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HINDERED INTERNAL ROTATION ABOUT A C–N BOND IN SOME TRISUBSTITUTED 1,3,5-TRIAZINES

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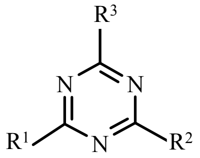
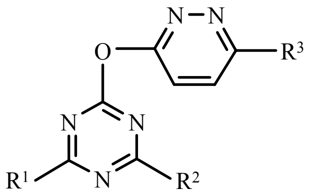
We have studied the temperature dependence of the ^1H NMR spectra of some 2,4,6-trisubstituted 1,3,5-triazines having an NHAlk or $NAlk_2$ group or groups at the position 2 or 2 and 4 of the heterocycle. We have shown that rotation of these groups about the C–N bond is hindered. We have calculated the free energies of activation for the rotation processes.

Keywords: 2,4,6-trisubstituted 1,3,5-triazines, hindered internal rotation, isomers, free energy of activation.

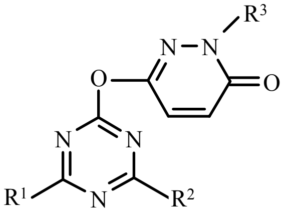
In the ^{1}H NMR spectra of triazine derivatives containing NHAlk or $NAlk_2$ substituents at the positions 2 and 4 of the heterocycle, we observed two or more sets of signals from protons of the N-alkyl and NH groups which may be connected with the presence in the solutions of different isomeric forms of the indicated compounds [1]. In order to study this question, we recorded the ^{1}H NMR spectra of trisubstituted triazines **1-3** in the temperature range 20-90°C.



1a–i



2a–h



3a–e

1 a $R^1 = R^2 = NMe_2$, $R^3 = Cl$; **b** $R^1 = NMe_2$, $R^2 = OMe$, $R^3 = Cl$; **c** $R^1 = NHMe$, $R^2 = OMe$, $R^3 = Cl$; **d** $R^1 = R^2 = NHEt$, $R^3 = CN$; **e** $R^1 = R^2 = NHCHMe_2$, $R^3 = CN$; **f** $R^1 = NHEt$, $R^2 = NHCMe_3$, $R^3 = Cl$; **g** $R^1 = NMe_2$, $R^2 = OMe$, $R^3 = OC_6H_4COOEt$-*p*; **h** $R^1 = NHEt$, $R^2 = SMe$, $R^3 = OC_6H_4COOEt$-*p*; **i** $R^1 = R^2 = NHCHMe_2$, $R^3 = OC_6H_4COOMe$-*p*;
2 a $R^1 = R^2 = NMe_2$, $R^3 = OH$; **b** $R^1 = NMe_2$, $R^2 = OMe$, $R^3 = OH$; **c** $R^1 = NHEt$, $R^2 = OMe$, $R^3 = OH$; **d** $R^1 = NHEt$, $R^2 = OMe$, $R^3 = OCHMe_2$; **e** $R^1 = R^2 = NHEt$, $R^3 = OH$; **f** $R^1 = R^2 = NHEt$, $R^3 = OEt$; **g** $R^1 = R^2 = NHCHMe_2$, $R^3 = OH$; **h** $R^1 = R^2 = NHCHMe_2$, $R^3 = OMe$;
3 a $R^1 = R^2 = NMe_2$; **b** $R^1 = NMe_2$, $R^2 = OMe$; **c** $R^1 = NHEt$, $R^2 = OMe$; **d** $R^1 = R^2 = NHEt$; **e** $R^1 = R^2 = NHCHMe_2$; **a-e** $R^3 = Me$

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In the spectrum of compound **1a** taken at 20°C, in the 3.0-3.2 ppm region there are two singlet signals of equal intensity ($\Delta\nu = 6.3$ Hz) from the NMe_2 groups (R^1 and R^2). When we raised the temperature at which we recorded the spectra, they coalesced into one signal (coalescence temperature 40°C), narrowing upon further increase in temperature. We see a similar pattern in the case of a substituent R^3 that is bulkier than Cl in compounds **2a** and **3a**.

For the triazines under consideration, obviously states are stable in which the free electron pair of the exocyclic nitrogen atom is conjugated with the π-electron system of the triazine. The magnetic nonequivalence of the N-methyl groups in the spectra of compounds **2a** and **3a** is more pronounced in this case ($\Delta\nu = 30\text{-}32$ Hz), due to the anisotropic effect of the pyridazine ring for the R^3 substituent.

The observed change in the shape of the signals as a function of temperature is typical for a dynamic exchange process and may be explained by hindered rotation about a C–N bond, the order of which is increased as a result of interaction of the unshared electron pair of the exocyclic nitrogen atom with the π-electrons of the triazine system, and rotation of the NMe_2 groups can occur according to a "gear" mechanism [2].

Based on the indicated temperature dependence of the ^1H NMR spectra, we determined the activation parameters for rotation for some compounds. We calculated the free energy of activation (ΔG^*) from the Eyring equation, and we determined the exchange rate constant from the coalescence temperature and the difference between the chemical shifts of the signals in the low-temperature spectra [3] (Table 1).

The fact that the values of the energy barriers match for compounds **1a** and **2a** suggests that in the latter, the 6-OR substituent deviates from the plane of the triazine ring as a result of rotation about the C–O bond and has practically no effect on the size of the activation barrier.

Replacing one of the NMe_2 groups by an OMe group (**1b,g, 2b, 3b**) does not change the overall pattern for the temperature dependence of the signals from the N-methyl groups. The OMe group appears as a singlet over the entire temperature range, which is explained by its "fast" rotation.

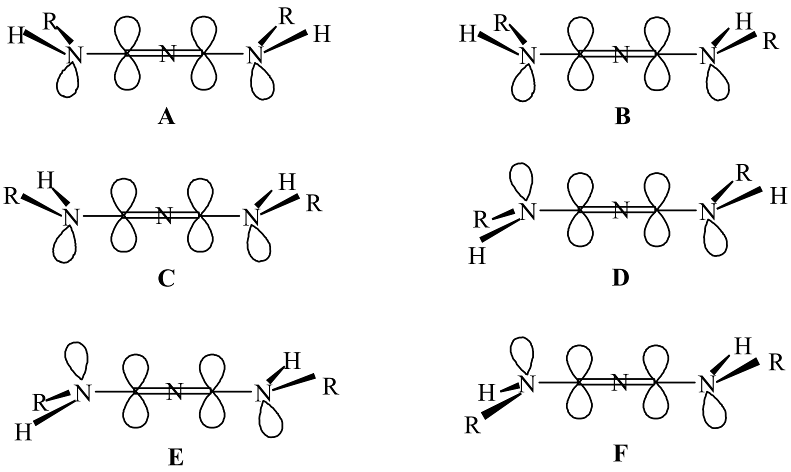
The situation is different for monoalkylamino-substituted **1c,h, 2c,d, 3c** (R^1 = NHAlk). At 20°C, in the spectra of these compounds there are two sets of signals for all the protons of the molecule (the ratio of the intensities is 45:55), which upon heating broaden and coalesce. Such a pattern can be explained by the fact that the rotational isomers of the molecules of these compounds are asymmetric, and consequently the protons corresponding to the two rotamers are seen as individual signals. The energy barriers to rotation in molecules of compounds **1c,h** are much higher than the corresponding values for triazines **1a** and **2a**, which may be due to stabilization of the rotamers as a result of hydrogen bond formation between the proton of the NH group and the solvent molecules.

In the molecules of compounds **1d,e,i, 2e-h, 3d,e** with $R^1 = R^2$ = NHAlk, the pyramidal configuration of the exocyclic nitrogen atoms is less flattened than in the dialkylamino-substituted derivatives, so six possible states (**A-F**) may be realized for them, in which the hydrogen atom and the alkyl group are located above or below the plane of the triazine ring.

Realization of structures **C** and **F** is not likely due to the fact that the N-alkyl groups are closer to each other. The structure of molecular models for the remaining four forms shows that steric hindrances increase in the order **D** < **A** ~ **E** < **B** (Scheme 1).

In fact, in the ^1H NMR spectra of the indicated 2,4-bis-NHAlk-substituted derivatives that were recorded at 20°C, in the 7.0-9.0 ppm region there are four signals from the protons of the NH groups, the ratio of the integrated intensities of which in the case Alk = Et is 46:23:22:9, and when Alk = Pr-*i* we have 40:25:25:10. The signals from the protons of the NCH_2 or NCH groups have the shape of two multiplets in the 3.5-4.2 ppm region (the ratio of the integrated intensities is 55:45 and 65:35 respectively), each of which in turn is the superposition of two multiplets (quintet and octet respectively, $J_{NH\text{–}CH} = J_{CH\text{–}CH} = 5.8$ Hz). Under double resonance conditions, the triplet or doublet signals for the protons of the NH groups are converted to singlets and we also observe splitting of the signals for all the protons of the substituent at the position 6 of the triazine ring. As the temperature is raised, each of the indicated signals broadens and coalesces into a singlet, which suggests that the observed spectral features are due to the same process.

Scheme 1



Obviously the most stable isomer is the **D** isomer, the contents of forms **A** and **E** are approximately the same, while state **B** is the least favorable. With an increase in the steric bulk of one of the substituents (**1f**, R^2 = NHCMe$_3$), in the spectra there are signals for only two isomers (80:20). The activation parameters for rotation in molecules of compounds **2f** and **3e** were calculated for two processes, taking into account the unequal populations [4], and proved to be close to the corresponding values for compounds **1a** and **2a**. The values for the free energies of activation ΔG^*, kJ/mol, were: 68.97 (**1a**); 68.55 (**2a**); >76.5 (**2b**); >76.5 (**1g**); 76.5 (avg) (**1c** and **1h**); 70.22, 68.55 (**3e**); 69.39, 67.72 (**2f**). Consequently, even in this case rotation of the monoalkylamino group is possible according to a "gear" mechanism.

We note that exchange between two different isomers can occur not only according to a rotational mechanism but also according to an inversion mechanism [5]. However, in the latter case, an increase in steric hindrances should have led to a decrease in the energy parameters for isomerization [6], which does not correspond to the observed characteristic behavior.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Mercury Varian spectrometer (300 MHz) for DMSO-d$_6$ solutions in the temperature range 20-90°C, internal standard TMS. In this work, we use the previously synthesized triazine derivatives [1, 7].

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