Stereochemistry of the S_N2' Reaction in Cyclohex-2-enyl Esters

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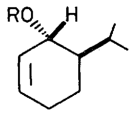
Summary The S_N2' displacement of the cyclohex-2-enyl esters (**1**), (**2**), and (**5**) by piperidine proceeds with *syn* stereochemistry; the apparent *anti* products originate by S_N2 reaction of the rearranged esters (**15**), (**12**), and (**14**).

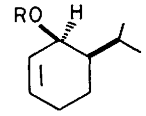
In 1956 Stork and White published a report[1] on the stereochemistry of the S_N2' reaction with cyclohex-2-enyl esters, whose conclusions have been frequently quoted and widely accepted. Their main finding was that piperidinolysis of *trans*-6-alkyl-cyclohex-2-enyl 2,6-dichlorobenzoate (**1**) led exclusively to the S_N2' product (**8**) resulting from entry of the attacking nucleophile *syn* to the departing benzoate anion. In view of the key importance of this reaction and the opportunity of subjecting the products to the more searching analytical methods now available, we have re-investigated the reaction of piperidine with the *trans*-ester (**1**) and extended our study to the *trans*-ester (**2**) and *cis*-ester (**5**).[2] Although the course of the reaction is more complex than was revealed by Stork and White's analytical methods, our findings support their conclusion that in the system under study the S_N2' reaction proceeds probably entirely with *syn* stereochemistry.

Piperidinolysis of the 2,6-dichlorobenzoate (**1**),[1] either in neat piperidine or in *m*-xylene solvent, afforded, in contrast to the previous report, the four isomeric amines (**8**), (**9**), (**10**), and (**11**), separable after hydrogenation by g.l.c. (5% Carbowax 20M + 1% KOH; 130 °C; r.i.'s of saturated amines, respectively, 2010, 1890, 1805, and 1730) and identified by g.l.c.–m.s. comparison with authentic samples.

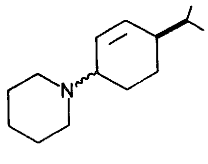
The probable origin of these products was revealed by more detailed studies with the *trans*-3,5-dinitrobenzoate (**2**). As before, the amines (**8**)—(**11**) were formed. Product analysis after different reaction times (0—70 h in *m*-xylene at 125 °C) showed that the ratio of apparent *anti*-S_N2' product (**9**) to *syn*-S_N2' product (**8**) increased with time, indicating that these products cannot both be formed from the same ester (**2**). The allylically rearranged ester (**12**) was suspected as the probable source of amine (**9**). Examination of the recovered ester fraction showed that ester (**12**) was indeed formed progressively in the course of the reaction, reaching an apparent equilibrium value of about 20% of total esters after 40 h. There were also minor amounts of the epimerised ester (**5**). (The esters, being unstable to g.l.c., were analysed by g.l.c. of the alcohols obtained with $LiAlH_4$ under conditions where no



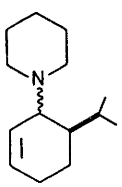
(1) R = 2,6-$Cl_2C_6H_3CO$
(2) R = 3,5-$(NO_2)_2C_6H_3CO$
(3) R = H
(4) R = 2,4,6-$Me_3C_6H_2CO$



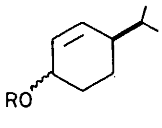
(5) R = 3,5-$(NO_2)_2C_6H_3CO$
(6) R = H
(7) R = 2,4,6-$Me_3C_6H_2CO$



(8) *trans*
(9) *cis*



(10) *trans*
(11) *cis*



(12) *trans*; R = 3,5-$(NO_2)_2C_6H_3CO$
(13) *trans*; R = H
(14) *cis*; R = 3,5-$(NO_2)_2C_6H_3CO$
(15) *trans*; R = 2,6-$Cl_2C_6H_3CO$

rearrangement occurred.[3]) The alcohols (**3**), (**6**), and (**13**) from aminolysis of the corresponding esters were also obtained in these experiments. Extrapolation to zero reaction time of the ratio of *syn*:*anti* S_N2' products [(**8**):(**9**)] showed this corresponded exactly to the ratio of *trans*:*cis* esters [(**2**):(**5**); 97:3] undergoing solvolysis. Similar extrapolation for piperidinolysis of a mixture of esters (**2**) and (**12**) again showed exact correspondence at time zero between the ratios (**2**):(**12**) and the amine products (**8**):(**9**). We conclude that S_N2' reaction in this case proceeds with *syn* stereochemistry and that the apparent *anti*-S_N2' product is formed predominantly by S_N2 reaction of the rearranged ester (**12**). *syn* S_N2' displacement of the epimerised ester (**5**) may also play a minor role in the formation of (**9**).

The *cis*-3,5-dinitrobenzoate (**5**), m.p. 102—103 °C, also afforded the four amines (**8**)—(**11**) with piperidine. The ratio of (**9**):(**8**) changed with time and increasing amounts of the rearranged ester (**14**) appeared in the product. The available evidence suggests that in this case also the S_N2' reaction proceeds predominantly with *syn* stereochemistry.

These results are in accordance with theoretical predictions[4] for the S_N2' reaction, but may reflect special constraints existing in cyclohexenyl esters. We have investigated an acyclic counterpart of this system and will report our findings elsewhere.

Very recently Stork and Kreft have reported[5] on the displacement of (**1**) and the 2,4,6-trimethyl-benzoates (**4**) and (**7**) by piperidine and similarly conclude that with this nucleophile the S_N2' reaction proceeds with *syn* stereochemistry.

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