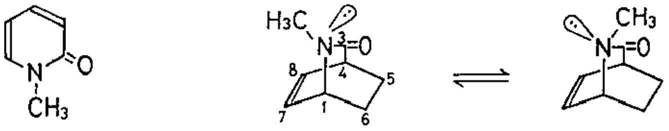
STUDY OF ORIENTATION OF THE NITROGEN LONE-PAIR ELECTRONS IN 2-METHYL-3-OXO-2-AZABICYCLO[2.2.2]OCT-7-ENE DERIVATIVES

Hiroshi Tomisawa and Hiroshi Hongo
Tohoku College of Pharmacy, Komatsushima, Sendai 983, Japan
and
Julien B. Chiasson and Christopher K. Jankowski
University of Moncton, Moncton, N. B., Canada

Abstract - The ^{13}C NMR spectra of 5 or 6-cyano- and carboxy-2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-enes have been studied in the presence of $Ni(acac)_2$. The calculated contact shifts have been compared to experimental ones. According to NMR evidence the nitrogen lone-pair electrons are preferentially anti relative to the double bond - showing some n-π nonbonded interaction. The simulation of the shift reagent experiment program, SIMULATION, written in APL, is used in this calculation.

Our previous works in this series have shown that the Diels-Alder thermal or catalytic condensation of 1-methyl-2(1H)-pyridone (1) as a diene with different dienophiles leads to 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-enes (2)[1-4] (Chart 1). This skeleton is quite interesting as a model compound for some alkaloid studies as well as for evaluation of the nitrogen lone-pair electron orientation when complexed to the shift reagent[5,6]. An especially interesting question is to evaluate syn-anti equilibration of the inverted nitrogen by studying the ^{13}C NMR spectra of



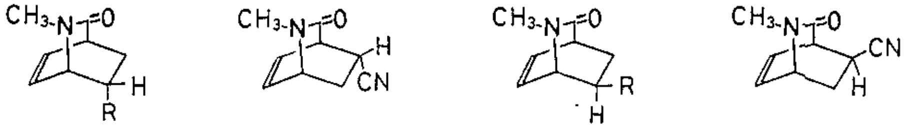
1 2:anti 2:syn

Chart 1

compounds having an electronattracting group placed in a rigorously established position on the cycle.

The carbon chemical shift δ_c as well as a direct coupling constant measurement $^1J_{CH}$ enable us to relate the hybridization character of different carbons to the syn-anti ratios and the complexation. The contact shift experiments, performed using nickel bisacetylacetonate [Ni(acac)$_2$] have been carried out and compared to the computer simulated results.

We have studied six 2-methyl-3-oxo-2-azabicyclo[2.2.2]oct-7-enes; four isomeric nitriles 3-6 and two acids 7 and 8 (Chart 2).



3: R=CN
8: R=COOH

4

5: R=CN
7: R=COOH

6

Chart 2

Result and discussion

1) ^{13}C NMR Spectra

The ^{13}C NMR spectra are presented in Table 1. The interpretation of data has been done using off-resonance technique. The spectra of four nitriles (3-6) recorded without a shift reagent show some particularities; the C-1 and C-3 signals are deshielded by 2-3 ppm where the cyano group is placed on the C-6. However the cyano group placed on the C-5 above all deshields the N-$\underline{C}H_3$ signal, but does not affect the C-4. This observation when compared to Morishima's study[5] is a strong indication of a lack of possible stabilization of nitrogen lone-pair electrons by electrophilic C-6 carbon via trans (zig-zag) path (compound 3 and 5). Thus the electron pair must be oriented preferentially in anti. At the same time there is a possibility of explaining the deshielding of the CH_3 signal by a better stabilization of the nitrogen lone pair via the electrophilic C-5 carbon in the compound 4 and 6. In this case the preferential anti orientation of the nitrogen lone pair could be accompanied by some conformational change of the skeleton, more visible during complexation. The effect of the cyano group on C-7 and C-8 signals is small and independent of its position.

The direct coupling constants $^1J_{CH}$ show that the cyano group placed on the C-5 or C-6 decrease its s-character. The cyano group placed on the endo face (compound 3 and 4) of the molecule on C-5 or C-6 decreases s-character of the double bond C_7, C_8 more than those of compounds 5 and 6 ($^1J_{CH}$ change 1.5-2 Hz).

This observation is conclusive with the homoallylic interaction discussed by Morishima[5]. Where the cyano group is placed on the exo side of the cycle (compounds 5 and 6) there is no apparent effect on any chemical shift. Two isomeric acids 7 and 8 do not show any abnormality; the carboxyl group placed on the endo side of the skeleton increases $^1J_{CH}$ of C-7 and C-8 by 3 Hz, while the corresponding cyano group increases them by 2 Hz (Table 1).

2) Nickel bisacetylacetonate [Ni(acac)$_2$] induced ^{13}C contact shifts

The complexation of the N-methyllactam group of compounds 3-6 by Ni(acac)$_2$ has been studied using 0.1-0.25 equivalents of the shift reagent. The result has then been compared to the simulation of the spectra recorded in the presence of the shift reagent. The lactam group complexation has been simulated first by assuming the shift reagent position being placed in the carbonyl axis and secondly by placing it on the lone-pair electron axis in two possible conformations, syn and anti. In the first case we have covered 22-40 nm distance between the oxygen and nickel atoms, in the other 28-38 nm distance between the nitrogen and nickel atoms. The δ_c contact shift data have been fitted and the results are presented in Table 2.

First, it has been found that the contact shift study confirms the assignment of all isomers as far as the cyano group is concerned. This assignment is particularly easy for compounds 3 and 6. The compound 6 has a CN slope almost twice as "fast" as the compound 3. Second, the important conclusion is that the nitrogen lone-pair orientation is in anti. Third, the best fit has been obtained (agreement R factor better than 95%) when there is 75% (average) of the complex via C=O at 30 nm and 25% of the complex via the N-Me lone-pair electrons at 34 nm distance between the donor and the nickel atom. Finally, there is no complexation involving the cyano group and there is no effect on the complexation when the cyano group is oriented on the exo side of the molecule (5 and 6).

In Table 2, the data show that the C-7 slope is much more negative than for the C-8. This observation is conclusive with Morishima's work[5] and our previous one[4] concerning the anticoplanar orientation of the nitrogen lone-pair electrons to this carbon. This effect is stronger for compounds 3-6 than in previously discussed series[5], assuming a higher complexation at C=O than on the N-Me group of the

Table 1

NMR data for compounds 3-8[a]

Compound C	1	3	4	5	6	7	8	CH_3	CN	COOH
3 δ_C ppm, (M)[b]	57.3(D)	172.2(S)	31.9(D)	28.6(T)	28.1(D)	134.8(D)	130.5(D)	43.6(Q)	120.2(S)	-
J_{CH}(Hz)	149.0	-	135.2	140.2	141.5	175.0	175.5	139.0	-	-
4 δ_C, ppm (M)	55.6(D)	170.1(S)	32.7(D)	24.2(D)	31.9(T)	135.1(D)	129.9(D)	46.2(Q)	120.7(S)	-
J_{CH}(Hz)	145.3	-	138.7	144.6	137.6	174.5	175.0	138.8	-	
5 δ_C, ppm (M)	58.2(D)	172.3(S)	33.2(D)	29.3(T)	27.1(D)	133.9(D)	131.6(D)	43.3(Q)	120.6(S)	-
J_{CH}(Hz)	150.0	-	133.5	138.7	148.2	173.0	173.5	139.0	-	
6 δ_C, ppm (M)	55.4(D)	169.8(S)	32.4(D)	24.5(D)	32.1(T)	134.9(D)	130.6(D)	46.6(Q)	120.4(S)	-
J_{CH}(Hz)	149.8	-	139.2	146.1	135.5	173.1	173.5	139.8	-	
7 δ_C, ppm (M)	33.0(D)	173.6(S)	44.7(D)	25.9(T)	59.2(D)	133.8(D)	133.5(D)	44.7(Q)	-	175.3(S)
J_{CH}	138.6	-	140.7	136.2	150.5	173.1	171.1	142.4		-
8 δ_C, ppm (M)	31.6(D)	173.7(S)	44.9(D)	26.7(T)	58.3(D)	133.7(D)	132.2(D)	44.8(Q)	-	178.7(S)
J_{CH}	139.2	-	141.2	138.0	151.3	176.0	174.0	143.5		-

a) See experimental for details.

b) Multiplicity: S - singlet, D - doublet, T - triplet,
Q - quartet from off-resonance ^1H.

lactam system. With the reduction of this effect we can observe the clean presence of n-π trans annular interaction in azabicyclo molecules. The shift reagent study of acids 7 and 8 is difficult to perform because of the possible hydrolysis of the reagent and presence of the third complexation group.

Table 2

Ni(acac)$_2$ induced ^{13}C contact shift data

Carbon	calculated r.i.s.[a] compound				observed r.i.s. compound			
	3	4	5	6	3	4	5	6
3	3.080	3.080	3.080	3.080	3.240	3.170	3.260	3.000
4	1.546	1.546	1.546	1.546	1.417	1.461	1.540	1.600
5	1.133	1.133	1.133	1.133	1.130	1.180	1.257	1.270
6	0.862	0.862	0.862	0.862	0.880	0.880	0.895	0.850
1	1.397	1.397	1.397	1.397	1.412	1.467	1.400	1.440
7	0.918	0.918	0.918	0.918	0.844	0.880	0.824	0.900
8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
CH_3	2.650	2.650	2.650	2.650	2.890	3.100	2.800	2.580
CN	0.433	0.524	0.382	0.747	0.438	0.550	0.410	0.768
				R[b]	4.9	5.9	5.2	3.3

a) r.i.s. : relative induced shift (see experimental for details).

b) agreement factor $R = \frac{\text{exp r.i.s.} - \text{calc r.i.s.}}{\text{exp r.i.s.}}$ %

Experimental

The compounds 3-8 have been synthesized as previously described[1]. Ni(acac)$_2$ (Aldrich Chemicals Co.) was dried in vacuo. The NMR spectra were recorded on Varian FT-80A and Bruker XF-x-10 (25.1 and 22.6 MHz respectively) with an internal lock standard. The δ_c values were measured in ppm using Me$_4$Si as a standard.

A solution of 3-6 (2.5-5%) in CDCl$_3$ has been treated with the shift reagent. The Ni(acac)$_2$ relative induced shifts for all carbons were measured from the slopes of linear plots of observed ^{13}C contact shifts plotted vs. concentration of the shift reagent expressed in millimoles (0.1 and 0.2 ratios). The "true" shift (3.2 ppm) of C-8 carbon at 0.2 millimoles of Ni(acac)$_2$ was normalized to unity. The spectra of acids 7 and 8 have been recorded in pyridine-d$_5$.

The fitting of data as well as simulation of the shift reagent spectra has been done using SIMULATION program[6]. The molecular geometry parameters have been computed using a three dimensional Mitutoyo coordinate measuring machine and Dreiding models[7]. The agreement factor for the relative induced shift R is given as the ratio of the sum of measured minus calculated values over the sum of measured values.

Acknowledgment

The authors thank the NSERC for a research grant, Miss N.L.Landry and Mr.R. Luce for technical assistance.

References

1. H.Tomisawa, H.Hongo, H.Kato, T.Naraki, and R.Fujita, Chem. Pharm. Bull., 27, 670 (1979).
2. H.Tomisawa and H.Hongo, Tetrahedron Lett., 2465 (1969), idem, Chem. Pharm. Bull., 18, 925 (1970), H.Hongo, ibid., 20, 226 (1972).
3. H.Tomisawa, R.Fujita, K.Noguchi, and H.Hongo, Chem. Pharm. Bull., 18, 941 (1970).
4. K.Jankowski, J. Org. Chem., 41, 3321 (1976).
5. I.Morishima and K.Yoshikawa, J. Am. Chem. Soc., 97, 2950 (1975).
6. Program written in APL, copy available on request from the authors.
7. K.Jankowski, Chem. in Canada, 31(5), 15 (1979).

Received, 19th December, 1981