TRANSANNULAR INTERACTION: MOLECULAR STRUCTURE AND CONFORMATIONAL PROPERTIES OF N-ARYL-1- AZACYCLOOCTAN-5-ONES

Ghiaci, Mehran **
Mohajeri, Ali
Department of Chemistry, Isfahan University of Technology, P.O.Box 84156, Isfahan, Iran.

(Received: Feb. 26th 1994 , Accepted: Nov. 21st 1994)

ABSTRACT : *Conformational properties of N- aryl -1- azacyclooctan -5- ones with a p- methyl-, m- methyl-, and p- methoxy group as a substituent have been studied by ^{1}H-NMR, ^{13}C-NMR and IR spectroscopies. Transannular interaction of the two functional groups have been examined from the ring inversion barriers and the carbonyl vibrational frequencies with reference to the corresponding data of the respective monofunctional and difunctional compounds.*

KEY WORDS : *Transannular Interaction, Ring Inversion, Pseudorotation, Conformational Analysis, Eight- membered Rings.*

INTRODUCTION :

Conformational properties of eight-membered rings like cyclooctane and its derivatives [1], cyclooctanone [2,3], 1- oxacyclooctan- 5- one [4], 1- thiacyclooctan-5- one [5], and N- methyl- 1- azacyclooctan- 5- one [6] have been studied extensively by experimental and theoretical methods. It has been shown that cyclooctanone exist primarily in a boat- chair conformation with the carbonyl group at the 3-position. Eight- membered ring compounds containing the carbonyl group and suitably placed heteroatoms can exhibit transannular interactions.

Transannular interactions can exist across difunctional medium sized cyclic compounds from 8- to 11- membered rings and even larger [7]. Such interactions can be detected by dipole moment and spectral measurements.For example, that the carbonyl group in 1-4 is effected by the nitrogen has been demonstrated by photoelectron spectroscopy, which shows that the ionization potentials of the nitrogen n and C=O π orbitals in these compounds differ from those of the two reference molecules 5 and 6 (Scheme 1) [8]

* Corresponding author
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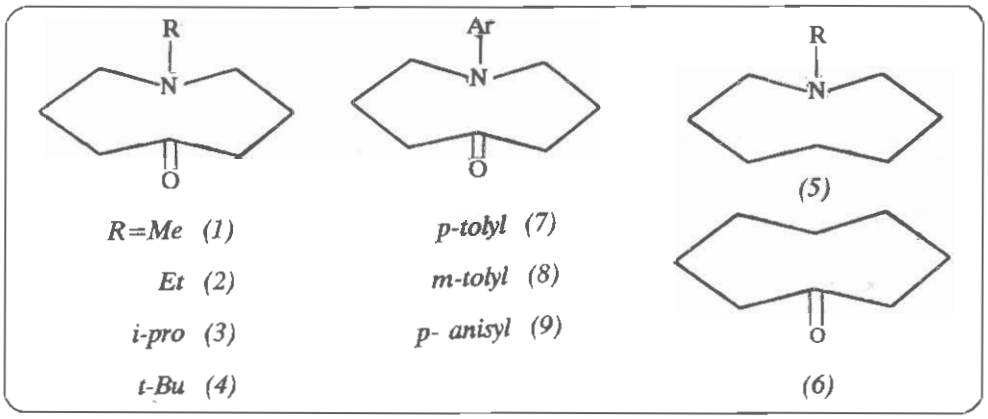


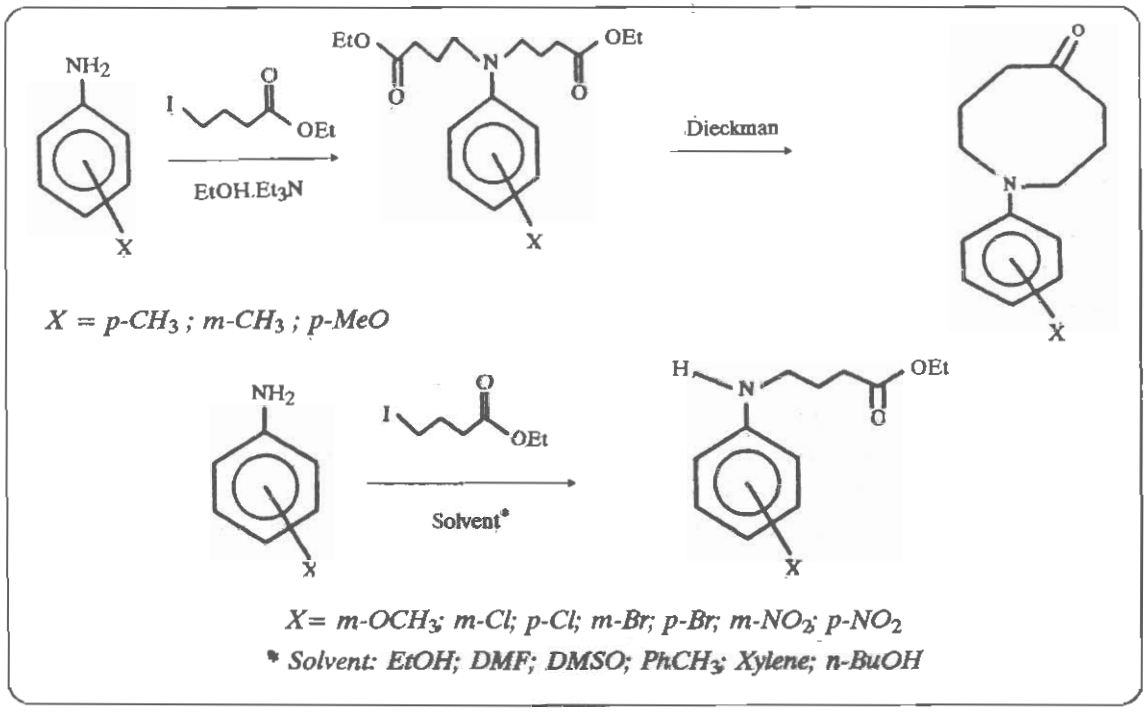
Scheme 1

EXPERIMENTAL:

N- aryl-1- azacyclooctan-5- ones were synthesized by the *Dieckmann* cyclisation of the corresponding diethyl γ, γ- N- aryl- azabis-butirate using potassium tert- butoxide in xylene under high dilution condition [9]. As shown in scheme 1, we were able to dialkylate only those substrates were X= p-CH_3, m-CH_3, and p- MeO. If the substituent on the aromatic moiety was X= m-MeO, m-Cl, p- Cl, m-Br, m- NO_2, the monoalkylated compound was the main product. In this respect we used high boiling aprotic solvents, but we were not able to produce the corresponding dialkylate products (Scheme 2).

N- (p- anisyl)-1- azacyclooctan-5- one:
m.p. 53-54°C; ^{1}H-NMR ($CDCl_3$, 90MHz) 6.8(4H, s), 3.8(3H,s), 3.2(4H,t), 2.4-1.8(10H, m); Ms,m/e 233(M^+).

N-(m-tolyl)-1- azacyclooctan-5- one:
m.p. 58-59°C, ^{1}H-NMR ($CDCl_3$, 90MHz), 10(1H,m), 6.3(3H,m), 3.4(4H,t), 2.41-9(13H, m); Ms, m/e 217(M^+).



Scheme 2

N-(p- tolyl)-1- azacyclooctan-5-one:
m.p. 63-64°C, ^{1}H-NMR ($CDCl_3$, 90MHz), 6.8 (4H, dd), 3.3(4H, t), 2.4(4H, t), 2.2(3H, s), 2.1(4H, m); Ms, m/e 217(M^+).
^{13}C-NMR spectrum of 7 ($CDCl_3$, 100MHz, ^{1}H noise decoupled), 19.67 (p-$^{13}CH_3$), 26.72 (3,7-$^{13}CH_2$), 39.53 (4,6-$^{13}CH_2$), 48.83 (2,8-$^{13}CH_2$), and 211.82 (^{13}C=O).

The variable temperature ^{1}H-NMR spectra were measured on a 400MHz NMR spectrometer *(Brucker)*, using CD_2Cl_2 as solvent. The coalescence approximation was used to evaluate the barrier to ring inversion. At T_c, the unimolecular rate constant for the reaction is given by $k_c = \pi\Delta\nu/\sqrt{2}$, and the free energy of activation $\Delta G^{\#}$ at the coalescence temperature can be calculated from $\Delta G^{\#} = 2.3RT_c(10.32 + \log T_c/k_c)$. Two peaks centered at 2.95 and 3.5ppm in spectrum taken at -81°C were used for evaluating the $\Delta\nu$= 220Hz. These two coalescenced at -60°C and eventually appeared as a triplet at 3.30ppm at room temperature.

RESULTS AND DISCUSSION:

It has become of interest to investigate the extent of transannular interaction in a more quantitative manner.

The ^{1}H-NMR spectrum of N- (p- tolyl) -1-azacyclooctan-5- one (7) at 400MHz shows well-separated multiplets for the three chemically different CH_2 groups [$CDCl_3$, δ3.28 (2,8-CH_2), 2.35(4,6- CH_2) and 2.18(3,7- CH_2)]. One dynamic NMR effect can be observed over the temperature range 25 to -100°C in CD_2Cl_2 (Fig. 1). Because of the difficulties reaching temperatures lower than -100°C, we were not able to detect any other dynamic process in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum of 7 was temperature independent in the temperature range 25 to -100°C. The observed conformational process in 7 has a $\Delta G^{\#}$ of 9.6kcal/mole and is expected, in analogy with cyclooctanone, 1- oxacyclooctan-5- one and 1- thiacyclooctan-5-one (Table 1), to be ring inversion process having a chair transition state.

If it is assumed that any one of the compounds in Table 1, pass through a chair transition state in the process of ring inversion, any transannular interaction in the ground state should disappear at the transition state, and the extent of transannular interaction should be reflected in the barriers to ring inversion in these rings (Fig. 2). The NMR data are in a good agreement with the statement that the lone

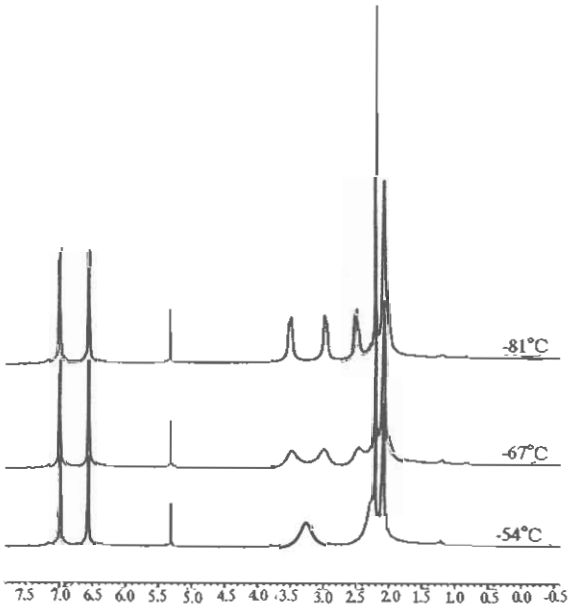


Fig. 1: The 400MHz ^{1}H-NMR of N- (p- tolyl)-1- azacyclooctan-5-one in CD_2Cl_2 at various temperatures.

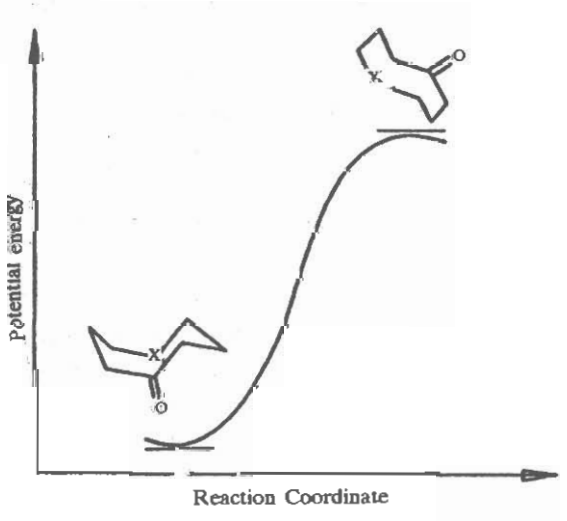


Fig. 2: The expected path for ring inversion in 8-membered ring ketones.

Table 1: Conformational barriers in 8- membered ring ketones.

Name of compound	$\Delta G^{\#}$ kcal mol^{-1} ring inversion	$\Delta G^{\#}$kcal mol^{-1} pseudorotation	Ref.
Cyclooctanone	7.6	6.3	a,b
1- Thiacyclooctan-6-one	8.16	6.7	c
1- Oxacyclooctan-6-one	9.0	7.6	d
N-p-tolyl-1-azacyclooctan-6-one	9.6		e

a: F.A.L. Anet, and M.St. Jacques, J. Amer. Chem. Soc. 88, 2585, 2586 (1966).

b: M. Ghiaci, Iran. J. Chem. & Chem. Eng., No. 10, 11, (1988).

c: F.A.L. Anet, and M. Ghiaci, J. Org. Chem, 45, 1224 (1980).

d: F.A.L. Anet and P.J. Degan, Tetrahedron Letters, 3613 (1972).

e: Present Work

Table 2: Comparison of the carbonyl stretching frequencies in 8- membered ring ketones.

Name of compound	Carbonyl stretching(cm^{-1})	Ref.
Cyclooctanone	1694	a
N-(p- tolyl)-1- azacyclooctan-5-one	1680	a
N-(m-tolyl)-1-azacyclooctan-5-one	1694	a
N-(p-anisyl)-1-azacyclooctan-5-one	1683	a
1-oxacyclooctan-5-one	1696	b
1-thiacyclooctan-5-one	1686	c

a: Present Work

b: F.A.L. Anet and P.J. Degan, Tetrahedron Letters, 3613 (1972).

c: F.A.L. Anet and M. Ghiaci, J. Org. Chem., 45, 1224 (1980).

pair on the nitrogen is more prone for transannular interaction in comparison with the lone pair on oxygen and even on the sulfur atom. Perhaps, the soft-hard criterion could also justify this statement. Ofcourse, this is in contrast to previous deduction made on the basis of infrared spectra (Table 2) that transannular interaction is stronger in 1-thiacyclooctan- 5-one than its oxygen and nitrogen analogues. One difficulty in interpreting the NMR and IR data is that the bond lengths and bond angles at C, N, O and S are significantly different. The observed changes in conformational barriers and the carbonyl vibrational frequencies therefore may reflect these differences as well as those due to changes in transannular interactions.

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