DIPOLE MOMENTS AND MOLECULAR CONFORMATIONS OF ACETYLPYRIMIDINES

M. A. Mikhaleva, I. V. Beregovaya,
and V. P. Mamaev

By comparing experimentally determined dipole moments with those derived from vector-addition and semi-empirical computation using MNDO and AM 1 approximations the conformations of 4- and 5-acetylpyrimidines were found to be close to planar, while that of 2-acetylpyrimidine exhibited a torsion angle of ~90°.

The influence of the ring nitrogen atom on the properties of the substituents (aza effect) is of fundamental significance in the chemistry of heterocyclic compounds. In the course of research on the equilibrium CH acidity of the acetyl azines the additive effect on this parameter of the two ortho-positioned pyrimidine ring nitrogen atoms was seen to be disturbed in the case of 2-acetylpyrimidine [1]. A comparative study of the reactivity of the isomeric acetylpyrimidines (unlike the methylpyrimidines [2]) has not been reported in the literature, and additional information on the effect of the ring nitrogen in methylpyrimidylketones can be obtained, for example, by investigating their molecular conformations. There are numerous works on the conformational structure of aromatic methyl ketones (e.g., [3-6]), but as regards the acetyl azines data has only been acquired for the acetylpyridines [7-10]. From an examination of dipole moments (DM) and Kerr molecular constants for all isomers the conclusion was drawn that the acetyl group was inclined at an angle of about 25° to the plane of the pyridine ring and it was noted that inaccuracies resulted from calculating the stability of conformers using the CNDO/2 method [7].

In the present work we have approached the conformational structure of acetylpyrimidines by comparing experimentally determined and calculated values of DM for various conformers of the isomeric methylpyrimidinylketones.

When analyzing DM values for molecules capable of possessing internal rotation by means of the vector-addition scheme, it is essential, first and foremost, to contrast them with values calculated assuming free rotation [11]. On this basis DM for 2-acetylpyrimidine was calculated by assuming free rotation of the acetyl group from the equation

$$\mu^2 = \mu_1^2 + \mu_2^2 + 2\mu_1\mu_2 \cdot \cos\varphi \cdot \cos\omega,$$

where φ is the angle between dipole moment vectors and ω is the angle between rotational axes [11, p. 88] which for 2-acetylpyrimidine are 48° and 0° respectively. In this case DM for 2-acetylpyrimidine proved to be ~1 D greater than the experimental value. This disparity may be due to the fact that the group moments used were not appropriate for the pyrimidine heterocyclic system, or it might suggest that there is a retardation of acetyl group rotation. In view of the fact that aromatic ring group moments have been successfully applied in calculating DM for azine derivatives [11-13] and that the mesomeric moment of the $COCH_3$ group in 4-acetylpyridine is quite small (0.21 D compared with 0.46 D in the benzene series [11], we concluded that there was retardation of acetyl group rotation in 2-acetylpyrimidine. This appears to follow logically from the interaction between the unshared pair of the carbonyl group and the two ring nitrogen ortho atoms and, as a result, it causes the acetyl group to be deflected from the plane of the pyrimidine ring. This deflection was corroborated by the fact that the experimental DM value could only be obtained using in the same equation the deflection angle of the planes of rotation rather than the axes. By employing in the computation a torsion angle of 90°, which eliminated a cross member from the equation, good agreement was obtained when comparing the experimental and calculated values of DM for 2-acetylpyrimidine. The

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TABLE 1. Dipole Moments of Acetylpyrimidines

Acetylpyrimidine	DMexp., D	Torsion Angle $C_{pyr.}$-CO.°			ΔHf^o, kcal/mole		Calculated DM, D		
		vect. addn.	MNDO	AM 1	MNDO	AM 1	vect. addn.	MNDO	AM 1
2-	3,73	free rot.	0	0	-1,28	13,04	4,75	3,92	4,04
		90	90	88*	-5,07	10,74	3,70	3,93	4,02
4-	0,86	0	0	0	1,50	12,56	4,22	3,70	4,00
			(cis-)						
		90	85*	75*	-3,46	10,00	3,70	2,74	2,70
		155	—	—	—	—	1,42	—	—
		—	—	174*	—	9,29	—	—	0,71
		180	180	180	-0,92	9,31	0,88	0,65	0,66
			(trans-)						
5-	2,44	free rot.	0*	0*	-0,50	6,74	2,21	2,03	2,32
		25	—	25	—	7,04	2,39	—	2,34
		—	90*	88*	-3,02	8,93	—	2,22	2,50
4,6-Dimethyl-2-	—	free. rot	—	0	—	-0,40	5,08	—	4,45
		90	—	90	—	-2,82	3,94	—	4,42

*Varied with geometry optimization.

significant reduction in conjugation between the substituent and the ring that results "shuts out" the aza effect. This is graphically illustrated in the almost identical CH acidity of the 2- and 5-acetylpyrimidines, and indeed explains the closeness of these values.

As was to be expected, in the case of 5-acetylpyrimidine DM calculation by means of the vector-addition scheme (assuming free rotation) was in good agreement with experiment.

In terms of its conformational structure 4-acetylpyrimidine should probably be similar to 2-acetylpyridine or 3-acetylpyridazine [12], i.e., it should have a planar or almost planar transconformation. It must be stressed that it differs significantly from the 2- and 5-isomers. In these, by virtue of C_{2v} type symmetry of the pyrimidine ring, rotation of the substituent about the axis of symmetry did not alter the molecular dipole moment, as the relative alignment of the polar group vectors in different conformations (disregarding induction) remains constant. In 4-acetylpyrimidine rotation of the acetyl group about the $C_4-C{=}O$ bond resulted in continuous change in the DM due to the changing angle between the pyrimidine DM vector and the group moment vector. As Table 1 indicates, calculation of DM for various rotating models of 4-acetylpyrimidine using the vector-addition scheme gave good agreement with experiment for the planar trans-conformation.

We also made calculations for the acetylpyrimidines using quantum-chemical methods, since they have the advantage of enabling effects that do not fall within the scope of the additive scheme to be taken into account. An assessment of the suitability of semiempirical methods of calculating parameters (including DM) for a specific class of compound is of itself important and cannot be undertaken a priori [14]. Therefore, quantum-chemical calculations for the compounds were carried out using MNDO approximation and the improved AM 1 version, which enabled parameters for molecules containing oxygen and nitrogen atoms (including azines) to be calculated with enhanced accuracy [15].

Since all the calculated data presented in Table 1 clearly confirm the fact that DM in the 2- and 5-isomers is independent of the deflection angle of the substituent, as explained above, the most energetically favorable conformation of these isomers can be determined by comparing the ΔH_f0 (heat of formation) values. In assessing the suitability of the methods used we should mention that the heat of formation calculated using the MNDO method pointed towards conformers with a torsion angle of about 90° for all the compounds. However, in the case of the 4-isomer this was at variance with the experimentally determined DM value, and in evaluating the stability of the 5-acetylpyrimidine conformations the methods contradicted each other. It follows from these divergences that the MNDO method probably overestimates the stability of the perpendicular conformations (similar to the CNDO/2 method in acetylpyridines [7]) and the results obtained in AM 1 approximation (cf. [15]) are more reliable.

In acetylpyrimidine and its 4,6-dimethyl derivative it was found from heats of formation using the AM 1 method that the conformation with a large torsion angle (88-90°) was energetically most favorable. Data for 4-acetylpyrimidine suggested that it exists in the trans conformation with the acetyl group making an angle of 6° with the plane of the ring. A planar structure is in accord with the surface potential energy minimum of 5-acetylpyrimidine, but the closeness of the heat of formation values means that a conformer with a torsion angle in the order of 0-25° cannot be ruled out.

To sum up, an assessment was made of preferred conformations in the acetylpyrimidines. It was shown that stereoelectronic interaction in the 2-acetylpyrimidines influenced the conformation in the same way as the steric effect in the 2,6-disubstituted acetophenones [11, p. 179] and that 4-acetylpyrimidine has a more planar conformation than 4-acetylpyridine [7, 10].

EXPERIMENTAL

Experimental dipole moments were determined by means of the Guggenheim–Schmitt method. Dielectric constants of acetylpyrimidine solutions in benzene were found using the heterodyne oscillatory circuit method on a Tangens dielectric meter at 25°, refractive indices were measured on an Abbe refractometer. Theoretical DM were calculated by means of the vector-addition scheme using group DM cited in [11]. Quantum-mechanical computations were performed using the AMPAC program (EC version) [17] with geometry optimization.

Acetylpyrimidines were obtained using the known methods and their constants were in line with values quoted in the literature [18].

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