Tetrahedron Letters, Vol. 33, No. 26, pp. 3805-3808, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Conformational Selectivity in the Formation of H-bonded Assemblies between Di- and Triamino Triazines and Bemegride

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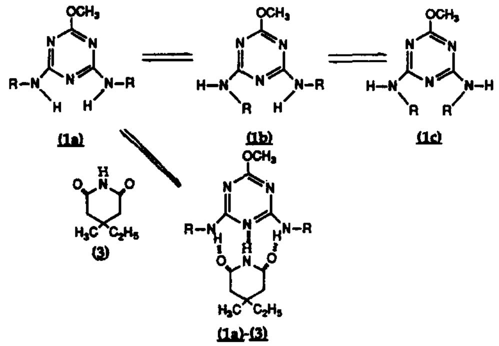
Abstract
2,6-Bis(aminocyclohexyl)-4-methoxy triazine (1) and 2,4,6-tris(aminocyclohexyl) triazine (2), act as molecular hosts for bemegride (3) by complementary H-bonded interactions. ^{1}H-NMR and ^{13}C-NMR spectra reveal that association of (3) proceeds through discrimination of selected conformations of the host molecules. The association constants of (3) to (1) and (2) are $K=449\ M^{-1}$ and $K=915\ M^{-1}$, respectively.

Conformational selectivity plays an important role in the association of compounds to biomaterials[1]. Extensive research activities are directed towards the design of supramolecular host-guest assemblies originating from complementary H-bonded intermolecular interactions[2,3]. Hamilton and coworkers have recently highlighted the selective association of a single conformation of a guest by a host molecule[4]. Several recent studies have applied aminotriazines and diazines as building sites for multi-dimensional H-bonded networks[5,6]. Interestingly, the formation of H-bonded assemblies between diaminotriazine and a complementary guest molecule has recently been demonstrated at a water-air interface[7]. Here we report on the conformational discrimination of specific conformers of 2,6-bis-(aminocyclohexyl)-4-methoxy triazine, (1) and 2,4,6-tris(aminocyclohexyl) triazine, (2), along with the formation of H-bonded complexes with bemegride, (3).

At room temperature (T=295 K), 2,6-bis(aminocyclohexyl)-4-methoxy triazine (1), is present in three conformations, (1a-c), eq. 1. The ^{1}H and ^{13}C NMRspectra of a dry $CDCl_3$ solution of (1) reveal that rapid exchange between the conformers occurs at this temperature. This is evident by the appearance of a broad singlet at $\delta=5.03$ ppm for all NH protons and two single ^{13}C bands at $\delta=166.24$ and 171.63 ppm for the aromatic carbons and CH_3O-aromatic carbon, respectively. The methoxy carbon appears as a single band at $\delta=52.38$ ppm. Cooling of the sample to T=270 K results in slow exchange between conformers (1a)-(1c), as evident from the ^{1}H and ^{13}C NMR spectra: The amine protons appear as four doublets at $\delta=5.13$, 5.15, 5.24 and 5.32 ppm. The OCH_3 carbons appear as three distinct bands at $\delta=53.50$, 53.68 and 53.81 ppm. The aromatic carbon atoms are resolved into 7 bands: three bands for carbon atoms adjacent to the methoxy group at $\delta=170.47$, 170.77 and 171.18 ppm and four bands corresponding to the other carbon atoms at $\delta=165.58$, 165.89, 166.05 and 166.40 ppm. The activation barrier for interconversion between conformers (**1a**)-(**1c**) is $\Delta G^{\#}=14.5\pm0.2$ kcal·mole^{-1}.

equation 1



Addition of bemegride, (**3**) to a dry $CDCl_3$ solution of (**1**) (at T=298 K) results in the spectral changes displayed in Figure 1. The amine protons of (**1**) appearing as a broad shouldered band at $\delta=4.85$-5.03 ppm are split into three bands upon addition of (**3**). One band is shifted downfield and depends on the concentration of (**3**). The other two bands appear at constant chemical shifts, at $\delta=5.11$ and 4.94 ppm. Furthermore, as the concentration of (**3**) is increased, the two non-shifted amino bands decrease in their intensities. At high concentration of (**3**) these two bands almost disappear and the chemical shift of the downfield shifted amine protons reaches a constant value, $\delta=6.95$ ppm. Thus, the amino groups of (**1**) are divided into three groups: The chemical shifts of two amine groups are unaffected by addition of (**3**), while their population is strongly influenced by added (**3**). The signal corresponding to the third group of amine protons is downfield shifted upon addition of (**3**) and its population increases relative to the former two groups upon addition of (**3**). The amino group being downfield shifted is attributed to conformation (**1a**), and thus, addition of (**3**) to (**1**) results in selective association to conformer (**1a**)[8]. The rapid exchange associated with the complex formation, (**1a**)+(**3**) $\rightleftharpoons$ (**1a**)-(**3**), eq. 1, results in an averaged downfield shift of the amino protons of conformation (**1a**) as the concentration of (**3**) increases. The other two conformations (**1b**) and (**1c**) do not participate in the complexation process. Yet, upon increasing the content of (**3**), the equilibrium is shifted, (eq. 1), towards the H-bonded ligating conformation, (**1a**). From the chemical shift dependence of (**1a**) amino protons on (**3**) concentration, the calculated association constant[9] for the H-bonded (**1a**)-(**3**) assembly is $K=449$ M^{-1}. This value is in good agreement with structurally related complexes[3c].

Similar conformational selectivity is observed in the association of (**3**) to 2,4,6-tris(aminocyclohexyl) triazine, (**2**). The host molecule (**2**) is present in two

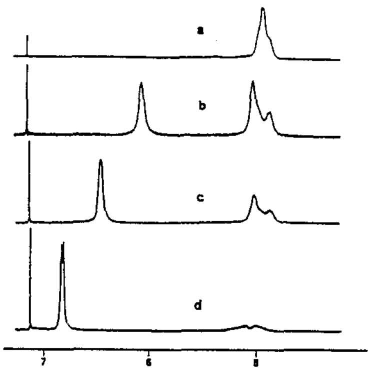
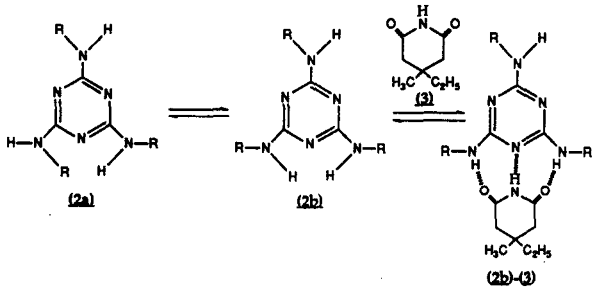
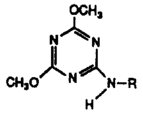


Figure 1: 400 MHz ^{1}H NMR spectra of 0.082M of (1) in the presence of (3). Concentration of (3) is: a) 0 M; b) 0.024 M; c) 0.049 M; d) 0.17 M.

conformations, eq. 2, as evident by 0.074M ^{1}H and ^{13}C-NMR spectroscopy. Addition of (3) to a $CDCl_3$ solution of (2), results in N-H groups that are downfield shifted upon increasing the content of (3), 0.220M, while other N-H groups are not shifted and appear at δ=4.86 ppm. The integration ratio between the downfield shifted N-H protons and the non-shifted N-H protons increases upon addition of (3) and approaches a constant value of 2:1 respectively, at high content of (3). These results clearly indicate that association of (3) proceeds by conformational discrimination of the host structure (2), by complexation with the conformation (2b), eq. 2. Complexation of (3) is driven by complementary H-bond interactions between conformation (2b) and (3)[10]. At low concentrations of (3), 0.024M, the non-associated N-H groups of (2a) and (2b) are non-shifted in the ^{1}H-NMR spectrum. At high content of (3), 0.220M, the equilibrium (2a) $\rightleftharpoons$ (2b) is shifted towards the complex structure (2b)-(3). In this structure, the ratio of H-bonded NH-protons and free NH-protons correspond to 2:1 respectively[11,12]. The calculated association constant for the H-bonded complex (2b)-(3) is K=915 M^{-1}. It should be noted that with 2-aminocyclohexyl-4,6-dimethoxytriazine, (4), exhibits very weak association to (3), K=16 M^{-1}. This

equation 2





(4)

weak association constant might be attributed to the presence of only two anchoring H-bonding sites in (4), while (1) and (2) include three H-bonding sites. Alternatively, the weak association constant might reflect to electrostatic repulsion between the non-associated carboxyl function of (3) with the methoxy substituent of (4). These electrostatic repulsions oppose the stabilizing two-point H-bonded interactions.

We thus conclude that the association of bemegride (3) to diamino- and triamino-triazines proceeds via conformational discrimination of the host structure.

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8. The ^{13}C NMR spectrum of the H-bonded complex at high concentrations of (3) shows two singlets for aromatic carbons at $\delta = 165.87$ and 170.80 ppm, implying a C_2-symmetry of the complex. This excludes (1b) as active conformation in the H-bonded assembly. Molecular mechanics calculations show that the N-H distances in conformation (1c) are not appropriate for a bidentate H-bonded structure. Detailed molecular mechanics calculations of (1a)-(1c) will be described later.
9. Association constants were calculated using the Benesi-Hildebrand equation. Cf. Joesten, M.D.; Schaad, L.J., Hydrogen Bonding; Marcel Dekker, Inc. New York, 1974, pp. 173-175.
10. It should be noted that although ligand (2) shows rapid conformational exchange at T=290 K, the process is under slow conformational exchange at T=290 K upon addition of (3). This originates from decrease in the molar fractions of the free conformations as a result of the complexation process. In accordance with this explanation, the coalescence temperature of the different conformations depends on (3) content (for example T_c = 325 K and 315 K at ratios corresponding to 1:1 and 2:1, respectively).
11. The formation of the H-bonded intermolecular structure (2b)-(3) is supported by the ^{13}C NMR complex that shows three bands for triazine aromatic carbons at $\delta = 164.5$, 164.67 and 164.83 ppm and two bands for the α-aminocyclohexyl carbon atoms at $\delta = 48.64$ and 49.47 ppm. Molecular mechanics calculations further support that conformation (2b) exhibits proper structural properties for association to (3).
12. Consistent with this interpretation, we find that the energy barrier for exchange between conformations (2a) and (2b) and between associated and free NH groups in complex (2b)-(3) depends on the relative population of the conformer and complex. At low content of (3) the energy barrier for exchange is lower ($\Delta G^{\neq} = 14.77$ kcal·mole^{-1}) than at high bemegride concentration ($\Delta G^{\neq} = 15.03$ kcal·mole^{-1}).

(Received in UK 24 February 1992)