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## 91. Model Calculations on the Squalene Cyclization

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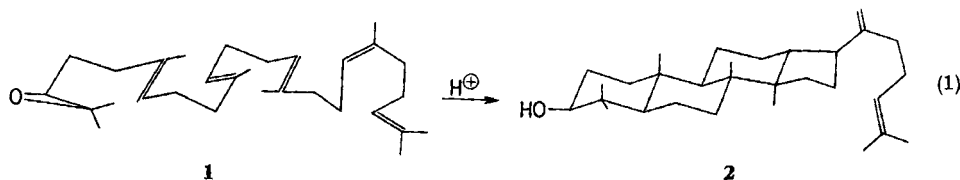
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**Summary.** As a model for the squalene cyclization the interaction between a methyl cation or a methyl radical and two double bonds has been studied using the CNDO/2 and INDO method. In both cases bond formation between the CH<sub>3</sub>-group and one double bond is facilitated by a second one, but not in a concerted way.

One of the most interesting and exciting reactions in terpene biosynthesis is the cyclization of squalene oxide (1) to lanosterol [1] [2]. A somewhat simpler example of this kind of cyclization, that of 1 to damaradienol (2), is shown below.



When squalene oxide is converted to lanosterol, a product is formed with no less than seven asymmetric centers. This reaction is of particular interest to organic chemists since only one product is formed in the biosynthesis instead of a mixture of isomers. Besides this high stereospecificity of the reaction it is found that no isotopic

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exchange occurs when the biosynthesis from squalene is carried out in a medium containing  $\text{H}_2\text{O}^{18}$  and  $\text{D}_2\text{O}$  [3].

Although these facts indicate a concerted process [1–4], a stepwise mechanism would explain the situation just as well if the conformation of squalene were similar to that shown above: namely a helical arrangement of the double bonds. A stepwise mechanism in such an arrangement should work like a zipper, one bond being formed after another.

Besides the carbonium ion mechanism indicated in (1), a radical mechanism has been postulated for the ring closure of squalene [5]. Although this mechanism seems to be of less importance for the biochemical process it is still very interesting, since studies on model reactions [5] also show a high stereospecificity.

We discuss here the two possibilities, concerted or stepwise ring closure for both the cationic and radical process, with the aid of molecular orbital calculations. The calculations should also provide us with some indirect information concerning the role of the enzyme *i.e.* at what distance the reaction between a positive center and one double bond is facilitated by a second. Our efforts are perforce limited to model calculations, and we cannot estimate the entropy factors involved. The methods used are CNDO/2 and INDO [6].

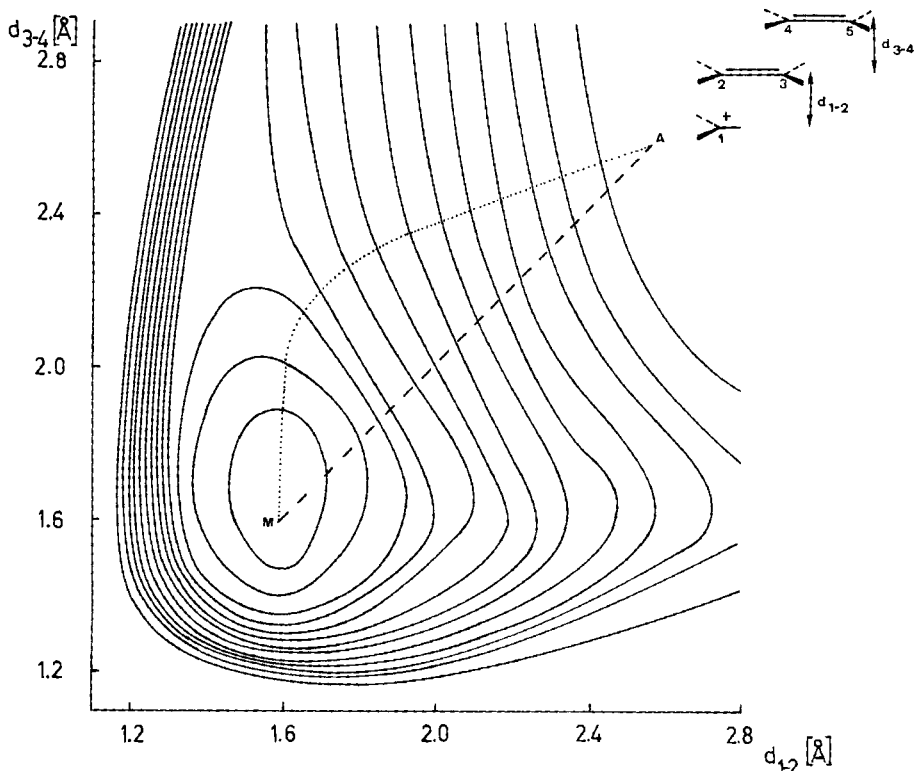


Fig. 1a

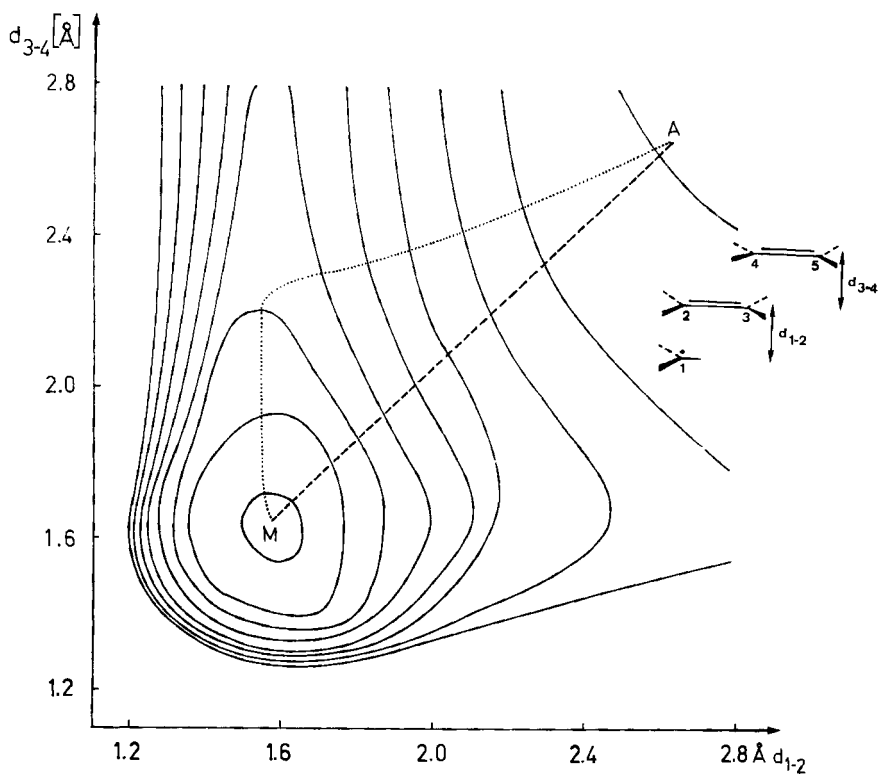
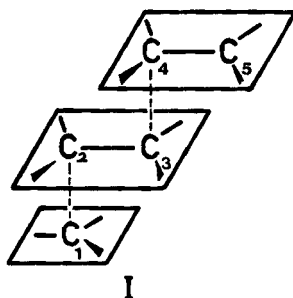


Fig. 1b

Figure 1. *Potential surface for model I. In a a methyl cation and in b a methyl radical interacts with two double bonds. The path of minimum energy (.....) and for a concerted mechanism (-----) is indicated*



Our first hypothesis for the geometry of the transition state is, that the positive or radical center and double bonds interact as shown in eq. (1). Molecular models show that such a chair-like arrangement of olefinic and  $\text{CH}_2$  groups is practically strainfree. A reasonable model for MO-calculations is obtained if we exclude both  $\text{CH}_2$ -groups and the  $\text{CH}_3$ -substituents in squalene. A p-orbital centered on a terminal  $\text{CH}_2$ -group which interacts with the double bonds in a helical arrangement results. A

further simplification is introduced if we consider only two double bonds and assume that all bond angles and bond lengths of the olefinic groups and of the  $\text{CH}_3$ -group remain constant.

For a model incorporating all these simplifications the arrangement of the five centers 1-5 is in three planes as shown in I [7].

In our calculations we have varied the distances  $d_{1-2}$  and  $d_{3-4}$  independently. The resultant energy, as a function of the two distances, is shown in Fig. 1a for a cationic and in Fig. 1b for a radical mechanism.

In both cases nearly the same potential surfaces result with the minimum at  $C_1-C_2=C_2-C_3=1.6 \text{ \AA}$ . As anticipated the potential surface for the cationic mechanism shows a steeper valley extending farther out than that for the radical mechanism.

In view of this similarity we will focus mainly on the cationic process. Considering the corresponding potential energy surface (Fig. 1a) we notice that it is not symmetric with respect to the diagonal, indicated by the broken line. There is a deep long valley with a relatively flat bottom, extending towards large  $C_3-C_4$  distances for  $d_{1-2} \approx 1.6 \text{ \AA}$ . The potential energy as a function of  $d_{3-4}$  at  $d_{1-2} = 1.6 \text{ \AA}$  is shown in Fig. 2a.

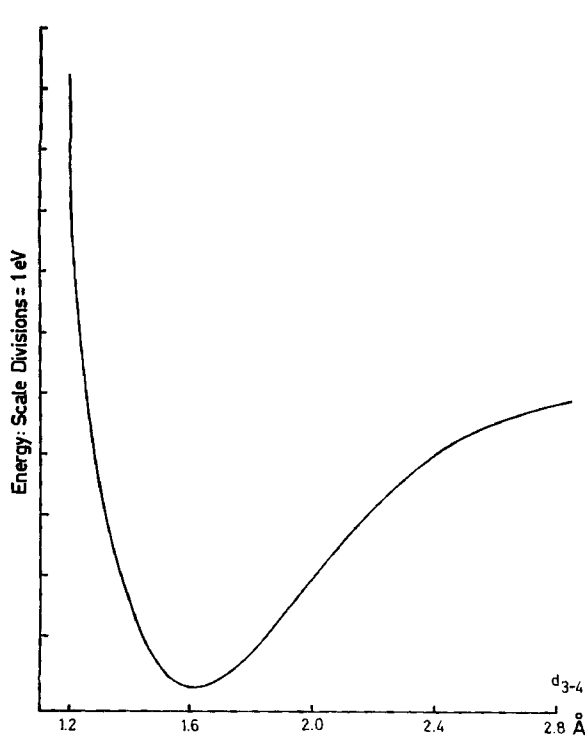


Fig. 2a. Potential energy for  $d_{1-2} = 1.6 \text{ \AA}$  as a function of  $d_{3-4}$  for the cationic mechanism of model I

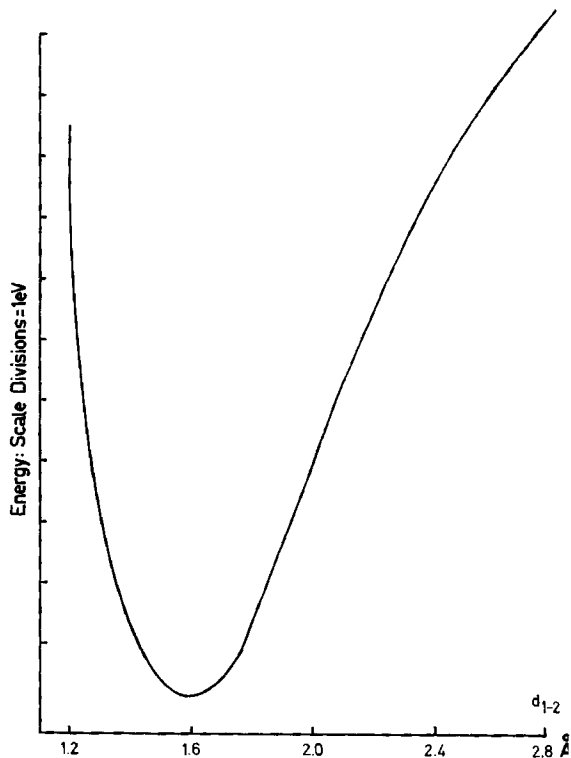


Fig. 2b. Potential energy for  $d_{3-4} = 1.6 \text{ \AA}$  as a function of  $d_{1-2}$  for the cationic mechanism of model I

The reason for the shape in this part of the surface is that at  $d_{1-2} \approx 1.6 \text{ \AA}$  the bond between center  $C_1$  and  $C_2$  has already been formed and the presence of the second double bond  $C_4-C_5$  is not very important. On the other hand for a larger  $C_3-C_4$  distance in model I, say  $d_{3-4} = 2.8 \text{ \AA}$ , the approach of the cationic center  $C_1$  is very favourable, leading to the steep slopes indicated in Fig. 1a.

Furthermore, we notice in Fig. 1a a short side valley extending towards large  $d_{1-2}$  distances for  $d_{3-4} \approx 1.6 \text{ \AA}$ . The potential energy as a function of  $d_{1-2}$  for  $d_{3-4} = 1.6 \text{ \AA}$  is shown in Fig. 2a. In contrast to the main valley, we find here a steep bottom meaning that there is a large energy gain by approaching the positive center when the two double bonds are close together.

There is still a third area which merits our attention. This is the plateau starting at the right upper corner of Fig. 2a. Looking from the energy-minimum  $M$  along the diagonal we find the plateau centered on the left side of the diagonal. This plateau is due to the fact that for large  $C_1-C_2$  distances ( $d_{1-2} > 4 \text{ \AA}$ ) the approach of a second double bond has no effect.

To decide whether our model reaction proceeds by a concerted or a step-wise mechanism, we will first consider a potential surface for the concerted [8] reaction (2)



Fig. 3 shows the contours of the energy as a function of the distances  $a \dots c$  and  $b \dots d$ . We notice two minima, one called  $A$  for the separated species  $a-b$  and  $c-d$  and one  $M$ , the minimum for the product. The path of minimum energy, *i.e.* the path of steepest descent is the one along the diagonal *via* the saddlepoint  $S$ . The bonds  $a \dots c$  and  $b \dots d$  are formed at the same time.

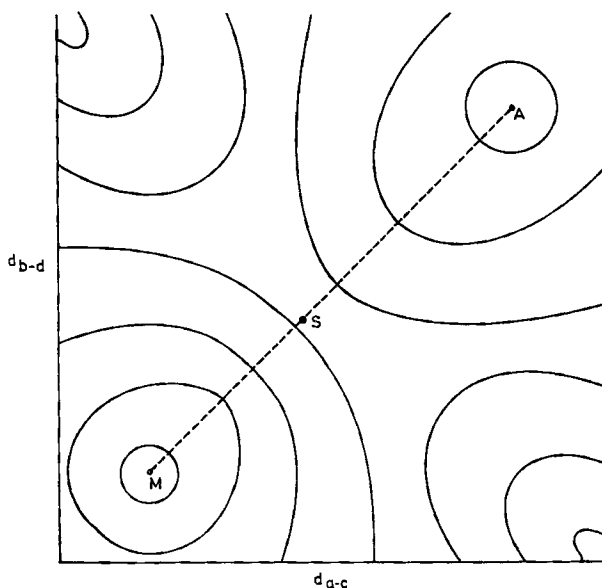


Fig. 3. Potential surface for the concerted reaction of eq. (2)

For our model I, a minimum for large separations is missing. Instead of this the plateau emerges with  $d_{3-4} > d_{1-2} > 3 \text{ \AA}$ .

If we start at *A*, a point on the diagonal, then the path of steepest descent will lead *via* the main valley to *M* as indicated by the dotted line. While the bond between  $C_1$  and  $C_2$  is being formed, the second double bond approaches the first one to within about  $2.5 \text{ \AA}$ , forming only a partial bond between  $C_3-C_4$ . For a concerted reaction of the kind we discussed on the basis of Fig. 3, the path of steepest descent should follow the diagonal. If we start at any point of the plateau for  $d_{1-2} \leq d_{3-4}$  the path of steepest descent will be similar to that indicated in Fig. 1<sup>3)</sup>. This means that our calculations for model I predict that the distance between the centers  $C_1-C_2$  is always shorter than that between  $C_3-C_4$ . The reaction proceeds in a way which is in between a concerted and stepwise mechanism. Once the carbonium ion is formed in (1) there is no activation energy and no intermediate predicted.

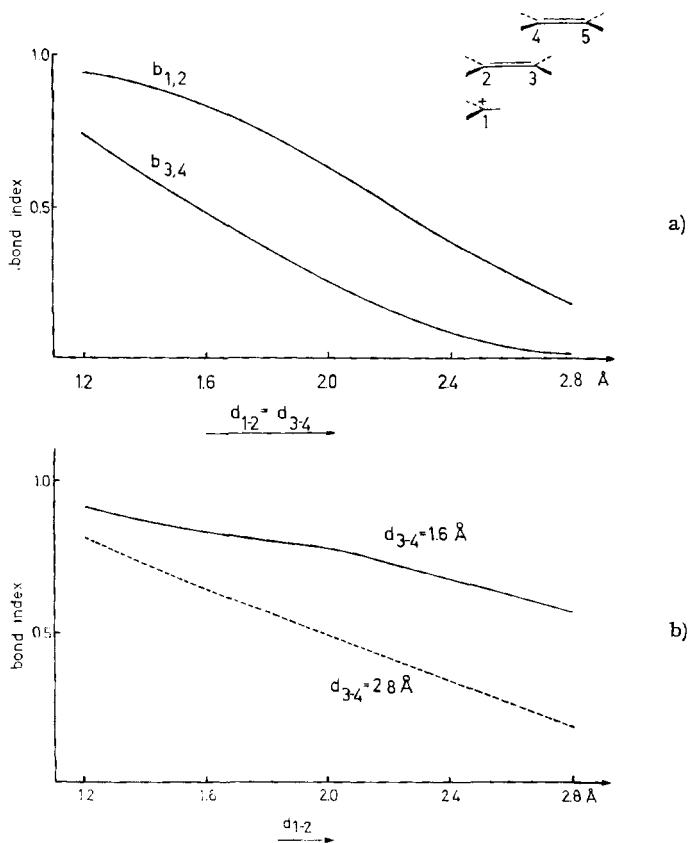


Fig. 4a. For the cationic mechanism of model I the bond indices between bonds  $C_1-C_2$  ( $b_{1,2}$ ) and  $C_3-C_4$  ( $b_{3,4}$ ) as a function of the distance are shown along the diagonal

Fig. 4b. For the cationic mechanism of model I the bond index between the bonds  $C_1-C_2$  ( $b_{1,2}$ ) is shown as a function of the  $C_1-C_2$ -distance for  $C_3-C_4 = 1.6 \text{ \AA}$  (—) and for  $C_3-C_4 = 2.8 \text{ \AA}$  (---)

<sup>3)</sup> It seems reasonable to assume that at the beginning of the ring closure (1)  $d_{1-2} \leq d_{3-4}$ .

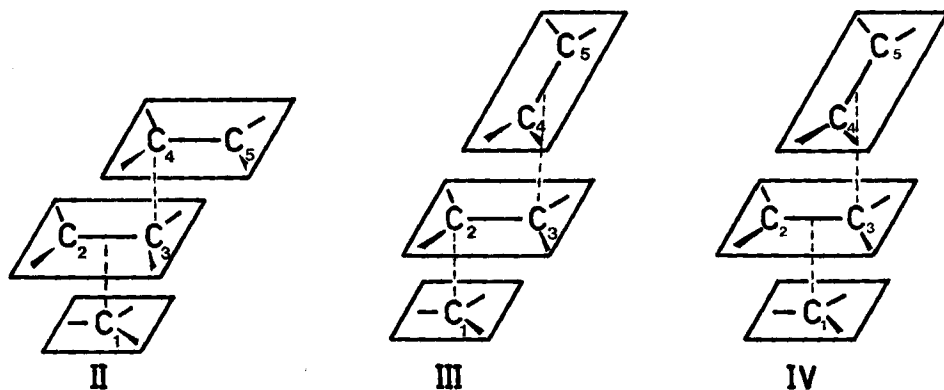
The conclusion that the reaction follows a reaction coordinate which lies in between a path for a concerted and a stepwise mechanism is also born out by comparing the bond indices [9] for the cationic mechanism between  $C_1-C_2$  ( $b_{1,2}$ ) and  $C_3-C_4$  ( $b_{3,4}$ ) along the diagonal ( $C_1-C_2=C_3-C_4$ ) as a function of the distance (Fig. 4a).

This figure shows that bond  $C_1-C_2$  is being formed before bond  $C_3-C_4$ . Moreover these curves indicate that for effective participation the second double bond should be within 3 Å of the first. This result suggests that the conformation necessary for the ring closure is realised during the reaction and not before, as suggested by (1). The partial bond formation between  $C_3-C_4$  on the other hand keeps the molecule from solvent incorporation and conformational flipping. In addition this result allows us to extrapolate to more than two double bonds. When the bond  $C_1-C_2$  is formed the new positive center ( $C_3$ ) will interact with the next two double bonds and so on.

In Fig. 4b we have shown the bond index between  $C_1-C_2$  for the cationic mechanism as a function of the distance of the second double bond. In one case the second double bond is 1.6 Å and in the other 2.8 Å apart. The outcome of this comparison corroborates the conclusions reached before: The second double bond facilitates bond formation between  $C_1$  and  $C_2$ .

The similarity between the contour diagrams for the cationic (Fig. 1a) and the radical (Fig. 1b) mechanism of model I, mentioned above is also born out by comparing the bond indices [9] for the cationic (Fig. 4) and radical mechanism along the diagonal. While for the cationic mechanism the second double bond is still effective at 3 Å, the bond indices for the radical mechanism are already negligible at 2.4 Å.

From molecular models we can also see that other transition-state geometries are possible, although for steric reasons less likely. With the assumptions mentioned above the resulting models are shown below.



With the CNDO/2 and the INDO method [6] a potential surface is obtained, which is very similar to that shown in Fig. 1. This is indicated in the table where we have listed the potential energy along the diagonal for model I–IV. In all cases a mechanism as discussed for Fig. 1 is favoured.

Besides numerous model reactions on squalene-like systems [1] [4] [10] there are some cyclization reactions on molecules with less flexible conformations *e.g.* the

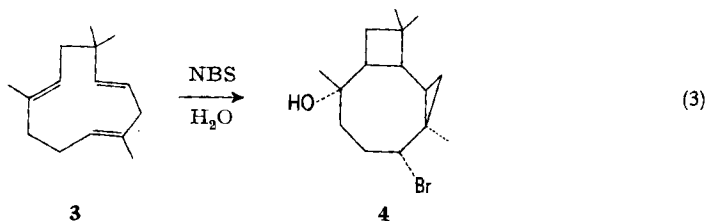
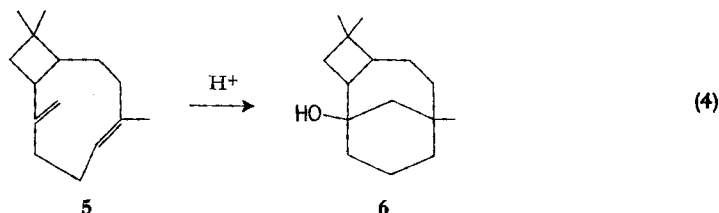


Table. Total energy (eV) for model I–IV along the diagonal

$C_1 - C_2 = C_3 - C_4$	I	II	III	IV
Å		<i>Cationic Mechanism (CNDO/2)</i>		
1.2	–1162.50	–1162.66	–1166.82	–1166.24
1.6	–1181.45	–1181.00	–1183.02	–1181.63
2.0	–1175.41	–1175.64	–1175.68	–1175.60
2.4	–1168.92	–1169.32	–1168.89	–1169.25
2.8	–1165.82	–1166.03	–1165.78	–1165.99
		<i>Radical Mechanism (INDO)</i>		
1.2	–1132.01	–1131.86	–1133.96	–1135.46
1.6	–1152.57	–1150.25	–1151.61	–1149.78
2.0	–1147.51	–1146.99	–1146.85	–1146.46
2.4	–1144.31	–1144.38	–1144.07	–1144.14
2.8	–1143.21	–1143.24	–1143.14	–1143.17

cyclization of humulene **3** with N-bromosuccinimide in aqueous acetone to the tricyclic **4** [11] and the cyclization of caryophyllene **5** on acid treatment to caryolan-1-ol **6** [12].



In the latter reaction *Nickon et al.* [12] showed in an elegant way that proton attack and ring closure is at least faster than conformational flipping. *Dreiding* models indicate that the two double bonds in **5** are about 3 Å apart and thus according to our calculations proton attack and ring closure should be 'coupled' and an independent flipping should not be possible.

A third system which bears some resemblance to our model calculations is that of the *endo, endo*-dimethanonaphthadienyl-system **7** [13]. The fact that the *p*-nitro-





benzoate of **7** solvolyses faster than the *anti*-7-norbornenyl-*p*-nitrobenzoate, by a factor of  $10^3$ , is attributed to a participation of the second double bond during solvolysis [13].

In accordance with this view we found, by minimizing the energy as a function of the geometry [14] of **7** and its cation **8**, that not only the distance between the formal positive center and the adjacent double bond is shortened (0.40 Å) but also the distance between the two double bonds (0.11 Å). All other bond lengths in the cation were found to be the same as the corresponding ones in **7**.

We appreciate very much the helpful discussion with Prof. R. Hoffmann, Cornell University.

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## 92. Die Addition von Imidazolderivaten an DCCI; eine Nebenreaktion bei der Synthese von Histidinpeptiden

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(26. III. 74)

*Summary.* In the synthesis of histidine peptides by means of the carbodiimide method the formation of N<sup>1m</sup>-amidino-histidine derivatives as secondary products has been observed. The reaction of imidazoles with DCCI leading to such compounds and their cleavage have been investigated. The significance of this side-reaction in peptide synthesis is discussed.

**1. Einleitung.** – Bei der Verknüpfung von längeren Peptidfragmenten nach der DCCI-Methode<sup>1)</sup> erweist es sich oft als notwendig, grössere Überschüsse an Carbo-

<sup>1)</sup> Abkürzungen: DCCI: N,N'-Dicyclohexylcarbodiimid, DCH: N,N'-Dicyclohexylharnstoff, HOBT: 1-Hydroxy-benzotriazol, Z: Benzylloxycarbonyl-, Boc: *t*-Butylloxycarbonyl-