# Molecular Models: A Means of Studying Catalytic Hydrogenations

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*Although in many cases it will not be necessary, the assembly of molecular models can prove extremely valuable in studying certain types of catalytic hydrogenations. They may, for example, help in understanding problems of selectivity when more than one reducible group is present, and they can also show whether poisoning by certain atoms will occur, offering a possibility of overcoming this by the use of more vigorous conditions or of more catalyst.*

To carry out successfully the catalytic hydrogenation of organic compounds contact must be effected between the surface of the catalyst and that portion of the molecule to be reduced. The importance of good contact should be emphasised because not all of the surface is capable of inducing hydrogenation. Reaction takes place only at active centres. Without going into the *modus operandi* of catalytic reduction, if the starting material is pure and contact with the catalyst is satisfactory, uptake of hydrogen will proceed more or less readily, unless an intermediate or the final product inhibits the activity of the catalyst used in the operation.

In many instances, the effect of substituents will be obvious. It should be easy to predict that ring reduction of 2-methylpyridine would take place more readily than 2,4,6-trimethylpyridine under similar reaction conditions. This is described in the reductions with ruthenium dioxide at 90° and 70 atmospheres pressure (1). Complete conversion to 2-methylpiperidine was completed in five minutes while the more substituted compound took about 15 hours. One might guess that 1-phenyl-2-aminopropane would be less difficult to hydrogenate than the branched compound 1-(4-isopropylphenyl)-2-aminopropane. The difference in reaction time is rather striking, 30 minutes against 12 hours at 90° and 70 to 80 atmospheres with ruthenium catalyst (2).

How will the chemist foresee less obvious difficulties, except from experience or perhaps by intuition? How can he get an understanding of why certain hydrogenations will present more problems than others? Molecular models can be of great help. A model of the last mentioned compound would have shown that, on rotation, portions of the ring were often out of contact with the catalyst. This observation could suggest increasing the temperature and pressure to bring about more rapid uptake of hydrogen.

In some instances, the reason for lengthy reaction is not always so obvious. In a series of hydrogenations of some substituted pyridines at 55 to 60° and 3 atmospheres pressure in the presence of rhodium on a carbon support, most of the compounds with a single substituent were readily reduced (3). Nicotinamide was converted to the corresponding piperidine in less than two hours, yet the N,N-diethylamide took 13 hours. It was not a question of purity since the compound had been recrystallised several times before use. It did not seem likely that the ring nitrogen of the substituted pyridine or piperidine amide would have any greater poisoning power than

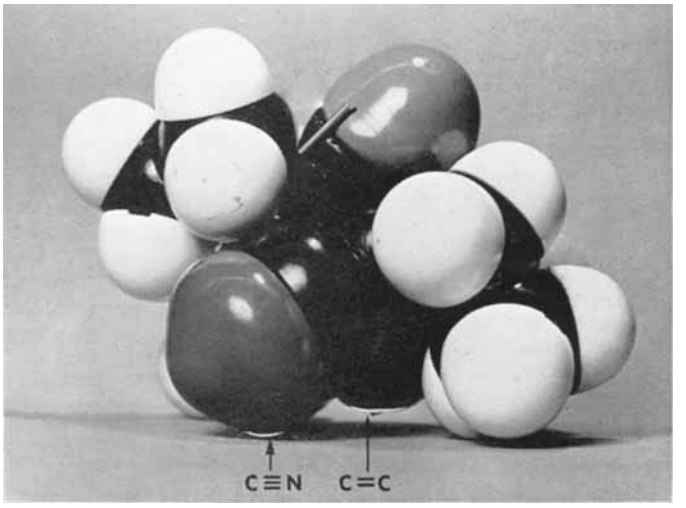
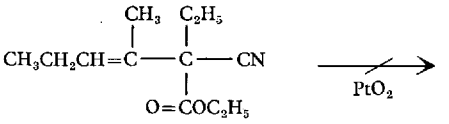


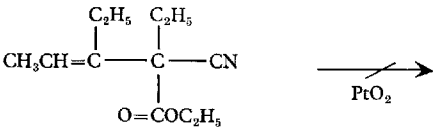

*Fig. 1 Ethyl 2-cyano-2-ethyl-3-methyl-4-hexenoate: the model shows that it is impossible to get the olefinic group in close contact with the catalyst surface and therefore it cannot be reduced*

the corresponding nitrogen atoms of unsubstituted amides. From models of the four compounds involved, no apparent difficulty could be envisaged. However, an examination of a model of a partially reduced diethylamide did offer a clue. It appeared that as hydrogens were added, portions of the ring were raised from the surface. It seemed likely that more vigorous conditions were necessary to force the intermediate back into better contact with the catalyst. When reduction was carried out at 90° and 70 atmospheres, conversion was complete in about 45 minutes (1).

An examination of models can help one to understand and at times to predict the results of hydrogenating compounds with several reducible groups. The reductions shown below are an illustration (4).



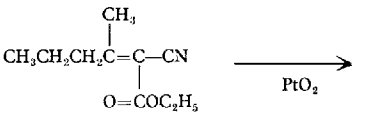

saturated cyano ester

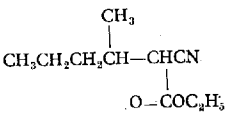



saturated cyano ester

In each instance a model of the unsaturated cyano ester made it clear (Fig. 1) that the cyano group would make good contact with the catalyst surface and therefore be amenable to conversion to the unsaturated primary and/or secondary amine. At the same time, it was not possible to manipulate the models to allow the C=C bond to make any contact whatsoever.

On the other hand, a model (shown in Fig. 2) predicted that the following reduction should yield the desired saturated compound:




It also showed that conversion to the saturated amine was possible. Indeed, the presence of amine has been noted as a by-product in the hydrogenation of similar compounds (5). The reduction shown above did give a high yield of the saturated cyano ester (4).

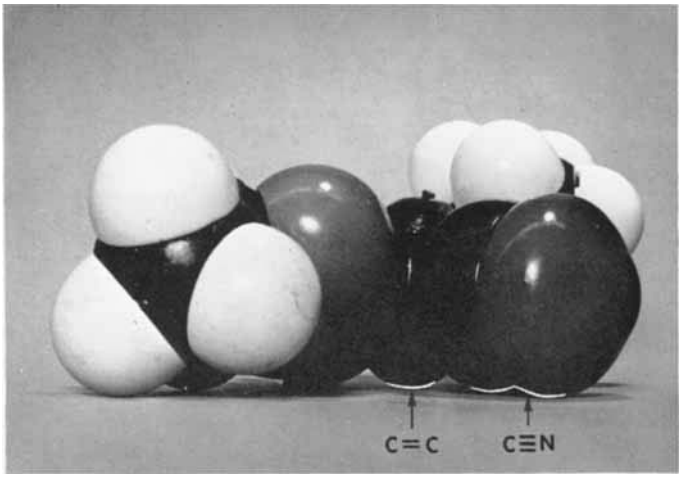
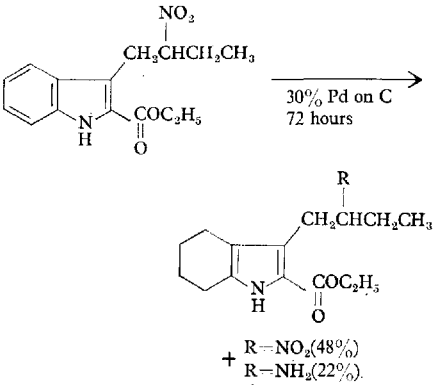



*Fig. 2 Ethyl 2-cyano-3-methyl-2-hexenoate: in this compound both the olefinic and nitrile groups are in contact with the catalyst surface and both can be reduced. The olefinic group is selectively reduced before the nitrile*

In an attempted conversion of dicyclopropyl ketone to the corresponding carbinol, no uptake of hydrogen was observed in the presence of platinum oxide (4). From the model (Fig. 3) it could be seen that the carbonyl group would be out of contact with the catalyst most of the time. When palladium was used in the reduction, 4-heptanol was obtained (4). The rings were undoubtedly ruptured, leaving the carbonyl group in a favourable position on the catalyst so that further reduction would take place. This is evident from models of cyclopropyl *n*-propyl ketone (Fig. 4) or di-*n*-propyl ketone.

The following is a very interesting example of the reduction of a ring system in preference to a more readily reducible group, with a catalyst not generally used for aromatic systems (6):




The authors repeated their work with a different lot of catalyst, in another piece of equipment, and obtained the same results. They reported that they made models which suggested that the terminal methyl group on the side chain prevented reduction of the nitro group because it could occupy only a restricted

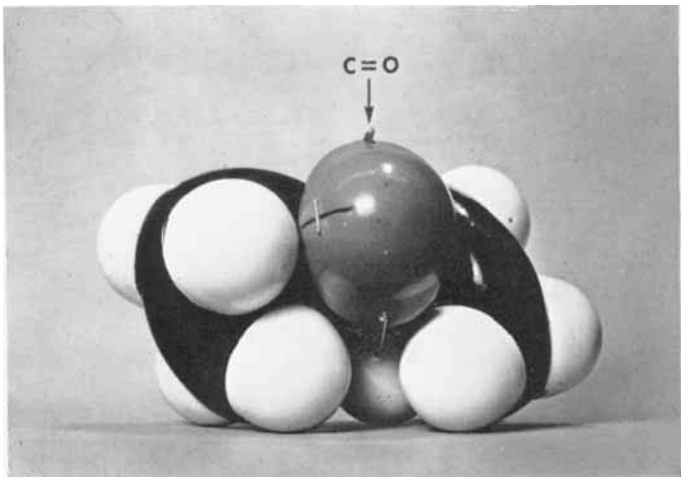



*Fig. 3 Dicyclopropyl ketone: the keto-group will be out of contact with the catalyst surface and this explains the lack of reactivity*

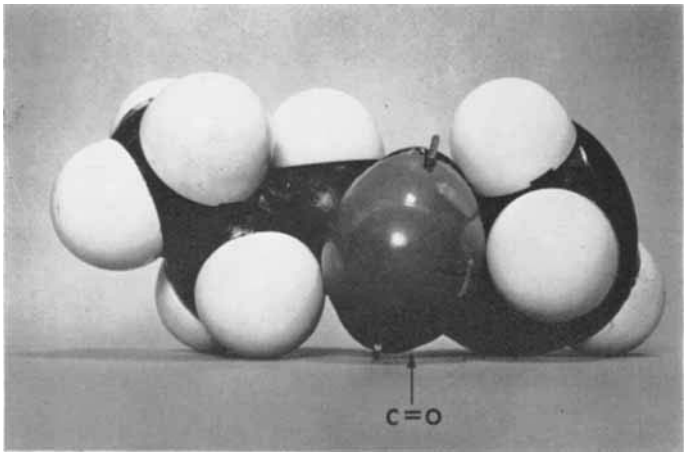
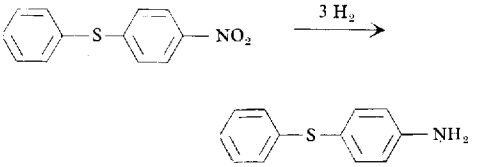



*Fig. 4 Cyclopropyl n-propyl ketone: opening one of the cyclopropane rings enables the keto-group to have better contact with the catalyst surface, thus enabling it to be reduced*

number of positions. Duplication of models by this author showed the aromatic portion of the molecule in good contact with the catalyst, while the nitro group was off in space more often than it was in contact with the catalyst.

When the same authors investigated the hydrogenation of the corresponding nitropropane under similar conditions, but in a much shorter time, they were able to reduce the nitro group without affecting the ring. A model of the shorter chain compound suggests that less difficulty should be encountered.

Models can often be useful in deciding whether catalytic reduction is feasible in the presence of known poisoning atoms. Maxted has suggested that poisoning of sulphur-containing compounds is due to the unshared electron pairs which allow strong bonding to the catalyst surface, or more pointedly, to the active centres on the surface of the catalyst (7). Nevertheless, it is possible to carry out catalytic reduction of certain groups in the presence of organic sulphides. The literature is full of examples:




A model of 4-nitrophenyl sulphide shows (Fig. 5) that the sulphur atom is sufficiently out of contact with the catalyst to allow reduction to proceed to completion. However, when one of the phenyl rings is removed and an aliphatic side chain is substituted, hydrogenation becomes more difficult. The model of ethyl 4-nitrophenyl sulphide (Fig. 6) suggests that poisoning can occur.

The model of the nitro compound given in the equation overleaf showed (Fig. 7) that the 2-methyl group interfered with contact between the sulphur atom and the catalyst. In view of the theory of active centres, the position of the sulphur atom suggested that

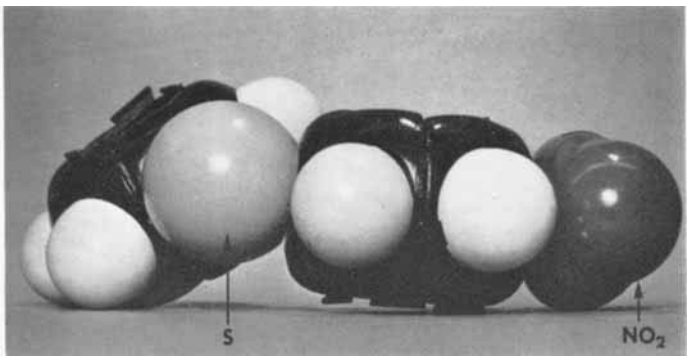



*Fig. 5 4-nitrophenyl sulphide: the sulphur atom is so far removed from the surface that it cannot act as a catalyst poison*

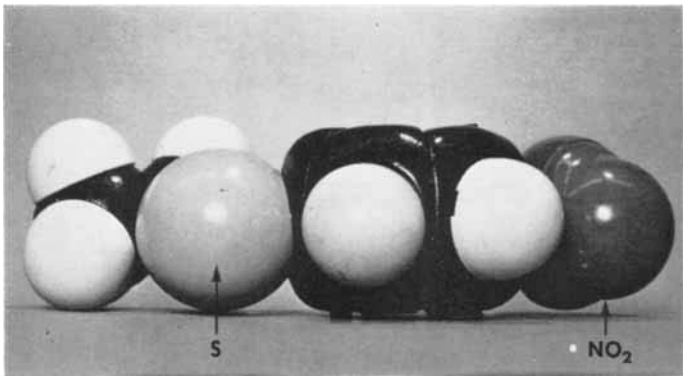
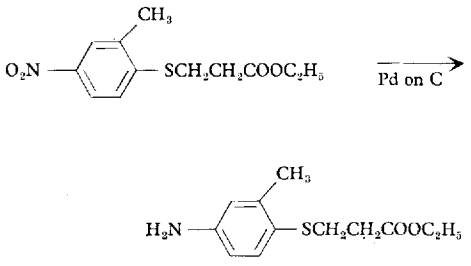



*Fig. 6 Ethyl 4-nitrophenyl sulphide: in this molecule the sulphur atom can easily touch the catalyst surface, suggesting that poisoning will occur*




complete poisoning would not take place and that complete conversion could be attained in the presence of a higher than normal amount of catalyst. Although uptake of hydrogen was slow, it was complete with a 30 per cent ratio of catalyst to compound (4).

The writer does not suggest that models should be studied before every reduction is carried out. There are many times when it will not be necessary. Nevertheless, with a knowledge of other factors in catalytic hydrogenation, the short time spent in assembling models could prove extremely valuable. They might give an insight into selectivity when more than one reducible group is present. They could also show whether poisoning by certain atoms would take place and perhaps offer a means of overcoming this by the use of more vigorous conditions or more catalyst or both. Our experience has shown that models can be of considerable value.

## References

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4 Unpublished work from this laboratory
5 A. C. Cope, C. M. Hoffman, C. Wyckoff and E. Hardenbergh, *J. Am. Chem. Soc.*, 1941, **63**, 3452, used a dilute acid wash to remove any bases formed by addition of hydrogen to the nitrile group
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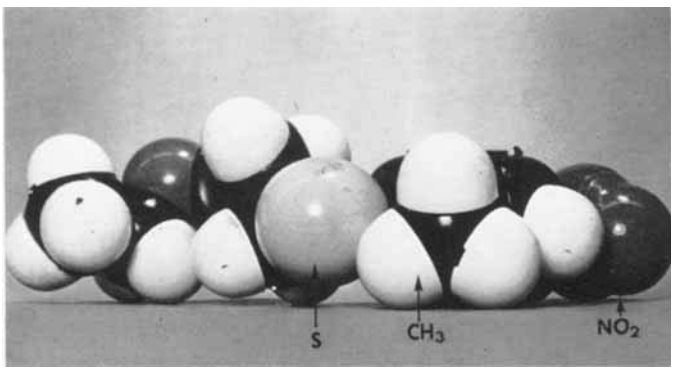


*Fig. 7 Ethyl (2-methyl-4-nitrophenyl) mercaptopropionate; the methyl group inhibits contact between the sulphur atom and the catalyst surface and hydrogenation of the nitro-group proceeds, although slowly. (This model is somewhat idealised for photographic purposes. The sulphur atom is actually closer to the surface and the 2-methyl group restricts rotation to prevent firm attachment of the sulphur to the catalyst)*