NMR studies of the dynamic behavior of 2-anilino-6-chloro-4-methoxy-1,3,5-triazine in solution

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2-Anilino-6-chloro-4-methoxy-1,3,5-triazine was synthesized and studied by dynamic NMR. The activation parameters of hindered internal rotation in unsymmetrically substituted arylamino-*sym*-triazine were determined for the first time. It was found that a sterically more hindered rotational isomer is thermodynamically more stable in this compound (slow-exchange NOE data).

Key words: 2-anilino-6-chloro-4-methoxy-1,3,5-triazine, hindered internal rotation, activation parameters, dynamic NMR spectroscopy.

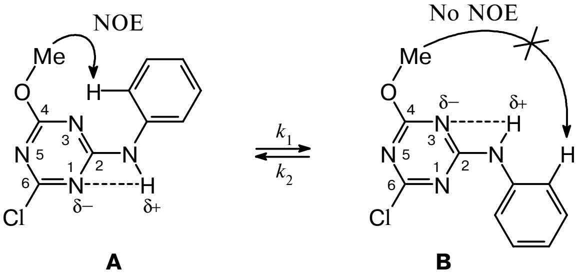
It is known that rotation about the C—N bond in aminotriazines is hindered because the order of this bond is higher than unity.[1] This phenomenon for *sym*-triazines was described only in a few papers,[1—5] but the thermodynamic characteristics of unsymmetrically substituted triazines are lacking. While measuring[2—4] the energy parameters of hindered internal rotation from the coalescence temperature of exchanging signals, one cannot determine $\Delta H^\#$ and $\Delta S^\#$.

A study of intramolecular rotation is of considerable interest since this phenomenon largely influences several essential properties of molecules and substances (thermodynamic, electrical, and optical), their reactivities (including biological activity), reaction mechanisms, *etc.*[6] However, experimental data on the barriers are scarce, while calculations usually provide rough estimates.[4] The goal of this study was to collect and analyze such data.

Results and Discussion

In the present work, the synthesis of 2-anilino-6-chloro-4-methoxy-1,3,5-triazine (**1**) containing three different substituents in the ring is described. Unlike aminotriazines with two identical substituents in the heterocycle,[1—5] the ratio between rotational isomers for compound **1** differed from 1 : 1 ($k_1 \neq k_2$) (Scheme 1). A simplified estimation[7] (from the coalescence temperature) of a barrier to hindered internal rotation is not correct as, strictly speaking, the coalescence temperature in such processes cannot be determined.[8] We performed complete analysis of the line shape in the dynamic NMR spectra. The analysis is based on the Bloch equation and was modified for the case of chemical exchange.[9] According to this method, spectra are recorded at different temperatures, which makes the operation longer, but allows one to determine activation parameters for a temperature range rather than a free activation energy in a single temperature point. The results thus obtained are more reliable, and the energy characteristics of different compounds can be compared under standard conditions.

Scheme 1



The activation parameters of hindered internal rotation in triazine **1** were found to be $\Delta H^\# = 57.4\pm1.9$ kJ mol^{-1}, $\Delta S^\# = -27.3\pm6.5$ J mol^{-1} K^{-1}, and $\Delta G^\#_{298} = 65.6\pm2.0$ kJ mol^{-1}.

The nuclear Overhauser effects[10] (NOE) obtained for slow exchange show that the sterically more hindered conformer **A** is dominant in solution (see Scheme 1).

In compound **1**, the steric factors insignificantly influence the relative stabilities of rotational isomers, as distinct from other known examples[11] of hindered inter-

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nal rotation about the C—N bond, while a higher stability of conformer **A** is due to electronic factors. Most probably, this is associated with an effective electrostatic interaction of the positively charged H atom of the amino group with the N(1) atom of the triazine ring (see Scheme 1), which bears more negative charge than N(3) owing to a stronger electron-acceptor effect of the Cl atom. The causes of this phenomenon will be elucidated in further investigations involving other triazines.

Experimental

^{1}H and ^{13}C-{^{1}H} NMR spectra were recorded on Bruker AC-200 (200.13 and 50.43 MHz, respectively) and Bruker AM-300 (300.13 and 75.43 MHz, respectively) spectrometers in a mixture of CD_2Cl_2, $CDCl_3$, and CCl_4 (60 : 27 : 13). Nuclear Overhauser effects were measured at −23 °C.

The NMR data were processed using a standard Bruker software (DISNMR on ASPECT-3000 with the Adakos OS). Spectra were transcoded into different data formats with the CODER7 program.[12] The ^{13}C-{^{1}H} signals from the methoxy groups were used to perform a complete analysis of the line shape with consideration of a temperature dependence of the resonance frequencies of exchanging signals. The temperature in the spectrometer was calibrated with reference to an external standard.[13] Seven spectra recorded in a temperature range from −4 to 31 °C were used for calculations. Two sets of narrow signals from both conformers in the spectrum at −23 °C indicated that the conditions of slow exchange were reached. At 54 °C, the spectrum contained an averaged set of narrow signals from both conformers, which is characteristic of rapid exchange. The resonance frequencies of exchanging signals were iterated with the DYNNMR program.[1] Relaxation times were measured at each temperature point.

Melting points were determined on a Boetius hot stage (the heating rate at the melting point was 4 °C min^{-1}). Mass spectrum was recorded on a Varian CH-6 instrument (direct inlet of a sample into the ion source, ionizing voltage 70 eV, accelerating voltage 1.75 kV, emission current 100 mA). The molecular ion peak in the mass spectrum of compound **1** relates to the ^{35}Cl isotope.

2-Anilino-6-chloro-4-methoxy-1,3,5-triazine (1). Coarsely ground (grain size 1—2 mm) LiH (190 mg, 23.75 mmol) was added with stirring at 0 °C to a solution of 2-anilino-4,6-dichloro-1,3,5-triazine[14] (5 g, 20.75 mmol) in 50 mL of MeOH. The reaction mixture was stirred at 0 °C for 2.5 h (a precipitate of a product is occasionally formed in the course of the reaction) and then allowed to warm for ~14 h. The resulting mixture was diluted with water, and the precipitate that formed was filtered off and dried to a constant weight. The yield of compound **1** was 4.70 g (96%), m.p. 140—141 °C (MeOH). Found (%): C, 50.78; H, 3.88; Cl, 14.52; N, 24.12. $C_{10}H_9ClN_4O$. Calculated (%): C, 50.75; H, 3.83; Cl, 14.98; N, 23.67. MS, m/z (I_{rel} (%)): 236 $[M]^+$ (86), 235 $[M - H]^+$ (100), 201 $[M - Cl]^+$ (18), 159 $[M - Ph]^+$ (10), 159 $[M - PhNH]^+$ (23), 118 $[PhNHCN]^+$ (42), 91 $[PhN]^+$ (25), 77 $[Ph]^+$ (60). ^{1}H NMR, δ: 4.02 (br.s, 3 H, OMe); 7.16 (m, 1 H, *p*-Ph); 7.37 (m, 2 H, *m*-Ph); 7.56 (br.m, 3 H, *o*-Ph and NH). ^{13}C-{^{1}H} NMR, δ: 56.2 (br.s, 1 C, OMe); 122.1 (br.s, 2 C, *o*-Ph); 125.4 (br.s, 1 C, *p*-Ph); 129.5 (s, 2 C, *m*-Ph); 137.5 (s, 1 C, *i*-Ph); 166.0 (s, 1 C, C(6) triazine); 171.1, 172.0 (both br.s, 2 C, C(2), C(4) triazine).

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