MECHANISTIC IMPLICATIONS OF PHOTOANNELATION REACTION
OF 4,4-DIMETHYL-CYCLOHEX-2-ENE-1-ONE AND ACRYLONITRILE -
REGIO AND STEREOCHEMISTRY OF THE MAJOR PHOTOADDUCT
BY ^{1}H AND ^{13}C NMR SPECTROSCOPY

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Abstract : Using a variety of ^{1}H and ^{13}C one and two-dimensional NMR experiments the structure and stereochemistry of the major photoadduct from 4,4-dimethyl-cyclohex-2-ene-1-one and acrylonitrile has been characterized as 7-(exo)-cyano-5,5-dimethyl-bicyclo[4.2.0]-octan-2-one. The preferred regioselectivity suggests the participation of transoid enone in the ground state in photoannelation with acrylonitrile.

In a classic paper Corey et al have investigated the photochemical cycloaddition reaction between cyclohex-2-ene-1-one and substituted olefins to determine the orientation and stereochemistry in 2+2 cycloaddition[1]. Synthetic applications and mechanistic aspects of such enone-olefin photoannelations have been reviewed from time to time and it is still an intriguing problem to spell out the factors governing the regio and stereochemistry in such reactions[2-6]. Whereas cyclopent-2-ene-1-one gives only cis- fused adduct, cyclohex-2-ene-1-one leads to both trans- and cis- fused adducts[1,7,8]. It has generally been observed that the reaction between an enone and an unsymmetrical olefin carrying an electron donor or accepter group leads, either exclusively or predominantly, to head to tail or head to head isomer respectively. We have carried out the photoannelation reaction between 4,4-dimethyl-cyclohex-2-ene-1-one and acrylonitrile in different media, as a part of an attempt to obtain a bicyclo[4.3.0]-nonane system, by ring expansion of the cyclobutane ring in bicyclo[4.2.0]-octane derivatives by using the cyano group in the photoadduct to generate a cyclobutylmethyl type carbocation via the primary amine and nitrous acid treatment. The feasibility of such a synthesis was shown already in a different context[9]. Of the several isomers possible, we obtained a photoproduct mixture that after base treatment (which converts the trans to the cis adduct)[1] contained two isomers in the ratio of 3:1 from which the major isomer was isolated in pure state. The final product ratio was the same irrespective of whether an organic solvent or micellar medium was used. The product obtained could be either 7- or 8-cyano-5,5-dimethyl-bicyclo[4.2.0]-octan-2-one. In this communication we report the structure, relative configuration and conformation of the major product in the above mentioned reaction by NMR spectroscopy using various multiple pulse experiments[10,11].

The proton coupled ^{13}C NMR spectra provided the multiplicities of the signals from which the quarternary carbons and the two methyl carbons (with same chemical shifts) could easily be assigned[12]. The assignment of other carbons, three methylenes and three methines, was obtained in a straight forward manner using the two-dimensional INADEQUATE experiments[13-15] and the ^{13}C chemical shifts are given in the table. The one bond carbon-carbon couplings ($^1J_{CC}$) for sp^3-sp^3 and sp^3-sp carbons are normally in the range 30-40 Hz and 50-70 Hz respectively[12]. We, therefore, tried two experiments

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where the double quantum coherences were optimized for $^1J_{CC}$ of 31 Hz and 50 Hz. However, these experiments failed to show the connectivity between cyanocarbon and the carbon adjacent to it, and also the carbonyl carbon and carbons 1 and 3 due to large relaxation time of the unprotonated carbons. Therefore, we had to take recourse to more sensitive one dimensional INADEQUATE experiments[15] to fix the position of the cyano group in the 4 membered ring. An interesting feature of the two dimensional INADEQUATE experiments was the creation of double quantum coherence between carbons 1 and 3 (see fig. 1) separated by two bonds implying large two bond couplings. This was confirmed when in the one dimensional INADEQUATE experiments $^2J_{CC}$ of 11.2 Hz was observed between C_1 and C_3. Such large two bond couplings are rare but not unusual for carbons flanking a carbonyl[12,16]. For obtaining $^1J_{CC}$ for

Table : ^1H and ^{13}C-Chemical shifts and ^1H-^1H indirect spin spin couplings of 7-(exo)cyano-5,5-dimethyl-bicyclo[4.2.0]-octan-2-one

	Chemical shifts*		Indirect spin spin couplings (^1H-^1H)			
	^1H(ppm)	^{13}C(ppm)		(Hz)		(Hz)
δ_1	2.788	42.28	J_{1-3ax}	0.5	J_{4ax}-J_{CH_3ax}	0.4
δ_2	-	212.27	J_{1-3eq}	0.5	J_{4eq}-J_6	1.9
δ_3	2.449(ax)	36.89	J_{1-6}	8.7	J_{6-7}	10.3
	2.335(eq)	-	J_{1-7}	1.0	J_{6-8}	0.1[a]
δ_4	1.788(ax)	34.43	J_{1-8}	9.5[a]	$J_{6-8'}$	0.4[b]
	1.722(eq)	-	$J_{1-8'}$	2.1[b]	J_{7-8}	10.3[a]
δ_5	-	30.63	J_{3ax}-J_{3eq}	-15.2	$J_{7-8'}$	8.3[b]
δ_6	2.924	53.37	J_{3ax}-J_{4eq}	5.9	$J_{8-8'}$	-11.4
δ_7	2.754	22.80	J_{3ax}-J_{4ax}	14.4		
δ_8	2.394[a]	27.14	J_{3eq}-J_{4eq}	2.9		
	2.523[b]	-	J_{3eq}-J_{4ax}	3.6		
δ_{CN}	-	121.07	J_{3eq}-J_{CH_3eq}	0.3		
δ_{CH_3}	1.153(ax)	25.52	J_{4ax}-J_{4eq}	-14.2		
	1.018(eq)	25.52				

*   The chemical shift values are with respect to TMS. The numbers in subscript in the columns refer to the position of H and C in structure A in fig. 2

a   -   Proton <u>cis</u> to H_1 referred to H_8

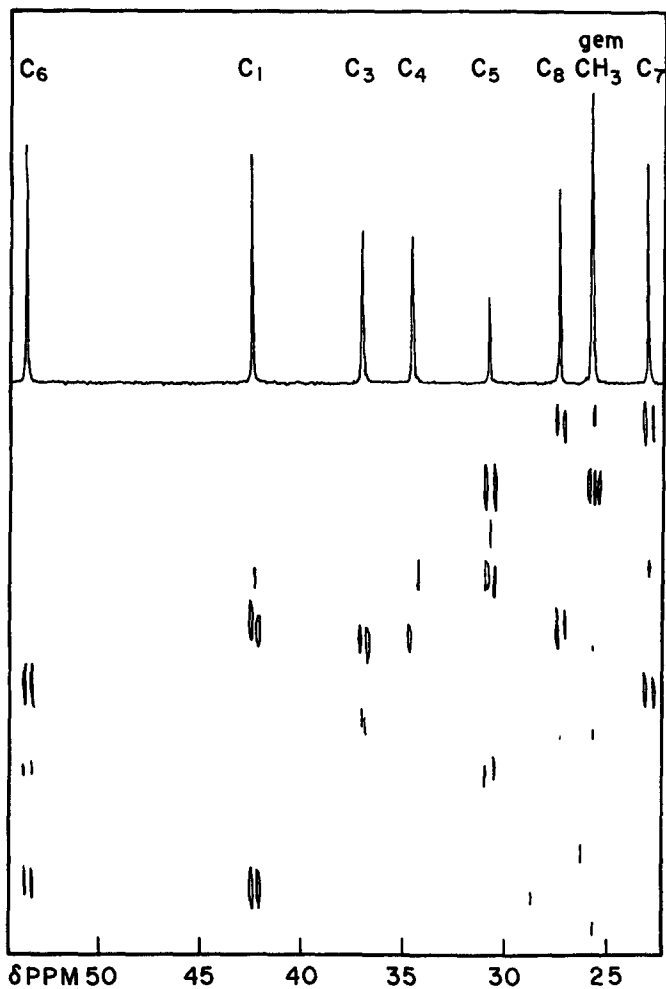b   -   Proton <u>trans</u> to H_1, referred to $H_{8'}$

Fig. 1 :   *Two dimensional* ^{13}C *INADEQUATE spectrum of 7-(exo)-cyano-5,5-dimethyl-bicyclo[4.2.0]-octan-2-one*
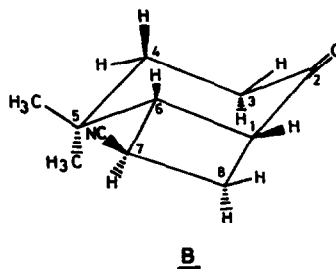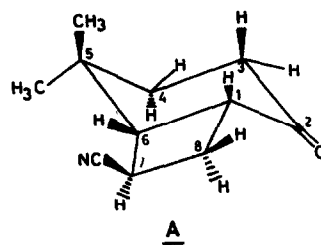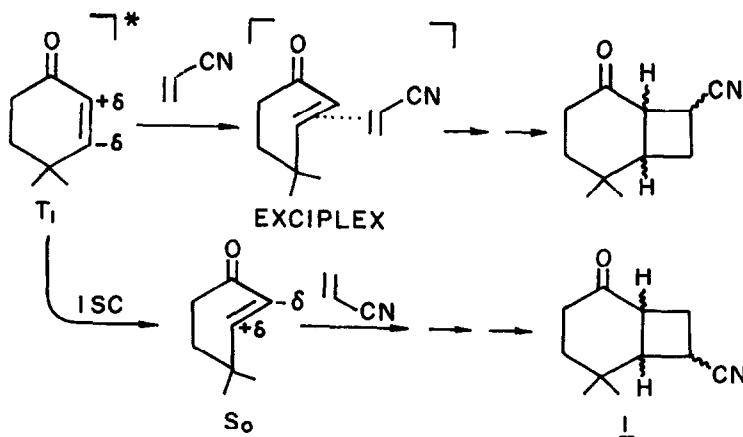

Fig. 2 :   *Two conformers of Compound* $\underline{1}$

SCHEME 1

all the carbons the double quantum coherence in the one dimensional INADEQUATE experiments was optimized for a value of J=50 Hz. These experiments clearly showed $^1J_{CC}$ of 61.3 Hz between the cyano carbon and the carbon at position 7 implying that the major product of the photochemical reaction is 7-cyano-5,5-dimethyl-bicyclo[4.2.0]-octan-2-one (a head to tail isomer).

The formation of a head to tail isomer defies many of the generalizations that have been made on the regio and stereo control in enone-olefin photoannelations. The reaction of acrylonitrile with cyclohex-2-ene-1-one and its 3-methyl derivative gives a head to head isomer as the major product[1,8]. It is consistent with the mechanism postulated by Corey[1] and subsequently elaborated by de Mayo[3] where the photoadduct results from an exciplex formed between an excited enone triplet (T_1) and the olefin. The formation of head to tail isomer may be understood with the help of the additional steps proposed by Schuster et al[17] based on the evidence obtained on the nature of the transient intermediates in the photochemistry of cyclohex-2-ene-1-ones. It was noted that the transoid enone in the ground state (S_0) generated by intersystem crossing from the twisted enone triplet is involved in the photo-addition reaction of 4,4-dimethyl-cyclohex-2-ene-1-one. In the reaction with acrylonitrile if the addition involved the enone transient in S_0 state then the regioselectivity is expected to be determined by the direction of polarisation of the enone and should lead to 7-cyano isomer. The transient in the T_1 state should give rise to 8-cyano-isomer. Taking these into consideration and omitting the finer details well described in literature[18], the two · mechanisms of photoannelation between 4,4-dimethyl-cyclohex-2-ene-1-one and acrylonitrile can be presented as shown in Scheme 1. The fact that we obtain 7-cyano isomer **1** as the major product appears to suggest the involvement of twisted enone in S_0 state.

Having fixed the position of cyano group, its configuration (exo or endo) in the cyclobutane ring can be obtained from $^3J_{HH}$ and the nuclear Overhauser effects (NOE) between the protons. Since the ^{13}C resonances have already been assigned. ^1H assignments as a first step were obtained with the help of ^1H-^{13}C hetero COSY experiments[10,11] optimized for one bond proton-carbon couplings. These experiments, however, do not permit the assignments of protons, either attached to the same carbon or the carbons having same chemical shifts. Therefore, further assignments have been made by the NOE considerations. For a chair conformation of the cyclohexanone ring, the axial methyl at C_5 would show NOE with the axial proton at C_3 and the equitorial proton at C_4 whereas the equitorial methyl would display NOE with both the protons at C_4 but not with the protons at C_3. Taking these facts into account all the proton assignments were made with the NOESY experiments[10,11] discussed later. Since the protons are strongly coupled, the ^1H spectrum was analysed with the PANIC program available with the spectrometer. The derived ^1H spectral parameters are given in the table.

The spin-spin coupling constants in a large number of substituted cyclobutanes investigated show that the <u>cis</u> coupling in the four membered ring are larger than the <u>trans</u> couplings[19-22]. This generaliza-tion, however, does not always hold good and necessitates the use of Karplus equation to ascertain the correct molecular structure[23]. In the fig. 2, two possible conformations of the ring system for 7-cyano-5,5-dimethyl-bicyclo[4.2.0]-octan-2-one are shown. Fig. 3 explicitly depicts the molecular confor-mation of the cyclobutane ring as the Neuman projections for the structure A in fig. 2 (with the CN at the exo position) along with the experimental coupling constants. The experimentally obtained $^3J_{HH}$ agree well with the couplings calculated with the help of modified Karplus relations[23] for the conforma-tion shown in fig. 3 and points to the fact that the cyano group is in the exo position. It is also worth mentioning that the $^3J_{HH}$ at C_3 and C_4 are consistent with a chair conformation at the cyclohexanone ring with large axial-axial coupling and rather small axial-equitorial and equitorial-equitorial couplings.

The conclusions derived from coupling constants have also been supported by the evidence relying directly on the inter proton distances. The final confirmation of the above structure was, therefore, deduced from NOESY experiments. In an experiment with a mix time of 2.5 sec. we observed equitorial methyl at C_5 have NOE cross peaks with axial methyl at C_5, with both the axial and equitorial H at C_4, and the protons at C_6 and C_7. The methyl in the axial position has, NOE cross peaks with equitorial
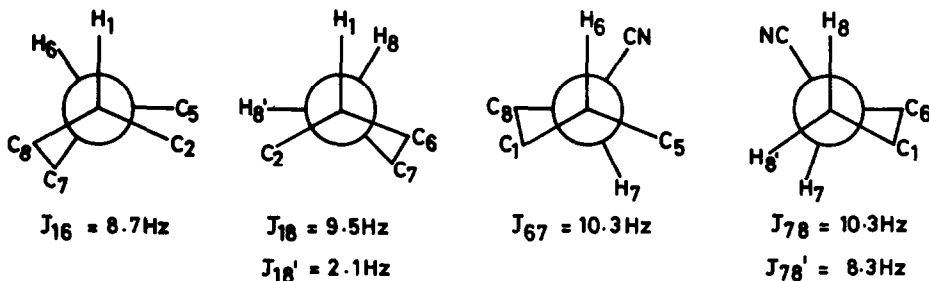
Fig. 3 : Neuman projections along the C-C bonds in the cyclobutane ring of
7-(exo)cyano-5,5-dimethyl-bicyclo[4.2.0]-octan-2-one

CH_3, equitorial H at C_4, axial H at C_3, H at C_6 and C_1. The H at C_6 has NOE cross peaks with both the methyls, protons at C_1 and C_7. NOE cross peaks for H at C_1 are observed with the protons at C_6 and C_8 whereas the H at C_7 has cross peaks with the protons at C_4, C_6 and C_8. All this data is found consistent with the structure A (fig. 2) and confirms the deductions derived from the coupling constants. It should be emphasized that the presence of a weak but characteristic NOE cross peak between the H at C_7 and the one in axial position at C_4 strongly supports on exo configuration for the nitrile at C_7 (in an experiment performed with a mix time of 1.5 sec. these cross peaks were not noticed). An alternative conformation B (fig. 2) can also be ruled out on the basis of the data on the coupling constants and NOE presented above.

Experimental

NMR spectra were recorded on Bruker AM-300 NM spectrometer with Aspect 3000 computer and an array processor operating at 300.13 MHz for ^1H and 75.47 MHz for ^{13}C. The spectra were obtained in $CDCl_3$ at room temperature (295 K) with TMS as internal reference.

^1H NMR   -   Normal one dimensional spectra were obtained with sweep width of 920 Hz with 16 K data points, zero filled to 64 K for better dizitization. The spectral resolution was enhanced by multiplication with Gaussian window function. The phase sensitive NOESY spectrum was obtained with sweep width of 700 Hz and 32 transients per t_1 were accumulated. A data matrix 256 x 2048 was collected with a mix time of 2.5 sec. The data was zero filled to 512 x 2048 before Fourier transformation. In order to remove the signal arising from zero quantum transitions the mix time was randomly varied by upto 2% of the mix time.

^{13}C NMR   - $^{13}C(^1H$ decoupled) spectra were obtained with a sweep width of 16666 Hz and composite pulse WALTZ decoupling, whereas the proton coupled spectra were run on gated decoupled mode to retain the NOE enhancements. The 2D INADEQUATE spectra were obtained with a data matrix 128 x 4096. For each of the t_1 value 64 transients were accumulated. The data was zero filled to 256 x 4096 before Fourier transformation. The one dimensional INADEQUATE spectrum was obtained with 8929 Hz sweep width with 16 K data points which was zero filled to 64 K before Fourier transformation. $^1H-^{13}C$ heteronuclear correlation experiments were optimized for one bond couplings and were obtained in the absolute value mode with a matrix 64 x 1024 which was zero filled to 256 x 1024 before Fourier transformation.

Photoaddition between 4,4-dimethyl-cyclohex-2-ene-1-one and acrylonitrile

The photoaddition was studied in different solvents like cyclohexane, t-butanol, acetonitrile, n-hexane and SDS micelles. In a typical experiment 6.2 g (0.005 mol) 4,4-dimethyl-cyclohex-2-ene-1-one and 31.8 g (0.6 mol) acrylonitrile (in micelles a 3-fold excess of acrylonitrile was sufficient) in 550 ml cyclohexane was irradiated for 8 hrs at 6° under continuous Ar purging, using pyrex immersion well

and a Hanovia 450 Watt medium pressure Hg.arc lamp. The solid polymer (in micelles solid polymer is not formed) was filtered and the filtrate concentrated in vacuo till the complete removal of starting material. The residue was dissolved in aqueous methanolic K_2CO_3, stirred for 4 hrs, solvent removed, diluted with water, acidified with dilute HCl and extracted with ether. The ether extract dried over Na_2SO_4, concentrated in vacuo and the residue chromatographed over silica gel using first pure hexane as eluent and progressively increasing the polarity by addition of ethyl acetate. Final elution was done with hexanes containing 10% ethyl acetate. The initial fractions gave pure 7-(exo)cyano-5,5-dimethyl-bicyclo[4.2.0]-octan-2-one. (Yield : 1.7 g, m.p. : 53.8°, IR(CHCl$_3$) : ν_{CO} 1710 cm^{-1}, ν_{CN} 2235 cm^{-1}. High resolution mass spectrum : M^+ at m/e 177.1158 (calculated for $C_{11}H_{15}NO$ 177.1153). The subsequent fractions contained a mixture of the above compound and one of its isomer (Yield : 950 mg) from which the second component could not be obtained in pure state. The number and ratio of the isomeric photoadducts was determined by GLC analysis on an SS 8' x 1/8" 10% SE-30 on chromosorb WHP (80-100 mesh), temperature programming (100°-15°/min -200°) and FID detector. Irrespective of the medium used for photoaddition 4 isomeric adducts with Rt at 8.58, 9.15, 9.26 and 10.98 min. are formed. The relative amount of the isomer with highest Rt value is negligible. This mixture after isomerisation contains two isomers with Rt at 8.58 and 9.15 min. in the ratio of 3:1. This infers the isomerisation of <u>trans</u> fused adducts with Rt at 9.26 and 10.98 min. to <u>cis</u> fused adducts with Rt 8.58 and 9.15 min. respectively.

References

1.   E.J. Corey, J.D. Bass, R. LeMahieu and R.B. Mitra, J.Am.Chem.Soc., <u>86</u>, 5570 (1964).

2.   P.E. Eaton, Acc.Chem.Res., <u>1</u>, 50 (1968).

3.   P. de Mayo, Acc.Chem.Res., <u>4</u>, 41 (1971).

4.   D.I. Schuster, in "Rearrangements in Ground and Excited States", P.D. Mayo, Ed., Academic Press, New York, 1980, Vol. 3, p. 167.

5.   S.W. Baldwin, In "Organic Photochemistry", A. Padwa, Ed., Marcel Dekker Inc., New York, 1981, Vol. 5, p. 123.

6.   S.S. Shaik, J.Am.Chem.Soc., <u>101</u>, 3184 (1979).

7.   R.M. Bowman, C. Calvo, J.J. McCullough, P.W. Rasmussen and F.F. Snyder, J.Org.Chem., <u>37</u>, 2084 (1972).

8.   T.S. Cantrell, W.S. Haller and J.C. Williams, J.Org.Chem., <u>34</u>, 509 (1969).

9.   J.M. Rao and D.I. Schuster, Ind.J.Chem., <u>22B</u>, 114 (1983).

10.   R.R. Ernst, G. Bodenhausen and A. Wokaun, "Principles of Nuclear Magnetic Resonance Spectroscopy in One and Two Dimensions", Clarendon Press, Oxford, 1987.

11.   H. Kessler, M. Gehrke and C. Griesinger, Angew.Chem.Int.Ed.Engl., <u>27</u>, 490 (1988).

12.   E. Breitmaier and W. Voelter, "Carbon 13 NMR Spectroscopy", Verlag Chemie, Weinheim, 1987.

13.   A. Bax, R. Freeman and S.P. Kempsell, J.Am.Chem.Soc., <u>102</u>, 4849 (1980).

14.   A. Bax, R. Freeman and T.A. Frenkiel, J.Am.Chem.Soc., <u>103</u>, 2102 (1981).

15.   J. Buddrus and H. Bauer, Angew.Chem., Int.Ed.Engl., <u>26</u>, 625 (1987).

16.   R. Jacquesy, C. Narbonne, W.E. Hull, A. Neszmelyi and G. Lukacs, J.Chem.Soc.Chem.Commun., 409 (1982).

17.   D.I. Schuster, P.B. Brown, L.J. Capponi, C.A. Rhodes, J.C. Scaiano, P.C. Tucker and D. Weir, J.Am.Chem.Soc., <u>109</u>, 2533 (1987) and references cited therein.

18.   D.I. Schuster, M.M. Greenberg, I.M. Nunez and P.C. Tucker, J.Org.Chem., <u>48</u>, 2615 (1983).

19.   H. Weitkamp and F. Korte, Tetrahedron Supplement No. 7, 75 (1966).

20.   I. Fleming and D.H. Williams, Tetrahedron, <u>23</u>, 2747 (1967).

21.   H. Herzog, H. Koch, H-D. Scharf and J. Runsink, Tetrahedron, <u>42</u>, 3547 (1986).

22.   G. Adembri, D. Donati, S. Fusi and F. Ponticelli, Heterocycles, <u>26</u>, 3221 (1987).

23.   C.A.G. Haasnoot, F.A.A.M. deLeeuw and C. Altona, Tetrahedron, <u>36</u>, 2783 (1980).