

RATES OF QUATERNIZATION REACTIONS OF CONFORMATIONALLY BIASED
TEN- AND TWELVE-MEMBERED N-METHYL-AZA-CYCLOALKANES :
THE REACTIVITY OF RING ATOMS OF DIFFERENT CONFORMATIONAL TYPES

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(Received in UK 17 July 1967)

The preferred conformations of some of the many-membered rings are now known (1). The most stable conformation of cyclodecane (2) is believed to be that shown in Fig. 1A, that of cyclododecane (3) that depicted in Fig. 1B.

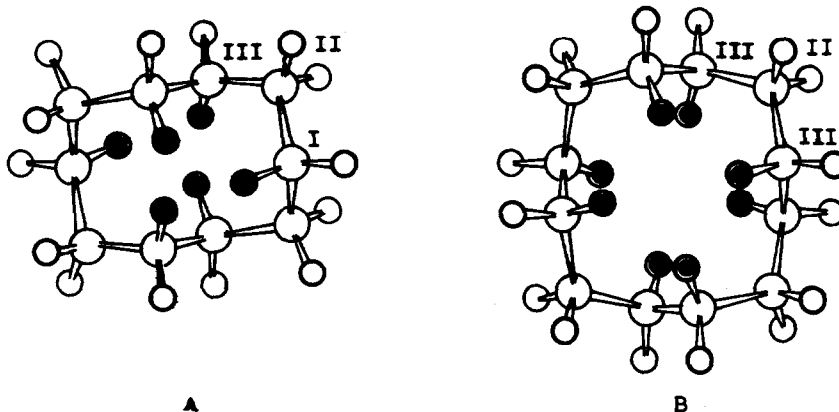


Fig. 1

Conformations of (A) cyclodecane (2) and (B) cyclododecane (3);
extra-annular positions are marked ○, intra-annular positions ●

The cyclodecane skeleton may be regarded as being built up of carbon atoms of three different conformational types (4) (I, II and III), the cyclododecane skeleton of ring atoms two different conformational types (II and III) (cf. also Fig. 2).

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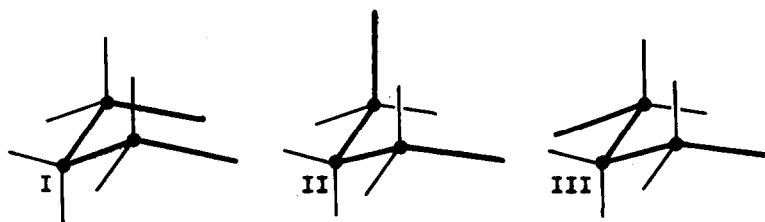


Fig. 2

Conformational types of ring atoms

It is of fundamental interest for conformational analysis in this area to determine qualitatively and, if possible, quantitatively, the reactivity behaviour of ring atoms of the different conformational types. Such a task is made difficult by the fact that the many-membered rings represent conformationally mobile systems, in the sense that the ring atoms of conformationally different types rapidly exchange positions. We have suggested (5) that one may arrive at conformationally stabilized (or biased) many-membered ring systems by the expedient of placing gem-dimethyl groups into suitable mutual positions on the ring skeleton. The conformation holding effect of the gem-dimethyl groups is thought to result from the fact that these groups will have a very strong tendency to occupy the energetically favourable extra-annular positions: in cyclodecane and cyclododecane this is possible only if the gem-dimethyl-substituted ring atoms are of the conformational type II.

In this note we report a quantitative study of the differential reactivities of ring atoms in the twelve- and the ten-membered rings, making use of rates of the quaternization reaction of the gem-dimethyl substituted N-methyl-aza-cycloalkanes 1, 2 and 4 - 7. Rates of quaternization reactions are well known (6) to reflect the steric environment of the -NMe-grouping. Second order rate constants of the reaction of the N-methyl-aza-cycloalkanes with methyl iodide in methyl cyanide have been determined by a polarographic procedure to be described in the full paper; the results are summarized in the Table.

Consider first the twelve-membered ring compounds. Provided the gem-dimethyl groups in the compounds 1 and 2 will indeed preferentially be located on ring atoms of the conformational type II in the conformation shown in Fig. 1B, then the nitrogen atom in compound 1 will replace a carbon

TABLE

Second order rate constants ($\text{l.mol}^{-1}.\text{s}^{-1}$) of the reaction
of the N-methyl-aza-cycloalkanes with methyl iodide in
methyl cyanide at 25°C

	<u>1</u>	<u>2</u>	<u>3</u>		
$k_2 \cdot 10^3$	133	2.14	5.45		
	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>
$k_2 \cdot 10^3$	3.81	0.29	0.57	0.16	1.15
	<u>9</u>	<u>10</u>			
$k_2 \cdot 10^3$	1.69	62.7			

of conformational type II but the nitrogen in compound 2 a carbon of conformational type III. The free electron pair on the NMe group will therefore be extra-annular in compound 1 but intra-annular in compound 2. Our data bring out this difference in a striking manner : the value of the quaternization rate constant for 1 may be seen to be some 60 times higher than that for 2, thus for the first time affording a quantitative measure of the different reactivities of ring atoms of different conformational types.

An analogous argumentation may be applied to the rates of the ten-membered ring compounds. In compound 4 the nitrogen atom is likely to occupy the position of conformational type II, so that the free electron pair of the NMe group can be extra-annular. By contrast in compound 5 the nitrogen can occupy only conformational positions III (or I) and in compound 6 only the conformational position III; unlike in the compound 4, the free electron pair in 5 and 6 will hence have to be intra-annular. The value of k_2 of 4 was indeed found to be higher than that of 5 and 6 by factors of about 13 and 7, respectively. The rate of the aza-cyclodecane derivative 7 requires more detailed consideration. The free electron pair on the nitrogen in this compound should be extra-annular and hence "reactive"; on the other hand, the nitrogen atom is in a 1,3-relationship to the gem-dimethyl groups, a feature which is bound to slow down the reaction. A crude correction factor for the latter feature may be obtained from a consideration of the reactions of N-methyl-piperidine 10 and N-methyl- β,β -dimethylpiperidine 9 (7) whose rate constants differ by a factor of 37. Applying this correction to the experimental rate constant of 7 we obtain an estimated rate constant of 5.9. This value indeed lies in the same range as that of 4, as conformational analysis predicts.

It is also instructive to compare the rates of the "gem-dimethylated" compounds 1, 2, 4 - 7 with those of the parent N-methyl-aza-cycloalkanes 3 and 8. The rate of the twelve-membered parent compound 3 may be seen to be intermediate between those of the biased compounds 1 and 2, but very much closer to that of 2 in which the free electron pair is intra-annular. These results suggest that the nitrogen atom in the conformationally mobile N-methyl-aza-cyclododecane will preferentially occupy the conformational position of the type III (8). An analogous, though less clear-cut picture may be observed in the case of the ten-membered ring compounds.

The N-methyl-aza-cycloalkanes 1, 2, 4 - 7 are new compounds; their synthesis will be reported in the full paper, together with a more detailed discussion of the present and related results.

Acknowledgement. We wish to thank Miss V. Valšubová for valuable technical assistance.

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- (7) We are greatly indebted to Dr K.C. Brannock (Tennessee Eastman Company, Kingsport, Tenn.) for a sample of this compound.
- (8) This is in contrast to the X-ray structure of azacyclododecane hydrochloride (J.D. Dunitz and H.P. Weber, Helv. Chim. Acta 47, 1138 (1964)) in which the (positively charged) nitrogen has been found to occupy the II-position.