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Conformational flexibility of the D-ring in steroid molecules : a statistical analysis from crystal data

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Abstract : The basic steroid skeleton consists of three fused cyclohexane rings and a cyclopentane like D-ring. The D-ring mostly carries a functional group and is known to induce or stabilise an essential conformational state in the receptor. Detailed understanding of its conformation is of interest in this connections.

We have now carried out a systematic conformational analysis on the D-ring pucker using the crystal structure data of about 300 steroids. Our analysis shows that there are preferred puckered states involving the C(13) and C(14) atoms. In 91% of the structures, the D-ring conformation is found highly restricted to a narrow range of pseudorotation cycle where the phase angle P is between 18° (C(13) β envelope) and −18° (C(14) α envelope). Exceptions are however found when the ring is heavily substituted. The hybridisation state at C(17) atom is found to have systematic effect on conformation or D-ring.

The conformational changes brought about by cyclisation between C(13) and C(17) atoms is discussed based on our recent X-ray crystallographic results.

Keywords : Steroids, pseudorotation parameters, puckering.

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1. Introduction

The steroid nucleus consists of three cyclohexane rings and one cyclopentane like D-ring as in Figure 1. The conformation of the five membered D-ring in steroids has received much attention during the past three decades (Altona *et al* 1968, Fuchs 1978 and Thomas 1982) because it is known to induce or stabilise the essential conformational state in the receptor (Duax and Weeks 1980, Duax *et al* 1988). We have carried out systematic X-ray crystallographic studies on a less studied class of steroids where an additional heterocyclic ring is fused with ring D of the steroidal skeleton (Radhakrishnan *et al* 1988a, 1988b, 1988c, 1989b, 1990, Radhakrishnan and Viswamitra 1990). Our major interest has been to find the conformational changes brought about by this ring on the steroid nucleus especially on the ring D conformation where it is fused.

2. Pseudorotation

The concept of pseudorotation was first introduced by Kilpatric *et al* (1947) in their discussion on the "indefiniteness" of the cyclopentane conformation. However, the presence of one or more substituents, endocyclic or exocyclic, will give rise to an induced potential energy barrier opposing "free" pseudorotation (Pitzer and Donath 1959). A quantitative description of puckering and conformation in terms of the "phase angle" of pseudorotation (Δ) and the maximum angle of torsion (ϕ) was developed by Altona *et al* (1968), based on the inter-relationship between the five torsional angles in a nonplanar five-membered ring.

The phase angle of pseudorotation (Δ) is defined as

$$\tan \Delta/2 = \frac{(\phi_2 + \phi_4) - (\phi_1 + \phi_3)}{3.0777\phi_0} \qquad (1)$$

where $\phi_0,\ldots,\phi_4$ are the endocyclic torsional angles previously defined in the original paper (Figure 1).

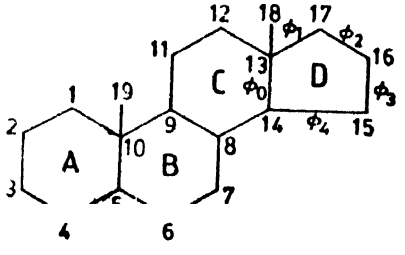

Figure 1. Steroid molecule with numbering scheme.

Altona and Sundaralingam (1972) modified the phase angle of pseudorotation to $P = \Delta/2$ and used it for the calculation of ribose and deoxyribose rings in nucleosides and nucleotides. For convenience we will follow this throughout this paper.

The Cambridge Structural Database (Release 1985, Allen *et al* 1979) contains crystallographic information on more than 50,000 organic compounds and the data stored can be systematically analysed to bring out interesting structural properties (Allen *et al* 1983, Allen and Lynch 1988). We have analysed the D-ring conformation in 300 steroids from chemical class 51.

Our major interest has been to find out the conformational distribution of ring D in the pseudorotation pathway and also to understand the transmission effect introduced by the cyclisation between C(13) and C(17) atoms on the steroid nucleus. The values of phase angle of pseudorotation P were taken from the literature wherever available otherwise they were calculated using eq. (1).

3. Results

3.1. Restricted flexibility :

Our analysis shows nearly 91% of the structures have their D-ring conformation restricted to a narrow range of the pseudorotation cycle (Figure 2, marked by

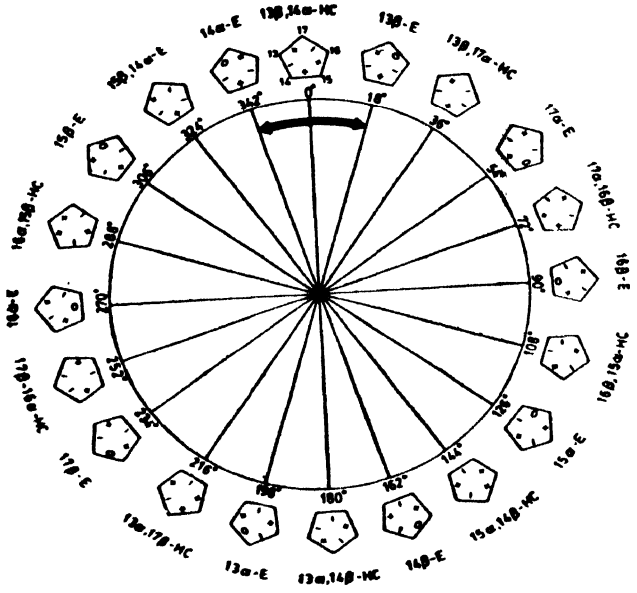

Figure 2. Pseudorotation cycle for D-ring. The marked region shows the most probable conformation for D-ring from X-ray crystallographic studies.

arrow). The phase angle P is confined to the range of $-18°$ [C(14) α envelope] and $+18°$ [C(13) β envelope]. This shows that D-ring conformation is highly restricted to a few conformations (Table 1).

Table 1. D-ring conformation with respect to hybridisation state of C(17) atom.

Conformation	Number of structures	Type
13β E	48	sp^3-hybridisation at C(17) atom
Intermediate between 13β E and 13β 14α HC	132	—
Intermediate between 14α E and 13β, 14α HC	21	sp^2-hybridisation at C(17) atom
14α E	32	—
13β, 14α HC	53	—
Others	26	—

D—Envelope and HC—Half-chair.

There are exceptions for this general trend due to the bulky substitutions. The best example in our analysis is the structure of aldosterone where the D-ring takes a flat 14α, 15β half-chair conformation with $P = 39.0°$ because of strain introduced by substituents (Duax and Hauptman 1972).

3.2. *The hybridisation effect :*

A steroid D-ring consisting of five sp^3 carbons is usually observed to have a 13β envelope conformation or one intermediate between a 13β envelope and a 13β, 14α half-chair (Griffin *et al* 1984), (e.g. DL-17α-hydroxy-8-androst-4-en-3-one, Chakrabarti *et al* 1981). The 14α envelope and the intermediate between 14α envelope and 13β, 14α half-chair conformations are most commonly observed in steroids having sp^2 hybridised C(17) carbon atom (e.g. Androstan-17-one, Banerjee *et al* 1978). In our extensive analysis with 312 structures we observe a similar kind of behaviour.

3.3. *Effect of cyclisation between C(13) and C(17) :*

We have carried out a systematic crystallographic analysis on steroids where a heterocyclic ring is fused with ring D of steroid between C(13) and C(17) atoms (Radhakrishnan *et al* 1988a, 1988b, 1988c, 1989b, 1990, Radhakrishnan and Viswamitra 1990). All of them have sp^3 hybridised carbons at C(17) atom, but with negative P values ($-13.5°$, $-17.2°$, $-21.3°$, $-27.6°$, $-21.0°$, $-25.3°$). This is unlike our statistical result, where compounds with sp^3 hybridised C(17) atom tend to take positive P values (Figure 2). Especially four of them fall in a particular region, between 14α envelope and 14α, 15β half-chair which is present outside the restricted range (Figure 2). Thus our X-ray crystallographic results show the cyclisation between C(13) and C(17) atoms not only changes the conformation of ring D but also restricts the flexibility in a particular range.

This is also supported by the crystal structure analysis done by Cesario and Guibham (1972) for compounds with similar kind of fusion ($P = -37.6°$). The structure of a related compound which is not cyclised (Radhakrishnan *et al* 1989a) has a positive P value of 5.0°, which agrees with our statistical result, gives an additional support to the cyclisation effect.

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