eventually providing information on the absolute configurations of their molecular framework.



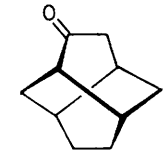
(1) R = CH_2-CH_2
(2) R = CH=CH



(3) R = CH_2-CH_2
(4) R = CH=CH



(5) R = CH_2-CH_2
(6) R = CH=CH
(7) R = CH_2



(8)

When molecular models of the substrate ketones are oriented in a three-dimensional system as shown in Figure 1, there are two, two, and four quadrant orientations for C_s, C_2, and C_1-ketones† respectively (Figure 2).

† In this communication, ketones are conveniently classified according to their symmetry. C_s-Ketones belong to the C_s point group and have the plane of symmetry coincident with the carbonyl plane; C_2-ketones belong to the C_2 point group and have the C_2 axis coincident with the carbonyl axis; C_1-ketones have no symmetry element passing through the carbonyl axis.

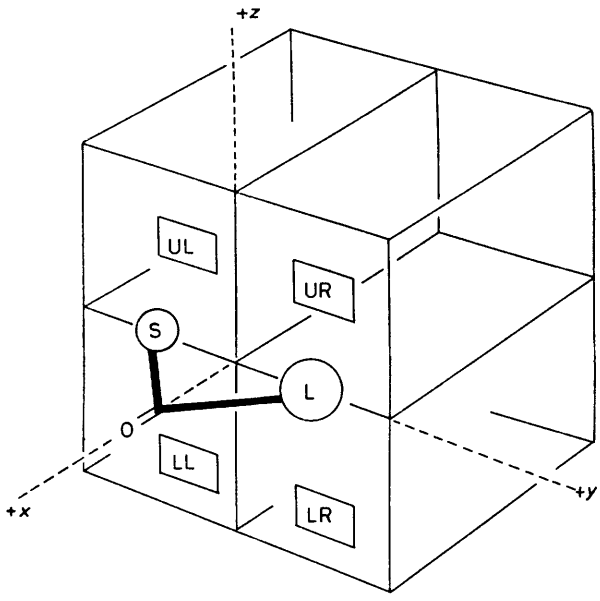


FIGURE 1. Quadrant orientation

The quadrant rule then states the following.
(i) C_S-Ketones: of the two possible orientations, *C. lunata* or *R. rubra* favour the C_S-1 orientation with the larger group on the $+y$ axis and the smaller group on the $-y$ axis, affording the B-*S*-alcohol‡ as the major reduction product as a result of hydrogen attack from the lower quadrants (B-*re*-face‡ attack).
(ii) C_2-Ketones: when a racemic C_2-ketone is treated with *C. lunata* or *R. rubra*, these microbes preferentially reduce the enantiomer with the C_2-1 orientation, leaving the enantiomeric ketone corresponding to the C_2-2 orientation which can be recovered from the culture solution.[2]
(iii) C_1-Ketones: since there are two diastereotopic carbonyl faces for each enantiomer, a racemic C_1-ketone gives four quadrant orientations. In almost all cases, the C_1-1 orientation is favoured by both *C. lunata* and *R. rubra*, followed by the C_1-4 orientation. Although both orientations are common in having larger group on the $+y$ axis and smaller group on the $-y$ axis, they are different in their steric requirements in upper and lower quadrants; C_1-1 requires less space in the lower quadrant than C_1-4.

When a racemic C_1-ketone is treated with these microbes, hydrogen attack from the lower quadrants will afford the B-*S*-alcohol corresponding to the C_1-1 orientation as the major product together with the diastereomeric B-*S*-alcohol corresponding to the C_1-4 orientation as the minor product, leaving the enantiomeric ketone corresponding to C_1-3 and C_1-4 orientations unchanged in the culture solution.

As a 'rule of thumb' for microbes in general, this quadrant rule for *C. lunata* and *R. rubra* should be applied with due caution, especially when the substrate ketones have substituents which are suspected to exert a disturbing effect by virtue of electronic effects or hydrogen bond formation.

The following examples show the reliability of this rule when applied to ketones with a wide variety of structural features.

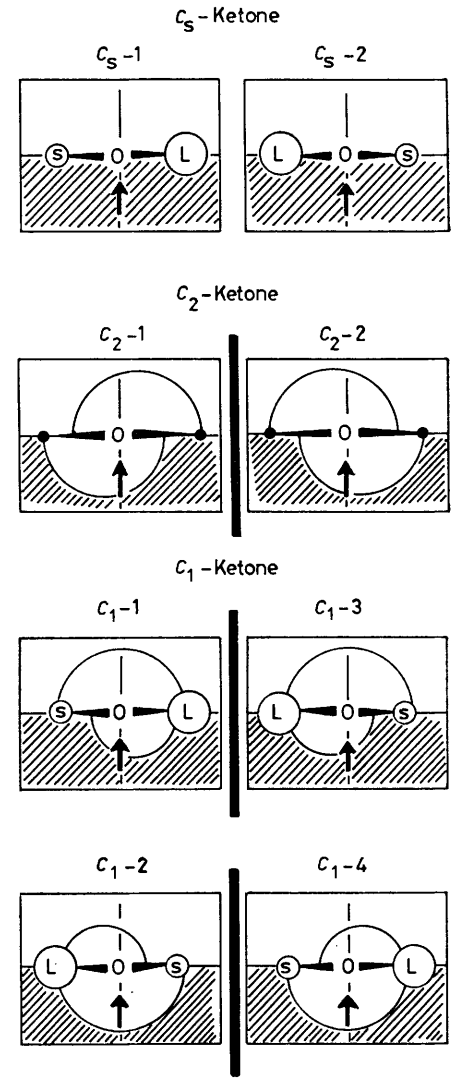
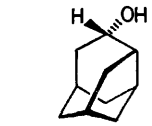


FIGURE 2. Schematic representations of possible quadrant orientations for C_s, C_2, and C_1-ketones.

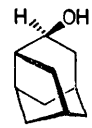
A culture solution of *R. rubra* with (±)-4-protoadamantanone[3] at 29 °C for 24 h gave a mixture of the (−)-*exo*-alcohol, m.p. 229—231 °C, $[\alpha]_D^{24}$ −32·3° ($CHCl_3$) and the (+)-*endo*-alcohol, m.p. 210—212 °C, $[\alpha]_D^{24}$ +36° ($CHCl_3$) in a 2·4 : 1 ratio. Molecular models of the enantiomeric ketones indicate that the major *exo*-alcohol[4] has the configuration (**9**) corresponding to the C_1-1 orientation (Figure 2), and the minor *endo*-alcohol[4] has the configuration (**10**) corresponding to the C_1-4 orientation.

On Jones' oxidation, the (−)-*exo*-alcohol (**9**) yielded (+)-4-protoadamantanone whereas the (+)-*endo*-alcohol (**10**)

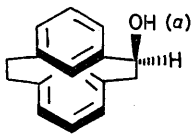
‡ The letter 'B' refers to the 'bulkiness sequence subrule' with priority sequence: oxygen atom > large group > small group > hydrogen atom (see ref. 2).



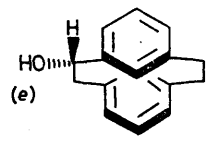
(−)-(9)



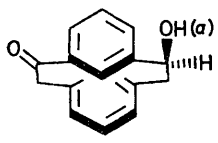
(+)-(10)



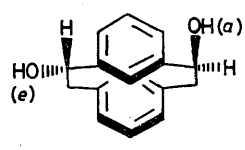
(+)-(11)



(−)-(12)



(−)-(13)



(−)-(14)

gave the (−)-isomer which was converted into (+)-protoadamantane by Wolff–Kishner reduction. This correlation indicates assignment of the (1*S*,3*R*,6*S*,8*S*) configuration to (+)-protoadamantane which is supported by our independent chemical correlation.[5]

When (±)-1-oxo[2.2]metacyclophane,[6] with planar chirality, was incubated with *R. rubra* at 30 °C for 45 h, the (+)-axial alcohol (**11**),[6] m.p. 138·5—139·5 °C, $[\alpha]_D^{26}$ +24·5° ($CHCl_3$) (optical purity 94%) was the major product and the (−)-equatorial alcohol (**12**),[6] m.p. 150·5—151 °C, $[\alpha]_D^{26}$ −125·7° ($CHCl_3$) (optical purity 100%) the minor product. Their (*pR*,1*S*)- and (*pS*,1*S*)-absolute configurations[7] imply that these alcohols had originated from the C_1-1 and C_1-4 orientations (Figure 2), respectively, as correctly predicted by the quadrant rule.

The same stereoselectivity was observed for 1,10-dioxo-[2.2]metacyclophane,[8] which, after 10 h incubation with *R. rubra* at 30 °C, afforded the (−)-axial keto-alcohol (**13**), m.p. 151—152·5 °C, $[\alpha]_D^{28}$ −400·5° ($CHCl_3$) (optical purity 100%) (55% yield) and the (−)-axial,equatorial diol (**14**), m.p. 178·5—179·5 °C, $[\alpha]_D^{28}$ −87·6° ($CHCl_3$) (optical purity 100%) (11% yield) which has a composite structure made up of units of (+)-(**11**) and (−)-(**12**).

Apart from its application to determination of the absolute configuration of carbonyl compounds, the quadrant rule seems to suggest a subtle stereochemical requirement around the active site of the alcohol dehydrogenase[9] of these microbes; the lower left quadrant (LL) shows more steric tolerance than the lower right quadrant (LR) (Figure 1).

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[1] Presented at the 26th International Congress of Pure and Applied Chemistry, Sept. 8, 1977, Tokyo, Abstracts p. 63.
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