The Stereochemistry of Nucleophilic Addition to Some Conjugated Cyclohexenes

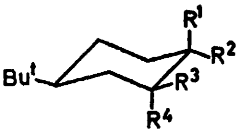
By C. W. Alexander, M. S. Hamdam, and W. R. Jackson*

(*Department of Chemistry, Queen's University, Belfast* BT9 5AG)

Summary The products of axial attack have been found to predominate from two extreme types of nucleophilic addition reactions to conformationally rigid cyclohexenes.

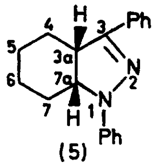
The stereochemistry of Michael type reactions in conformationally stable systems has been examined by Abramovitch and his co-workers.[1] From a study of thiophenoxide and malonate ion additions they proposed that axial attack was preferred except where the nucleophile was weak, highly solvated, and bulky. We have attempted to examine the generality of these proposals by studying the stereochemistry of two reactions which involve examples representative of the different classes of nucleophile.

(i) Strong, unsolvated nucleophile. Reaction of calcium cyanide with 1-acetylcyclohexene in *NN*-dimethylformamide[2] gave an equimolar mixture of *cis*- and *trans*-1-acetyl-2-cyanocyclohexanes which were separated by preparative g.l.c. The more easily eluted isomer had $J_{1,2}$ 10·0 Hz and was assigned the *trans*-structure as H^1 and H^2 are clearly *trans*-diaxial. The *cis*-isomer showed $J_{1,2}$ *ca.* 4 Hz. A similar reaction of calcium cyanide with 4-t-butyl-1-acetylcyclohexene gave two isomers in ratio *ca.* 2:1 which were again separated by preparative g.l.c. The coupling constants $J_{1,2}$ were derived by decoupling of the protons at C^3 and C^6, *i.e.* by using frequency modulated secondary irradiation at $\tau 8{\cdot}0$. They were found to be 1·5 Hz for the more abundant and 4·0 Hz for the less abundant isomer. The coupling constants clearly show that isomer (**4**) with *trans*-diaxial protons H^1 and H^2 is not formed. Additionally the individual isomers were found to equilibrate under the mildly basic reaction conditions to give an isomer mixture similar in composition to that formed in the initial addition reaction. No further isomers were detected. Thus epimerisation at only one carbon atom is occurring and as acetone is a stronger acid than acetonitrile (pK_a 20 and 25 respectively)[3] it is highly probable that it is at the carbon atom α to the acetyl group. Thus both isomers must have an axial cyano-group and can be represented as (**1**) and (**2**). The more abundant isomer with $J_{1,2}$ 1·5 Hz was tentatively attributed structure (**1**) and the minor isomer with $J_{1,2}$ 4·0 Hz, structure (**2**). Structure (**1**) which has a cyano-group *trans*-coplanar to H^1 would be expected to have a lower value of $J_{1,2}$ than structure (**2**) which has no electron-withdrawing substituents *trans*-coplanar with either of the protons H^1 or H^2.[4]

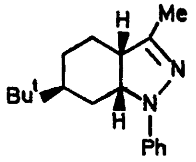


	R^1	R^2	R^3	R^4
(**1**)	H	Ac	H	CN
(**2**)	Ac	H	H	CN
(**3**)	Ac	H	CN	H
(**4**)	H	Ac	CN	H

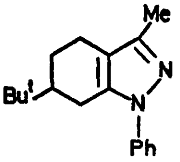
(ii) Weak, solvated nucleophile. Phenylhydrazones of αβ-unsaturated ketones cyclise on heating in acetic acid solution by nucleophilic attack of the solvated nitrogen atom on the activated double bond.[5] Cyclisation of benzoylcyclohexene phenylhydrazone gave the *cis*-ring fused pyrazoline (**5**) identical with a sample obtained from a 1,3-dipolar addition reaction of cyclohexene.[6] The two bridgehead protons had $J_{3a,7a}$ 9·8 Hz and H^{7a} also coupled equally with the protons at C^7, $J_{7a,7}$ 4·9 Hz. Cyclisation of 1-acetylcyclohexene phenylhydrazone gave a similar *cis*-ring-fused system ($J_{3a,7a}$ 8·4 Hz, $J_{7a,7}$ 5·0 Hz) as had a previous reaction of 1-acetylcyclohexene with hydrazine hydrate.[7] Cyclisation of the conformationally rigid 1-acetyl-4-t-butylcyclohexene phenylhydrazone in acetic acid solution gave, after chromatography, a single pyrazoline [(**6**) 50%] together with some of the corresponding pyrazole [(**7**) 15%]. The stereochemistry of the pyrazoline was assigned on the basis of its n.m.r. spectrum which showed H^{7a} as two triplets with $J_{3a,7a}$ 10·0 Hz and $J_{7a,7}$ 3·4 Hz. The low value of the coupling constants to *both* of the protons at C^7 indicates that axial–axial coupling is absent and thus the molecule has the preferred conformation (**8**). The initial nucleophilic attack has again been predominantly from the axial direction.



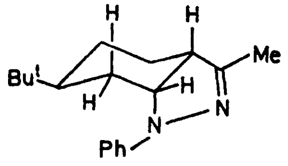
(**5**)



(**6**)



(**7**)



(**8**)

These results, together with those of Abramovitch and his co-workers,[1] suggest that in the absence of exceptional steric factors, axial nucleophilic attack is preferred. Delocalisation of the electron pair on the incoming nucleophile into the relevant π-orbitals of the electron withdrawing group is presumably facilitated by the axial transition state geometry.

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