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# Non-Covalent Interactions in Molecular Systems: Thermodynamic Evaluation of the Hydrogen-Bond Strength in Amino-Ethers and Amino-Alcohols

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**Abstract:** The intramolecular hydrogen bond (intra-HB) is one of the best-known examples of non-covalent interactions in molecules. Among the different types of intramolecular hydrogen bonding, the NH...O hydrogen bond in amino-alcohols and amino-ethers is one of the weakest. In contrast to the strong OH...N intramolecular hydrogen bond, the strength of the NH...O bond can hardly be measured with conventional spectroscopic methods, even for simple amino-alcohols, since the band belonging to the NH...O conformer merges with the free OH band. In this work, we developed a combination of G4 calculations, and a method based on experimental vaporization enthalpies to determine the NH...O

hydrogen bonding strength. The archetypal compounds for this study are 2-amino-1-ethanol and 3-amino-1-propanol as well as their respective methoxy analogs. Based on these molecules, different series were studied to investigate various factors influencing NH...O intra-HB strength. In the first series, the influence of alkylation near the hydroxy or methoxy group and the amino group in sterically hindered amino-alcohols was examined. In the second series, the influence of alkylation of the amino-group was investigated. In the third series, the effect of extending the alkyl chain between functional groups was studied.

## Introduction

A prime example of the intra-molecular hydrogen bonding in molecular systems are aminoalcohols. It is well known that there are three stable conformers of amino alcohols in the gas phase and in the dilute inert solvents (see Figure 1). The predominant conformer is the one with the relatively strong intra-molecular OH...N hydrogen bond. The second conformer with the intra-molecular NH...O hydrogen bond is significantly less present and the third conformer without the hydrogen bond is practically absent from the equilibrium mixture.<sup>[1]</sup>

The strength of the *intra*-molecular hydrogen bonding (*intra*-HB) is usually derived from temperature dependent IR spectra in dilute solutions,<sup>[2]</sup> using the "tailoring approach",<sup>[3]</sup> or by using quantum chemical calculations where the strength is

defined as the energetic difference between the H-bonded species and the conformer without HB.<sup>[4]</sup>

To our surprise, the focus of the experimental and theoretical studies of the *intra*-HB in aminoalcohols is OH...N intra-molecular hydrogen bond. The main reason for this is that this bond is relatively stronger than the intramolecular NH...O hydrogen bond. The theoretical results quantify, for example, the OH...N *intra*-HB strength at the level of  $-(11 \text{ to } 15) \text{ kJ mol}^{-1}$ .<sup>[4-6]</sup> The strength of the NH...O *intra*-HB is significantly lower at the level of  $-3 \text{ kJ mol}^{-1}$ .<sup>[5]</sup> Another reason is that the spectroscopic determination of strength suffers from technical complications. The *intra*-HB is derived from the temperature dependence of peak absorbance "ratios" (bonded/non-bonded conformer). This requires a sufficiently high proportion of NH...O conformers and non-bonded conformers in the mixture. However, in a recent paper on 3-amino-1-propanol, it was shown experimentally by infrared spectroscopy and nuclear magnetic resonance spectroscopy that the proportion of OH...N conformers in the gas phase and in non-basic solvents largely exceeds the other conformers.<sup>[7]</sup>

Due to very low concentrations of the NH...O conformer and the non-bonded conformer in the equilibrium mixture, the proper measurements of the bonded/non-bonded "ratios" is thwarted with complications. As a consequence, the slope of the weak, temperature-dependent "ratios" leads to very uncertain values of the *intra*-HB strength.

Theoretical methods to study NH...O hydrogen bonds include natural bond orbital (NBO), non-covalent interaction (NCI), quantum theory of atoms in molecules (QTAIM) and G4 analyses. In NBO analyses, the charge transfer from the oxygen atom to the antibonding NH orbital is examined for this purpose. This method was successfully used to identify NH...O

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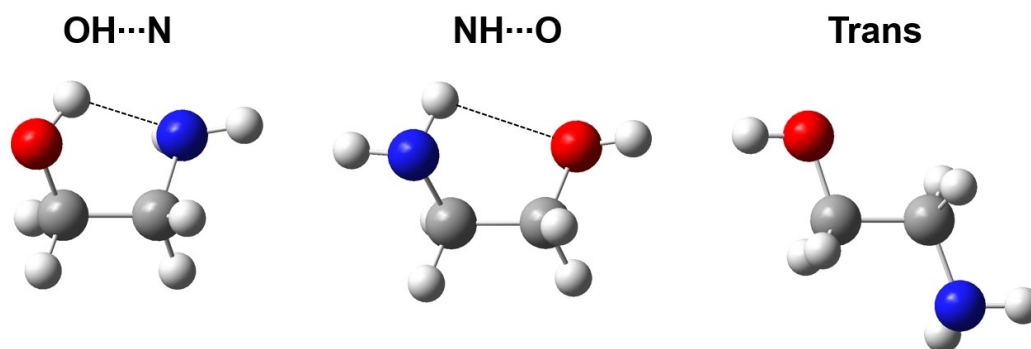


Figure 1. The OH...N and NH...O intra-hydrogen-bonded conformers, as well as non-H-bonded trans conformer of 2-aminoethanol.

hydrogen bonds in aminoalcohols<sup>[8]</sup> and competing intramolecular NH...O hydrogen bonds in thiourea derivatives.<sup>[9]</sup> In QTAIM, the chemical bonds are analyzed using their critical points and the minimum gradient paths and NCI analyses can be used to make statements about non-covalent interactions through electron density investigations. Quantitative information about the strength of hydrogen bonds can be obtained using the G4 method and isodesmic reactions. These theoretical methods were recently used to study intramolecular hydrogen bonds in alpha-omega amino alcohols and their derivatives that were halogenated in the alpha position.<sup>[10]</sup>

An interesting idea to ascertain the strength of the NH...O *intra*-HB is to study methoxy-substituted aminoalcohols. Indeed, the "first" predominant OH...N conformer in the methoxyamines is absent and it should be helpful for quantifying the *intra*-HB strength. However, it has turned out, that the temperature dependence of the "free" and "bonded" NH<sub>2</sub> bands of 2-methoxyethylamine shows that the non-bonded conformer appears to be more stable than the NH...O bonded conformer. The appropriate two bands in the IR spectra are badly overlapped and since the non-bonded conformer predominates, the high frequency side of this band was reflected across the ordinate at the band maximum and the resulting symmetrical band should be subtracted from the experimental

envelope to obtain the "bonded" band.<sup>[2]</sup> Such difficult data acquisition led to the *intra*-HB strength in 2-methoxyethylamine of  $+(6.9 \pm 3.8) \text{ kJ mol}^{-1}$ , as reported by Krueger and Mettee from the IR study in dilute C<sub>2</sub>Cl<sub>4</sub> solution.<sup>[2]</sup> This disappointing experimental result contradicts the general expectation of the energetically stabilizing *intra*-HB bond. In any case, one could assume that the expected stabilization is hardly detectable within the very large experimental uncertainties.

Are there other experimental methods that can be used to quantify very weak NH...O *intra*-HB strength in methoxyamines? Based on our recent experience with experimental and computational thermochemistry of amino alcohols,<sup>[11,12]</sup> in this work we suggest to involve two thermodynamic tools: a gas-phase standard molar enthalpy of formation,  $\Delta_f H_m^o(\text{g}, 298 \text{ K})$  and a standard molar enthalpy of vaporization,  $\Delta_1^9 H_m^o(298.15 \text{ K})$ , as a possible measure for deriving the *intra*-HB strength in alkoxyamines and aminoalcohols.

It has turned out, that  $\Delta_f H_m^o(\text{g}, 298.15 \text{ K})$  and  $\Delta_1^9 H_m^o(298.15 \text{ K})$  values are very limited in the literature. Hence, first of all we performed experimental thermochemical studies on compounds listed in Figure 2.

With these new experimental results together with the complementary quantum chemical calculations, we have quantitatively assessed the *intra*-HB strength in a selected set of

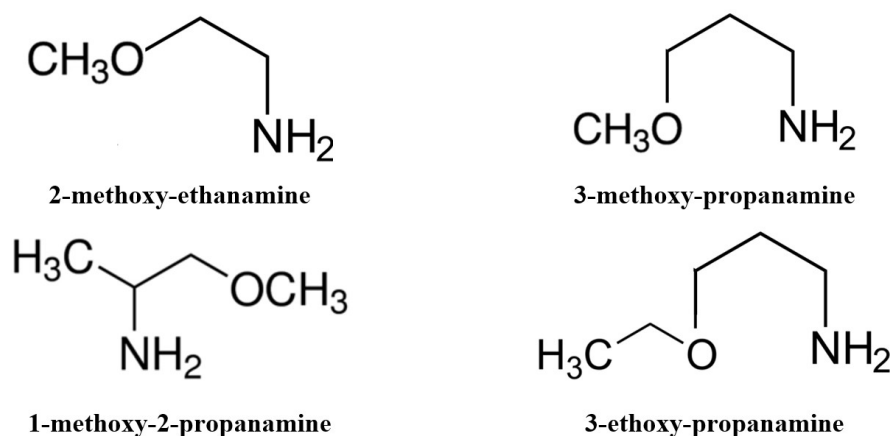


Figure 2. Alkoxyamines studied in this work.

alkoxyamines and the similarly structured aminoalcohols. The reason for the selection of compounds is based on the hypothesis that substitutions in proximity to the functional groups that form the hydrogen bond can lead to a change in the hydrogen bond strength. Such a relationship was shown for amino alcohols that were halogenated in the alpha position. Halogenation near the hydrogen bond donor leads to an increase in bond strength and halogenation close to the hydrogen bond acceptor causes a decrease in hydrogen bond strength.<sup>[10]</sup> The idea for the selection of compounds in this work is based on 2-methoxy-ethanamine and 3-methoxy-propanamine. Starting from the 2-methoxy-ethanamine archetypal for the first and 3-methoxy-propanamine for the second series, in which the intra-hydrogen-bridged conformers NH...O provide the “reference” quantity of the *intra*-HB strength, it is interesting to understand the changes in strength due to increasing non-covalent steric overcrowding of the space between NH<sub>2</sub> and OCH<sub>3</sub> substituents. For comparison, we studied the appropriate series of aminoalcohols, started from 2-amino-ethanol and 3-amino-1-propanol. In the third series of 2-methoxy-alkanamines and 2-amino-1-alkanols, it is expected that the growing alkyl substituent (methyl, ethyl, propyl, and butyl) placed in close proximity of the NH<sub>2</sub>-group will increase a disorder of the NH...O *intra*-HB. In the fourth series of alkoxyamines and aminoalcohols we study the effect of introduction of the CH<sub>3</sub> substituent in the amino group. In the last series, starting from 2-methoxy-ethanamine and 3-methoxy-1-propanamine, the consequent introduction of the CH<sub>2</sub>-group between the NH<sub>2</sub> and OCH<sub>3</sub> is expected to increase disorder of the NH...O-*intra*-HB.

The systematic investigation of the *intra*-HB-strength in alkoxyamines and aminoalcohols using simultaneously two thermodynamic tools:  $\Delta_f H_m^o$  (g, 298 K) and  $\Delta_i^o H_m^o$  (298 K) offers a unique opportunity to quantitatively evaluate such an imaginary non-covalent interaction as *intra*-molecular hydrogen bonding.

## Experimental Section

Samples of alkoxyamines were of commercial origin (see Table S1). The samples for vapor pressure measurements were used as received. The sample of 2-methoxy-ethanamine was additionally distilled shortly before the start of the experiment and stored under molecular sieves. Purities were determined using a gas chromatograph equipped with a capillary column HP-5 and a flame ionization detector. No impurities (greater than the mass fraction 0.0003) were detected in samples used for thermochemical measurements. A residual water amount in samples was determined using the Mettler Toledo DL38 Karl Fischer titrator.

A high-precision self-made calorimeter equipped with a static bomb<sup>[13,14]</sup> was used to measure combustion energies of 2-methoxy-ethylamine. The standard molar enthalpy of combustion,  $\Delta_c H_m^o$  (liq), and the standard molar enthalpy of formation,  $\Delta_f H_m^o$  (liq), of 2-methoxy-ethylamine was derived according to the Hess's Law. Brief descriptions of the measurements and data acquisition are given in Supporting Information.

The absolute vapor pressures of alkoxyamines at different temperatures were measured by using the transpiration method.<sup>[15–18]</sup> The

standard molar enthalpies of vaporization,  $\Delta_i^o H_m^o$ , were derived from the temperature dependences of vapor pressures.

The quantum-chemical method G4<sup>[19]</sup> implemented in the Gaussian 16 software<sup>[20]</sup> was used for calculations of enthalpies  $H_{298}$ -values, which were finally converted to the  $\Delta_f H_m^o$  (g) and discussed. The search for stable alkoxy-amine conformers was carried out with the CREST program package.<sup>[21]</sup>

## Results and Discussion

The direct quantification of the *intra*-HB strength is not possible, because this feature cannot be measured. Nonetheless, at least two thermodynamic tools can be used to indirectly assess this strength. The first one is the gas-phase standard molar enthalpy of formation  $\Delta_f H_m^o$  (g). Admittedly, in the liquid phase the competition between the *intra*- and *inter*-hydrogen bonding completely excludes the correct quantification of both two types. In contrast to this, the molecule in the gas phase is free from the neighbourhood and the *intra*-HB specific for alkoxyamines and aminoalcohols can be obtained from the total energetics of a molecule, represented by the enthalpy of formation  $\Delta_f H_m^o$  (g). The latter thermodynamic property is collected from the experimental standard molar enthalpy of formation in the liquid phase,  $\Delta_f H_m^o$  (liq), and the standard molar enthalpy of vaporization,  $\Delta_i^o H_m^o$ , as follows:

$$\Delta_f H_m^o (g) = \Delta_f H_m^o (liq) + \Delta_i^o H_m^o \quad (1)$$

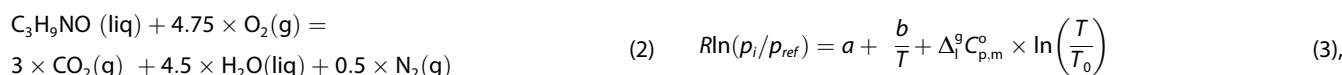
The  $\Delta_f H_m^o$  (liq)-values are usually derived by using combustion calorimetry and the  $\Delta_i^o H_m^o$ -values are usually derived from vapor pressure measurements.

The second thermodynamic tool for quantification of the *intra*-HB strength is  $\Delta_i^o H_m^o$  (298.15 K). This vaporization enthalpy has already been used successfully for the quantification of *inter*-HB in alcohols,<sup>[15]</sup> diols,<sup>[22–24]</sup> and amino alcohols<sup>[11]</sup>. In this work we show how this tool is applied to assess *intra*-HB strength in alkoxyamines.

Conventionally, all thermodynamic properties involved in Equation (1) are referenced to  $T=298.15$  K. Both contributors to Equation (1) were measured in this work and the resulting  $\Delta_f H_m^o$  (g)-values were used for interpretation of the *intra*-HB strength as it shown below.

### Combustion calorimetry: standard molar enthalpy of formation of 2-methoxy-ethylamine

The standard molar enthalpy of combustion  $\Delta_c H_m^o$  (liq) =  $-2243.4 \pm 1.3$  kJ mol<sup>-1</sup> and the standard molar enthalpy of formation  $\Delta_f H_m^o$  (liq) =  $-223.4 \pm 1.4$  kJ mol<sup>-1</sup> of 2-methoxy-ethylamine was derived from the specific energy of combustion,  $\Delta_c u^o = -29826.9 \pm 7.9$  J g<sup>-1</sup>. The combustion results for  $\Delta_c u^o$  and  $\Delta_c H_m^o$  refer to the reaction:



The specific energy of combustion,  $\Delta_c u^o$ , of 2-methoxyethylamine was measured in a series of five experiments. A typical combustion experiment is given in Table S2. The auxiliary quantities for the combustion experiments are collected in Table S3. The results for all combustion experiments are given in Tables S4 in Supporting Information. The combustion energy was reduced to the standard state using auxiliary data (see Table S3) and the conventional method.<sup>[25]</sup> The experimental  $\Delta_f H_m^o(\text{liq})$ -value was obtained by applying the Hess's Law to Equation (2) using standard molar enthalpies of formation of  $\text{H}_2\text{O}(\text{liq})$  and  $\text{CO}_2(\text{g})$  recommended by CODATA.<sup>[26]</sup> Uncertainties related to combustion experiments were calculated according to the guidelines developed by Olofsson.<sup>[27]</sup> They include the uncertainties from calibration, from the combustion energies of the auxiliary materials and uncertainties of the reaction products  $\text{H}_2\text{O}$  and  $\text{CO}_2$ .

#### Vapor pressure measurements: standard molar enthalpies of vaporization of alkoxy-amines

The vaporization enthalpies  $\Delta_i^g H_m^o(298.15 \text{ K})$  of alkoxy-amines required in Equation (1) and for evaluation of the *intra*-HB strength are compiled in Table 1. The vapor pressures of alkoxyamines,  $p_i$ , measured with help of the transpiration method at different temperatures (see Table S5) were approximated with Equation (3)<sup>[15]</sup>:

where  $R = 8.31446 \text{ J K}^{-1} \text{ mol}^{-1}$  is the molar gas constant, the reference pressure  $p_{ref} = 1 \text{ Pa}$ ,  $a$  and  $b$  are adjustable parameters, the arbitrary temperature  $T_0$  applied in Equation (3) was chosen to be  $T_0 = 298.15 \text{ K}$ , and  $\Delta_i^g C_{p,m}^o$  is the difference in the molar heat capacities of the gas and liquid phase (see Table S6).

The primary experimental results on vapor pressures for the 3-methoxy-propylamine, 3-ethoxy-propylamine, and optical isomers of 1-methoxy-2-propylamine from the transpiration method are given in Table S5. Experimental vapor pressures measured in this work (as well as those taken from the literature) have been used to obtain the enthalpies of vaporization of alkoxy-amines using the following equation:

$$\Delta_i^g H_m^o(T) = -b + \Delta_i^g C_{p,m}^o \times T \quad (4)$$

Experimental vapor pressures temperature dependences were also used to derive the vaporization entropies at temperatures  $T$  by using the following equation:

$$\Delta_i^g S_m^o(T) = \Delta_i^g H_m^o/T + R \times \ln(p_i/p^o) \quad (5)$$

with  $p^o = 0.1 \text{ MPa}$ . Coefficients  $a$  and  $b$  of Equation (3),  $\Delta_i^g H_m^o(T)$  and  $\Delta_i^g S_m^o(T)$  values are collected in Table S5. The combined uncertainties of the vaporization enthalpies include uncertainties from the experimental conditions of transpiration, uncertainties in vapor pressure, and uncertainties due to the temperature adjustment to  $T = 298.15 \text{ K}$ , as described elsewhere.<sup>[17,18]</sup>

**Table 1.** Compilation of the experimental standard molar enthalpies of vaporization  $\Delta_i^g H_m^o$  of substituted alkoxyamines.

Compound	M <sup>[a]</sup>	T- range [K]	$\Delta_i^g H_m^o [T_{av}]$ [kJ mol <sup>-1</sup> ]	$\Delta_i^g H_m^o [298.15 \text{ K}]^{[b]}$ [kJ mol <sup>-1</sup> ]	Ref.
2-methoxy-ethylamine [109–85-3]	n/a	278–318	38.4 ± 0.5	38.4 ± 0.6	[28]
	S	275.2–317.6	38.6 ± 0.1	38.4 ± 0.1	[29]
	$T_b$			39.5 ± 1.0	Table 2
				<b>38.4 ± 0.2</b> <sup>[c]</sup>	average
3-methoxy-propylamine [5332–73-0]	E	306.6–368.3	41.8 ± 0.2	44.5 ± 0.3	[30]
	n/a	278–390	41.7 ± 0.5	44.2 ± 0.6	[31]
	S	279.0–317.6	44.1 ± 0.1	44.1 ± 0.1	[29]
	T	277.4–317.3	44.2 ± 0.3	44.0 ± 0.4	this work
	$T_b$			43.8 ± 1.0	Table 2
				<b>44.1 ± 0.2</b> <sup>[c]</sup>	average
3-ethoxy-propylamine [6291–85-6]	T	278.2–312.3	47.5 ± 0.2	47.2 ± 0.3	this work
	$T_b$			47.2 ± 1.0	Table 2
				<b>47.2 ± 0.4</b> <sup>[c]</sup>	average
(R)-(-)-1-methoxy-2-propylamine [99636–38-1]	T	278.6–308.3	40.5 ± 0.3	40.1 ± 0.4	this work
	$T_b$			39.5 ± 1.0	Table 2
				<b>40.1 ± 0.4</b> <sup>[c]</sup>	average
(S)-(+)-1-methoxy-2-propylamine [99636–32-5]	T	274.6–298.4	41.0 ± 0.2	40.1 ± 0.3	this work
	$T_b$			39.5 ± 1.0	Table 2
				<b>40.1 ± 0.3</b> <sup>[c]</sup>	average

[a] Method instead of Techniques: T = transpiration method; S = static method; n/a = method is not available; E = ebulliometry;  $T_b$  – derived from empirical calculation between vaporization enthalpy and normal boiling point (see Table 2). [b] Uncertainties of the vaporization enthalpies is expressed as standard uncertainty (0.68 level of confidence,  $k = 1$ ). They include uncertainties from the experimental conditions and the fitting equation, vapor pressures, and uncertainties from adjustment of vaporization enthalpies to the reference temperature  $T = 298.15 \text{ K}$ .<sup>[17,18]</sup> [c] Weighted mean value (the uncertainty was taken as the weighing factor). Uncertainty of the vaporization enthalpy is expressed as the standard uncertainty (0.68 level of confidence,  $k = 1$ ). Values highlighted in bold were recommended for thermochemical calculations.

The experimental vapor pressures of 2-methoxy-ethylamine and 3-methoxy-propylamine were recently measured by Lepori et al. using the static method.<sup>[29]</sup> The new results agree very well with those previously reported (see Figures S1 and S2). Vapor pressures of 3-ethoxy-propylamine and 1-methoxy-2-propylamine are reported for the first time.

The experiments on the latter compound were performed with two enantiopure isomers (R)-(–)-1-methoxy-2-propylamine and (S)-(+)-1-methoxy-2-propylamine. According to the textbooks, it is expected that all physical and chemical properties of enantiomers are the same except for the chiroptical properties. In our recent work, however, we found a noticeable difference in vapor pressure, vaporisation and formation enthalpies of the chiral compounds like diols and alkyl lactates.<sup>[24,32]</sup>

In this work we deliberately carried out transpiration measurements on enantiomerically pure 1-methoxy-2-propylamines under identical experimental conditions in order to reveal an effect of stereoisomerism. But this time, the vapor pressures (see Figure S3) and vaporization enthalpies (see Table 1) of enantiopure compounds could not be distinguished.

### Validation of experimental vaporization enthalpies with help of the normal boiling temperatures

The available data on the liquid to gas phase transition for alkoxyamines are limited to the compounds listed in Table 1. In order to establish the consistency of this data, the “structure-property” correlations should be used. The correlation of vaporization enthalpies,  $\Delta_f H_m^o(298.15\text{ K})$ , with the normal boiling points,  $T_b$ , is a well-established phenomenon. Using the very limited data set (see Table 2) we have established a following linear correlation for alkoxy-amines (in  $\text{kJ mol}^{-1}$ ):

$$\Delta_f H_m^o(298.15\text{ K}) = -30.2 + 0.1889 \times T_b \text{ with } (R^2 = 0.953) \quad (6)$$

The results calculated from this linear correlation (see Table 1, designated as the  $T_b$ -values) agreed with those of other methods within of  $\pm 1.0\text{ kJ mol}^{-1}$ . This good agreement can be considered as an indicator of the internal consistency of the selected data set and as evidence of the reliability of the transpiration results.

### Gas-phase standard molar enthalpies of formation of alkoxy-amines and intra-HB strength

Having established the enthalpy of formation in the liquid phase,  $\Delta_f H_m^o(\text{liq})$  and the enthalpy of vaporization,  $\Delta_f H_m^o$ , of 2-methoxy-ethaneamine we are able now to apply Equation (1) to derive the *experimental* gas-phase enthalpy of formation for this compound as follows:  $\Delta_f H_m^o(\text{g})_{\text{exp}} = (-223.4 + 38.4) = -(185.0 \pm 1.4)\text{ kJ mol}^{-1}$ . This result helps to validate the theoretical value:  $\Delta_f H_m^o(\text{g})_{\text{theor}} = -(186.2 \pm 3.5)\text{ kJ mol}^{-1}$  calculated for the most stable intra-hydrogen bonded conformer (see Figure 3) by using the G4 and the atomization reaction. The theoretical value is in excellent agreement with the experiment, but it is slightly more negative. This slight deviation reinforced the reliability of the theoretical result, because the second stable *trans*-conformer (see Figure 3) of 2-methoxy-ethaneamine  $\Delta_f H_m^o(\text{g})_{\text{theor}} = -(180.0 \pm 3.5)\text{ kJ mol}^{-1}$  is also populated by a few percent in the gas-phase and the enthalpy of formation of the equilibrium conformers mixture will be closer to the experimental value according to the Boltzmann distribution rule. With the proven reliability of the G4 method for calculating the thermodynamic properties of alkoxyamines in the gas phase, we want to use this method systematically to quantify the strength of the intramolecular hydrogen bond in these compounds.

Admittedly, the intra-HB strength is defined in quantum-chemistry as the energetic difference between the H-bonded conformer and the *most stable* (designated as *mst* in Table 3) conformer without HB (see Figure 3).

Using the G4 method we calculated the gaseous standard molar enthalpies of formation  $\Delta_f H_m^o(\text{g})_{\text{NH}\cdots\text{O}}$  for the NH $\cdots$ O bonded conformers and  $\Delta_f H_m^o(\text{g})_{\text{mst}}$  for the most stable non-H-bonded conformers (see Table 3). The NH $\cdots$ O conformers were determined based on the most stable OH $\cdots$ N conformer, whose functional groups involved in the hydrogen bond were rotated until the most stable NH $\cdots$ O conformer was found by geometry optimization (see Figure S4). From these data we calculated the differences [ $\Delta_f H_m^o(\text{g})_{\text{NH}\cdots\text{O}} - \Delta_f H_m^o(\text{g})_{\text{mst}}$ ], which were considered as the quantum-chemical measure of the intra-HB strength of the NH $\cdots$ O type in *alkoxy-amines*.

For comparison with results on *alkoxy-amines*, we also calculated gas-phase standard molar enthalpies  $\Delta_f H_m^o(\text{g})_{\text{NH}\cdots\text{O}}$  for the NH $\cdots$ O bonded conformers and  $\Delta_f H_m^o(\text{g})_{\text{mst}}$  for the *most stable* (*mst*) non-H-bonded conformers of *aminoalcohols* (see Table 4), which are structurally similar to the appropriate

**Table 2.** Correlation of the experimental vaporization enthalpies  $\Delta_f H_m^o(298.15\text{ K})$  of alkoxy-amines with their normal boiling temperatures ( $T_b$ )<sup>[a]</sup>.

CAS	Compound	$T_b$ <sup>[b]</sup> K	$\Delta_f H_m^o$ [exp] <sup>[c]</sup> $\text{kJ}\cdot\text{mol}^{-1}$	$\Delta_f H_m^o$ [calc] <sup>[d]</sup> $\text{kJ}\cdot\text{mol}^{-1}$	$\Delta$ <sup>[e]</sup> $\text{kJ}\cdot\text{mol}^{-1}$
109–85-3	2-methoxy-ethylamine	369	38.4 <sup>f</sup>	39.5	-1.1
5332–73-0	3-methoxy-propylamine	392	44.0	43.8	0.2
6291–85-6	3-ethoxy-propylamine	410	47.2	47.2	-0.0
37143–54-7	1-methoxy-2-propylamine	367	40.1	39.1	1.0

[a] Uncertainty of the vaporization enthalpy  $u(\Delta_f H_m^o)$  in this table is expressed as the standard uncertainty (0.683 level of confidence,  $k=1$ ). [b] Normal boiling temperatures are from SciFinder.<sup>[33]</sup> [c] Experimental data measured by using the transpiration method from (see Table S5). [d] Calculated using Equation (6):  $\Delta_f H_m^o(298.15\text{ K})/(\text{kJ}\cdot\text{mol}^{-1}) = -30.2 + 0.1889 \times T_b$ . [e] Difference between experimental and calculated by Equation (6). [f] Experimental value from Table 1.

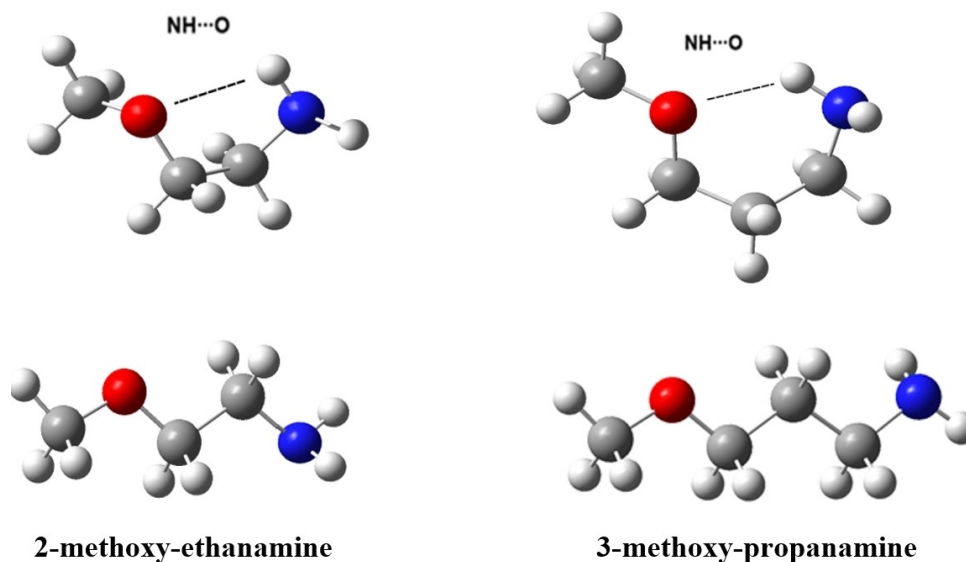


Figure 3. Definitions of intra-molecular hydrogen bonding strength in alkoxy-amines.

**Table 3.** Theoretical strength of the intra-HB in alkoxy-amines at  $p^\circ = 0.1$  MPa and  $T = 298.15$  K (in  $\text{kJ mol}^{-1}$ ).

Compound	CAS	$\Delta_f H_m^p(\text{g})_{\text{G4}}, \text{NH}\cdots\text{O}^{[a]}$	$\Delta_f H_m^p(\text{g})_{\text{G4}}, \text{mst}^{[b]}$	$\text{HB}_{(\text{NH}\cdots\text{O})}^{[c]}$
2-methoxyethanamine	109-85-3	-186.2	-180.0	-6.2
2-methoxyethylmethanamine	38256-93-8	-177.8	-175.4	-2.4
3-methoxy-N-methyl-1-propanamine	55612-03-8	-202.3	-199.8	-2.5
2-methoxy-1-propanamine	3124-96-7	-220.4	-214.7	-5.7
2-methoxy-1-butanamine	89282-64-4	-238.5	-235.8	-2.7
1-methoxy-2-propanamine	37143-54-7	-220.4	215.9	-4.5
1-methoxy-2-butanamine	63448-63-5	-240.8	-236.4	-4.4
1-methoxy-2-pentanamine	851669-44-8	-262.2	-257.6	-4.6
1-methoxy-2-hexanamine	1248971-00-7	-283.6	-279.3	-4.3
2-methoxy-ethanamine	109-85-3	-186.2	-180.0	-6.2
3-methoxy-1-propanamine	5332-73-0	-204.1	-203.4	-0.7
4-methoxy-1-butanamine	34039-36-6	-221.6	-223.9	2.3
5-methoxy-1-pentanamine	71259-63-7	-239.1	-244.8	5.7
6-methoxy-1-hexanamine	60730-30-5	-263.1	-266.4	3.3
2-methoxy-2-methyl-1-propanamine	89282-70-2	-253.2	-250.3	-2.9
1-methoxy-2-methyl-2-propanamine	20719-68-0	-259.1	-256.2	-2.9
3-methoxy-2-butanamine	408352-30-7	-252.7	-246.8	-5.9
4-methoxy-2-butanamine	98138-15-9	-239.0	-238.7	-0.3
3-methoxy-2-methyl-1-propanamine	26331-99-7	-232.4	-232.2	-0.2
3-methoxybutylamine	77689-67-9	-238.5	-236.7	-1.8
3-ethoxy-1-propanamine	6291-85-6	-238.4	-235.0	-3.4

[a] The standard molar enthalpy of formation of the  $\text{NH}\cdots\text{O}$  bonded conformer. [b] The standard molar enthalpy of formation of the most stable non-H-bonded conformer. [c] Quantum-chemical measure of the intra-HB strength, calculated as the differences  $[\Delta_f H_m^p(\text{g})_{\text{NH}\cdots\text{O}} - \Delta_f H_m^p(\text{g})_{\text{mst}}]$ .

alkoxyamines. From these data we calculated the differences  $[\Delta_f H_m^p(\text{g})_{\text{NH}\cdots\text{O}} - \Delta_f H_m^p(\text{g})_{\text{mst}}]$ , which were considered as the quantum-chemical measure of the *intra*-HB strength of the  $\text{NH}\cdots\text{O}$  type in *aminoalcohols*.

The comparison of the *intra*-HB strength of the  $\text{NH}\cdots\text{O}$  type in alkoxyamines and aminoalcohols is given in Figures 4–8. In the following discussion, *intra*-HB strength of the  $\text{NH}\cdots\text{O}$  type is given (in  $\text{kJ mol}^{-1}$ ) on Figures 4–8 below the structures of compounds.

### Intra-HB strength in 2-methoxy-ethylamine and 2-amino-ethanol derivatives: H-acceptor crowding

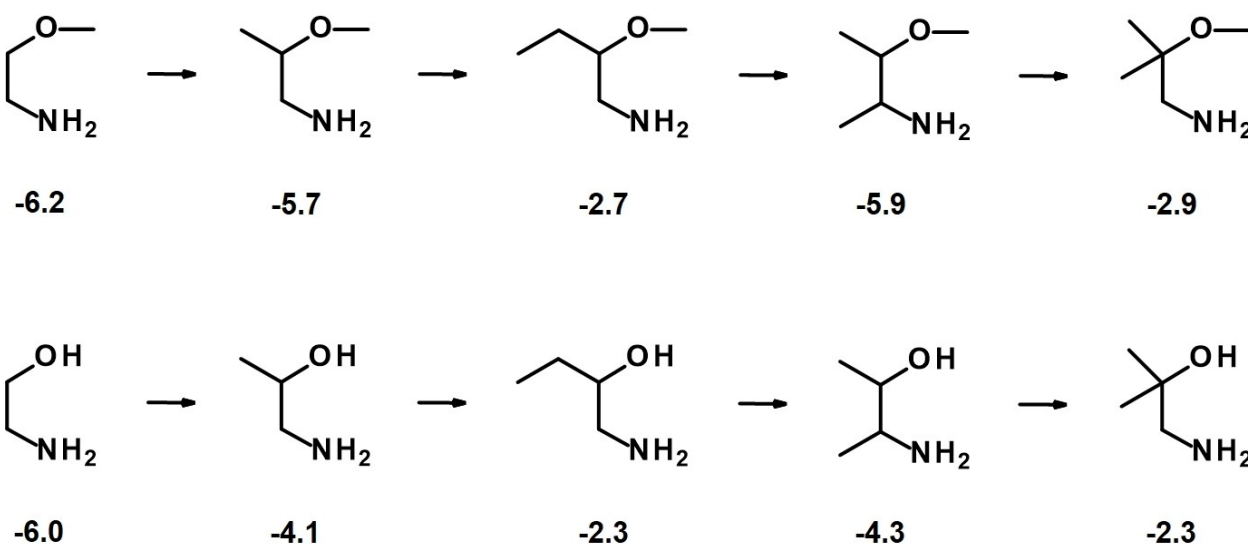
In the first series we compare 2-methoxy-ethylamine and 2-amino-ethanol derivatives, which are gradually branched on the carbon atom adjacent to the oxygen (see Figure 4). What do we expect? The formation of the  $\text{NH}\cdots\text{O}$  bond type in small molecules like 2-methoxy-ethylamine and 2-amino-ethanol is stipulated by the degree of crowding of both the H-donor



**Table 4.** Theoretical strength of the intra-HB in aminoalcohols at  $p^\circ = 0.1$  MPa and  $T = 298.15$  K (in  $\text{kJ mol}^{-1}$ ).

aminoalcohol/CAS	$\Delta_f H_m^\circ(\text{g})_{\text{OH}\cdots\text{N}}^{[a]}$	$\Delta_f H_m^\circ(\text{g})_{\text{NH}\cdots\text{O}}^{[b]}$	$\Delta_f H_m^\circ(\text{g})_{\text{G4 mst}}^{[c]}$	$\text{OH}\cdots\text{N}^{[d]}$	$\text{NH}\cdots\text{O}^{[e]}$
1-amino-2-propanol [78–96-6]	–248.4	–239.7	–235.6	–13.3	–4.1
1-amino-2-butanol [13552–21-1]	–269.8	–258.3	–256.0	–13.8	–2.3
2-amino-1-propanol [124–68-5]	–242.7	–237.9	–231.3	–11.4	–6.6
2-amino-1-butanol [13054–87-0]	–263.1	–257.9	–251.7	–11.4	–6.2
2-amino-1-pentanol [22724–81-8]	–284.3	–279.3	–272.8	–11.5	–6.5
2-amino-1-hexanol [5665–74-7]	–305.9	–300.9	–294.5	–11.4	–6.4
2-amino-ethanol [141–43-5]	–207.4	–201.7	–195.7	–11.7	–6.0
3-amino-1-propanol [156–87-6]	–231.1	–220.0	–218.0	–13.1	–2.0
4-amino-1-butanol [13325–10-5]	–253.5	–235.4	–239.0	–14.5	3.6
5-amino-1-pentanol [2508–29-4]	–263.6	–254.9	–259.8	–3.8	4.9
6-amino-1-hexanol [4048–33-3]	–289.0	–276.8	–281.4	–7.6	4.6
1-amino-2-methyl-2-propanol [2854–16-2]	–288.3	–279.2	–276.9	–11.4	–2.3
2-amino-2-methyl-1-propanol [124–68-5]	–281.3	–274.1	–272.2	–9.1	–1.9
3-amino-2-methyl-1-propanol [15518–10-2]	–260.4	–248.7	–248.2	–12.2	–0.5
3-amino-1-butanol [2867–59-6]	–266.7	–256.6	–253.3	–13.6	–3.3
3-amino-2-butanol [42551–55-3]	–281.4	–270.9	–266.6	–14.8	–4.3
4-amino-2-butanol [39884–48-5]	–265.7	–258.7	–256.5	–11.9	–2.2
2-(methyl-amino)-ethanol [109–83-1]	–202.7	–193.2	–190.9	–11.8	–2.3
3-methylamino-1-propanol [42055–15-2]	–228.8	–217.4	–215.0	–13.8	–2.4
2-(dimethylamino)-ethanol [108–01-0]	–209.7	–	–195.8	–13.9	–
2-(diethylamino)-ethanol [100–37-8]	–254.8	–	–241.1	–13.7	–
1-(dimethylamino)–2-propanol [108–16-7]	–251.2	–	–236.7	–14.5	–
3-(dimethylamino)–1-propanol [3179–63-3]	–236.6	–	–222.1	–14.5	–
3-(diethylamino)–1-propanol [622–93-5]	–287.2	–	–270.1	–17.1	–

[a] The standard molar enthalpy of formation of the OH $\cdots$ N bonded conformer. [b] The standard molar enthalpy of formation of the NH $\cdots$ O bonded conformer. [c] The standard molar enthalpy of formation of the most stable non-H-bonded conformer. [d] Quantum-chemical measure of the *intra*-HB strength, calculated as the differences  $[\Delta_f H_m^\circ(\text{g})_{\text{OH}\cdots\text{N}} - \Delta_f H_m^\circ(\text{g})_{\text{mst}}]$ . [e] Quantum-chemical measure of the *intra*-HB strength, calculated as the differences  $[\Delta_f H_m^\circ(\text{g})_{\text{NH}\cdots\text{O}} - \Delta_f H_m^\circ(\text{g})_{\text{mst}}]$ .

**Figure 4.** NH $\cdots$ O hydrogen bond strength (in  $\text{kJ mol}^{-1}$ ) in the series of 2-methoxy-ethylamine (first row) and 2-amino-ethanol (second row) derivatives.

and the H-acceptor group. It is expected that the gradual congesting of the carbon atom next to the H-acceptor group (oxygen in this first row) with alkyl substituents will aggravate H-bonding and decrease the *intra*-HB strength compared to

unsubstituted 2-methoxy-ethylamine and 2-amino-ethanol. The development of the H-bond energetics depending on crowding is shown in Figure 4.

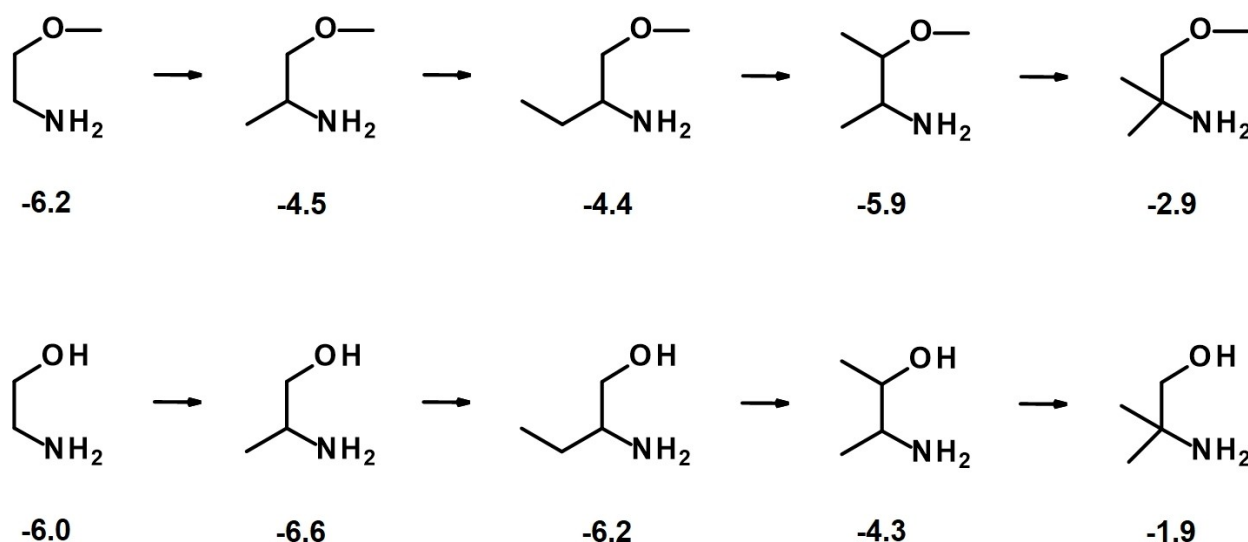


Figure 5. NH...O hydrogen bonding strength in 2-methoxy-ethylamine and 2-amino-ethanol series with branching near the amino group.

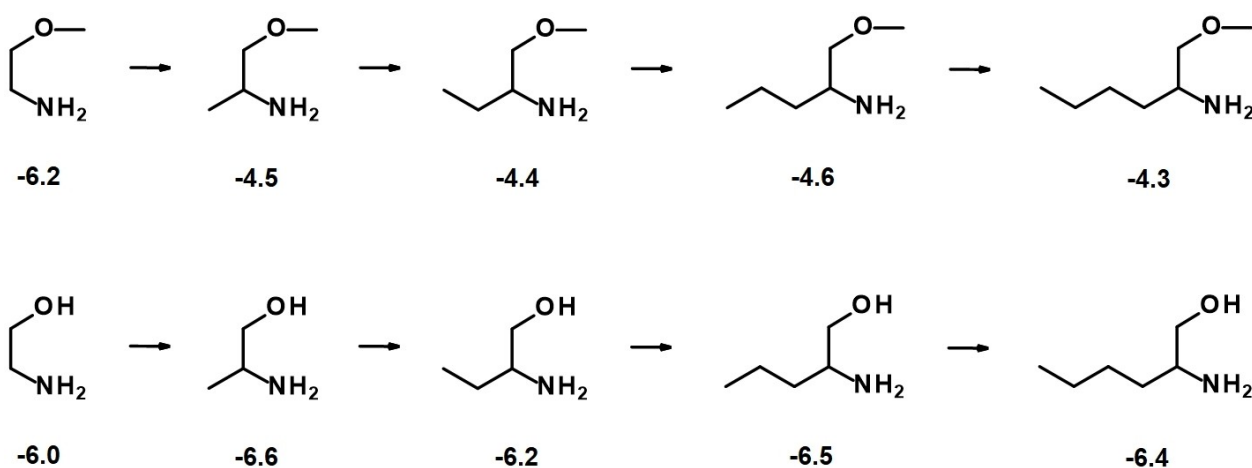


Figure 6. NH...O hydrogen bond strengths in 2-methoxy-ethylamine and 2-amino-ethanol derivatives with the NH<sub>2</sub> crowding by the growing alkyl chain length.

It makes already oneself conspicuous, that the intra-H-bond strength of  $-6 \text{ kJ mol}^{-1}$  in the first representatives of both series, namely 2-methoxy-ethylamine and 2-amino-ethanol is indistinguishable. The expected trend of the general decrease in intra-HB strength with the accumulation of substituents occurs, even if this decrease is only a few  $\text{kJ mol}^{-1}$ . Possibly, the +I effect of the alkyl group counteracts the steric effect here by increasing the electron density at the hydrogen bond acceptor so that an enhanced charge transfer into the antibonding N–H orbital can occur. In addition, it is noticeable that the methoxy analogs always have slightly stronger hydrogen bonds. This could be due to the increased electron density at the oxygen, which is caused by the +I effect of the additional methyl group. This hypothesis could be examined in a further study. The most surprising observation in this series is that the strength fluctuation in 2-methoxy-ethylamine derivatives (see Figure 4, first row) and in 2-amino-ethanol (see Figure 4, second row) is

remarkably synchronized. This fact might be an indicator that the NH...O bond strength is not influenced by the crowding of the H-acceptor. And what about the crowding of the H-donor (the NH<sub>2</sub> group in the next series)?

#### Intra-HB strength in 2-methoxy-ethylamine and 2-amino-ethanol derivatives: H-donor crowding

In the second series we also compare 2-methoxy-ethylamine and 2-amino-ethanol derivatives, which are now gradually branched on the carbon atom adjacent to the nitrogen of the NH<sub>2</sub>-group (see Figure 5). The expected trend in this series is similar to that discussed in the first series. Indeed, the crowding of the H-donor with the alkyl substituents should decrease the intra-HB strength.



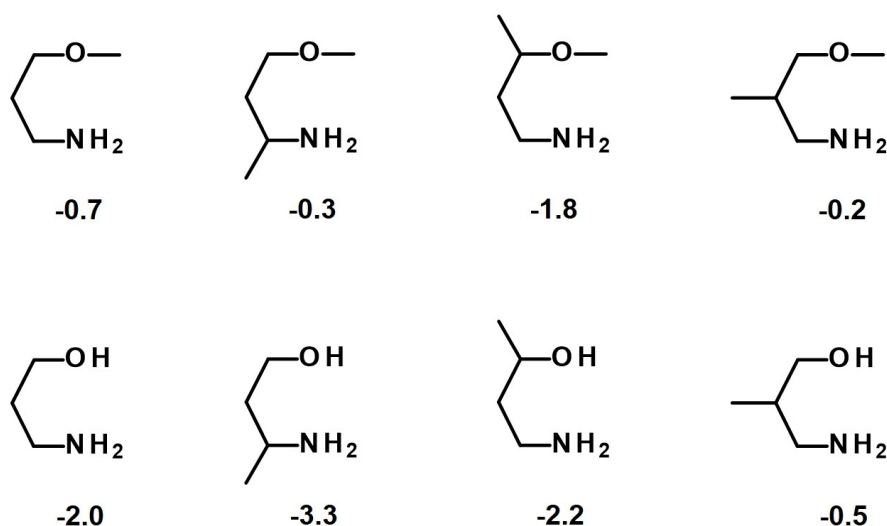
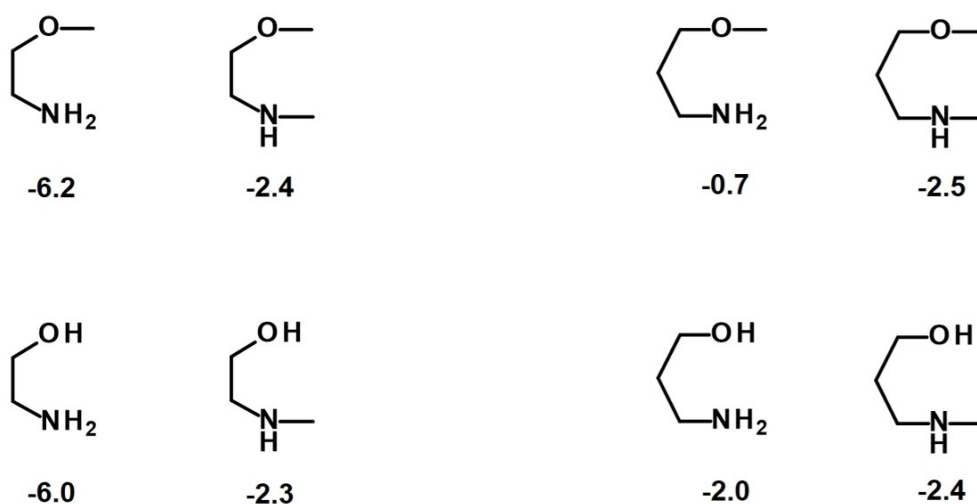


Figure 7. Strength of NH...O hydrogen bond in branched 3-methoxy-1-propanol and 3-amino-1-propanols series.



### N-methylated-ethanol derivatives

### N-methylated-propanol derivatives

Figure 8. NH...O hydrogen bonding strengths in 2-(methylamino)-ethanol, 3-(methylamino)-1-propanol and their methoxy analogues.

However, this trend is hardly traceable within the methoxyamines and amino-alkanols collected in Figure 5. As can be seen, the general level of the intra-H-bond strength of  $-6 \text{ kJ mol}^{-1}$ , which is characteristic of the first representatives 2-methoxy-ethylamine and 2-amino-ethanol, remains unchanged for both series, with the only exception of the quaternary substituted carbon in 1-methoxy-2-methyl-2-propanamine ( $-2.9 \text{ kJ mol}^{-1}$ ) and in 2-amino-2-methyl-1-propanol ( $-1.9 \text{ kJ mol}^{-1}$ ). This decrease in bond strength could be caused by a combination of the increase in electron density at the amino group due to the +I effect and the steric influence of the two methyl groups. Hence, a preliminary conclusion that can be drawn for the structural dependence of the intra-HB strength is that the HB energetics are not particularly sensitive to the moderate degree of crowding of the H-donor or H-

acceptor side of 2-methoxyethylamine and 2-amino-ethanol derivatives.

### Intra-HB strength in 2-methoxy-ethylamine and 2-amino-ethanol derivatives: H-donor crowding by the growing alkyl chain length

In the third series we continue to compare 2-methoxy-ethylamine and 2-amino-ethanol derivatives, which are now branched on the carbon atom adjacent to the nitrogen of the NH<sub>2</sub>-group, but this time the adjacent alkyl substituent grows gradually from methyl to n-butyl (see Figure 6). According to the preliminary conclusion in previous section, the strong fluctuations in intra-HB strength are hardly to be expected,

since the methoxy-amines and amino-alkanols collected on Figure 6 exhibit only the tertiary branching of the carbon atom adjacent to the nitrogen. Indeed, only the first step – introduction of the methyl group into 2-methoxy-ethylamine ( $-6.2 \text{ kJ mol}^{-1}$ ) with formation of 1-methoxy-2-propanamine ( $-4.5 \text{ kJ mol}^{-1}$ ) shows a slight decrease of the strength. The further extension of the alkyl chains up to *n*-butyl does not affect the energetics of the H-bond and the strength remains constant at  $4 \text{ kJ mol}^{-1}$  (see Figure 6, first row).

In the series of amino alcohols (see Figure 6, second row), the influence of the increasing chain length is practically negligible and remains constant at the same level of  $6 \text{ kJ mol}^{-1}$  as in 2-aminoethanol itself. Such behaviour could be understandable from the spacious requirements for the H-bond formation. The introduction of the  $\text{CH}_3$ -substituent near the H-donor  $\text{NH}_2$ -group somewhat restricts the rotational freedom of the  $\text{NH}_2$ . Introduction of the  $\text{CH}_3\text{-CH}_2$ -substituent in the same position could hardly have any consequences, since the  $\text{CH}_2$ -group near the H-donor is smaller than  $\text{CH}_3$ -group. This means that the longer alkyl chain is even further removed from the sphere that is essential for H-bond formation. Therefore, the intra-HB strength does not depend on the length of the alkyl chain.

#### The intra-HB strength in branched 3-methoxy-1-propanol and 3-amino-1-propanols series

In this series we study the effect of methyl-substitution of amino-propanol derivatives (see Figure 7). As already stated in previous section, the “moderate” branching of the alkyl chain connecting the H-donor and H-acceptor in alkoxyamines and aminoalcohols also has a moderate influence on the strength. It has turned out, that already in the archetypal molecules 3-methoxy-1-propanol ( $-0.7 \text{ kJ mol}^{-1}$ ) and 3-amino-1-propanol ( $-2.0 \text{ kJ mol}^{-1}$ ) the  $\text{NH}\cdots\text{O}$  type of hydrogen bonding is only slightly favourable. The further introduction of the  $\text{CH}_3$  group in the vicinity of the O atom leads to a slight bond strength increase and to a slight decrease in beta position of both functional groups. When the methyl group is located close to the nitrogen atom, opposite results are obtained for 3-amino-1-butanol ( $-3.3 \text{ kJ mol}^{-1}$ ) and 4-methoxy-2-butanamine ( $-0.3 \text{ kJ mol}^{-1}$ ). However, when uncertainties are taken into account, these effects are minimal.

#### Intra-HB strength in N-methylated-aminoethanol derivatives and N-methylated-aminopropanol derivatives

The  $\text{NH}_2$  group as the H-donor is flexible to provide one of two available H-atoms for the  $\text{NH}\cdots\text{O}$  hydrogen bonding. With two H-atoms as options, it is easy to form the strong H-bridge depending on the surrounding. The methylation of the nitrogen should reduce the rotational flexibility of the group and the decrease in strength is foreseen. The comparison of strength in non-methylated and N-methylated derivatives is given in Figure 8. As can be seen in Figure 8 (left), the N-methylated-

ethanol derivatives: 2-(methylamino)-ethanol ( $-2.3 \text{ kJ mol}^{-1}$ ) and 2-(methoxyethyl)-methylamine ( $-2.4 \text{ kJ mol}^{-1}$ ) follow the expected trend with the noticeable decrease of the strength compared to the non-methylated 2-amino-ethanol and 2-methoxy-ethylamine.

The results shown in Figure 8 (right) for amino-propanol derivatives make it clear that  $\text{NH}\cdots\text{O}$  type hydrogen bonding in 3-amino-1-propanol ( $-2.0 \text{ kJ mol}^{-1}$ ) and 3-(methylamino)-1-propanol ( $-2.4 \text{ kJ mol}^{-1}$ ) is hardly favourable, because twisting of the alkyl chain requires more energy than the  $\text{NH}\cdots\text{O}$  bond can compensate. Also, the formation  $\text{NH}\cdots\text{O}$  type hydrogen bonding in 3-methoxy-1-propanamine ( $-0.7 \text{ kJ mol}^{-1}$ ) and 3-methoxy-N-methyl-1-propanamine ( $-2.4 \text{ kJ mol}^{-1}$ ) is just possible due to the ample flexibility of these molecules.

#### Intra-HB strength in $\alpha,\omega$ -methoxy-alkylamines and $\alpha,\omega$ -aminoalcohols

The last two series taken for the evaluation of strength are  $\alpha,\omega$ -methoxy-alkylamines (2-methoxy-ethanamine, 3-methoxy-1-propanamine, 4-methoxy-1-butanamine, 5-methoxy-1-pentanamine, 6-methoxy-1-hexanamine) and their analogous  $\alpha,\omega$ -aminoalcohols (see Figure 9).

As usual (see Figures 4–8) we start the comparison with 2-methoxy-ethylamine ( $-6.2 \text{ kJ mol}^{-1}$ ) and 2-amino-ethanol ( $6.0 \text{ kJ mol}^{-1}$ ) and consequently introduce the  $\text{CH}_2$ -groups between OH and  $\text{NH}_2$ .

However, already the introduction of the first  $\text{CH}_2$  group, which leads to 3-methoxy-1-propanol ( $-0.7 \text{ kJ mol}^{-1}$ ) and 3-amino-1-propanol ( $-2.0 \text{ kJ mol}^{-1}$ ), shows that the weak  $\text{NH}\cdots\text{O}$  type of hydrogen bonding has almost disappeared. Further introductions of  $\text{CH}_2$  groups between OH and  $\text{NH}_2$  only indicate “positive” numerical values that are ascribed to the non-existent intra-HB. The obvious reason for the disappearance of the weak  $\text{NH}\cdots\text{O}$  type of hydrogen bonding of  $\alpha,\omega$ -methoxy-alkylamines and  $\alpha,\omega$ -amino alcohols is that as the  $\text{CH}_2$  groups between OH and  $\text{NH}_2$  increase, the alkyl chain twisting of these molecules increases and for such flexible structures, the formation of the stronger  $\text{OH}\cdots\text{N}$  type of hydrogen bonds is more favourable (the numerical values for the strength of the latter bond are given in Table 4).

#### Vaporization enthalpy as a measure of intra-HB strength in alkoxy-amines

The vaporization enthalpies measured and evaluated in this work (see Table 1) were first used to derive the experimental gas-phase enthalpies of formation (see previous section). However, these results can be used to independently derive intra-HB strength. Indeed, the standard molar enthalpy of vaporization,  $\Delta_v^{\circ} H_m^{\circ}$ , is the energy required to transfer 1 mole of a compound from the liquid to the gas phase. For the purposes of this study, it can be interpreted as the energy required to break up all intermolecular forces in the liquid phase in order to

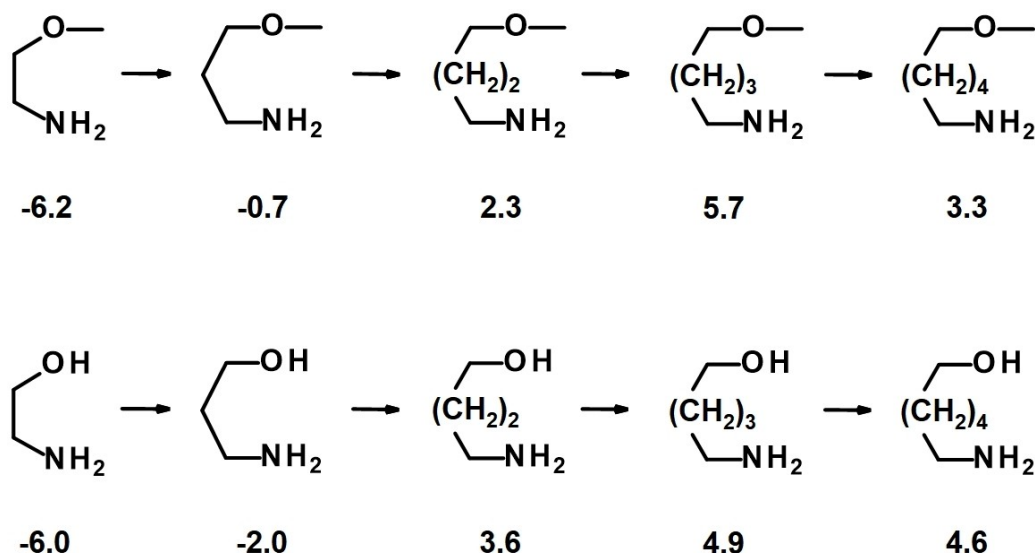


Figure 9. Strength of NH...O hydrogen bonding in  $\alpha,\omega$ -methoxy-alkylamines and  $\alpha,\omega$ -aminoalcohols.

release 1 mole of non-interacting molecules into the gas phase (see Figure 10).

The typical *inter*-molecular forces that must be disrupted to transfer a molecule to the gas phase are *van der Waals* (vdW) forces (including the dipolar interactions) and the hydrogen bonding present in molecular *associated* fluid systems. The specific of the vaporization process of alkoxyamines is that they are able to form the *intra*-HB entering the gas phase (see Figure 10). This peculiarity should be used for the quantification of *intra*-HB in alkoxy-amines as follows. We consider the experimental vaporization enthalpy,  $\Delta_1^g H_m^o(298\text{ K})$ , required to transfer 1 mole of an alkoxy-amine to the gas phase as a sum of

three contributions: the first one ( $\text{HB}_{\text{inter}}$ ) is responsible for the disruption of the *inter*-molecular hydrogen bonding network; the second ( $H_{\text{vdW}}$ ) is necessary to overcome the van-der-Waals attractions of molecules in the liquid phase ( $H_{\text{vdW}}$ ). The molecule released from the liquid phase is immediately bent by *intra*-molecular hydrogen bonding ( $\text{HB}_{\text{intra}}$ ), with the energy gain equal to the *intra*-HB strength. Then, the energetic balance of the vaporization is expressed by equation:

$$\Delta_1^g H_m^o(298\text{ K}) = \text{HB}_{\text{inter}} + H_{\text{vdW}} - \text{HB}_{\text{intra}} \quad (7)$$

The experimental vaporization enthalpies,  $\Delta_1^g H_m^o(298\text{ K})$ , of the alkoxyamines of interest in this work are summarized in Table 1. The contribution  $\text{HB}_{\text{inter}} = 14.0\text{ kJ mol}^{-1}$  was assumed to be a reasonable average value given as a measure for the *inter*-molecular hydrogen bonding for the systems ( $\text{R-O-CH}_3 + \text{RNH}_2$ ).<sup>[34–36]</sup> The contribution  $H_{\text{vdW}}$ , which is required to derive the desired *intra*-HB strength with help of Equation (7), was based on the molecular simulation results.<sup>[37]</sup> Simond et al.<sup>[37]</sup> separated the vaporization enthalpy for a series of differently structured aminoalcohols in electrostatic contributions and van-der-Waals contributions ( $H_{\text{vdW}}$ ). The latter contributions were adjusted to the alkoxy-amines (see Figure S5) and used in this work for calculation of the *intra*-HB strength (see Table 5, column 3). For example, for 2-methoxy-ethanamine it was made as follows:

$$\text{HB}_{\text{intra}} = \text{HB}_{\text{inter}} + H_{\text{vdW}} - \Delta_1^g H_m^o(298\text{ K}) = 14.0 + 18.3 - 38.4 = -6.1\text{ kJ mol}^{-1} \quad (8)$$

and this result is in very good agreement with the result derived from quantum chemistry (see Table 3, column 5). The  $\text{HB}_{\text{intra}}$  – values for the 3-methoxy-propylamine, 3-ethoxy-propylamine, and 1-methoxy-2-propylamine were derived in the similar way. The numerical results are collected in Table 5.

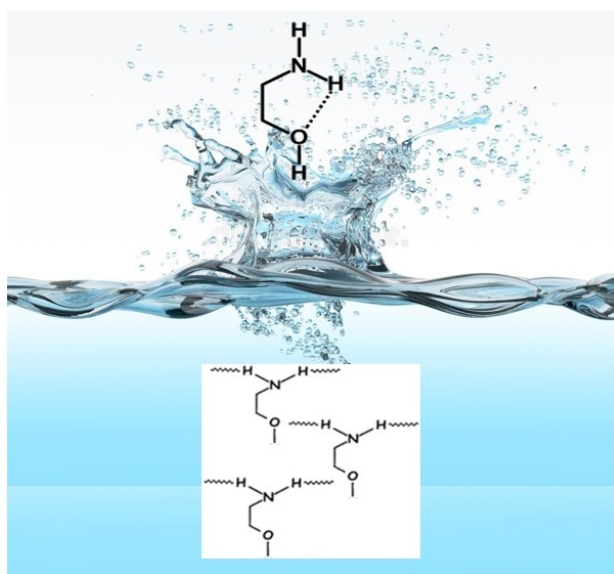


Figure 10. Interpretation of the intra- and inter-hydrogen bonding in alkoxyamines.

**Table 5.** Results for evaluation of the NH...O *intra*-HB strength from experimental vaporization enthalpies (at 298.15 K, in kJ mol<sup>-1</sup>).

Compound	$\Delta_v H_m^{\circ}(\text{exp})^{[a]}$	vdW <sup>[b]</sup>	HB <sub>inter</sub> NH <sub>2</sub> <sup>[c]</sup>	HB <sub>intra</sub> <sup>[d]</sup>
2-methoxy-ethylamine	38.4 ± 0.4	18.3	14.0	-6.1
3-methoxy-propylamine	44.1 ± 0.4	22.8	14.0	-7.3
3-ethoxy-propylamine	47.2 ± 0.8	25.7	14.0	-7.5
1-methoxy-2-propylamine	40.1 ± 0.6	19.7	14.0	-6.4

[a] Experimental vaporization enthalpies from Table 1. Uncertainties are expressed as the twice standard deviations. [b] Contribution for the van-der-Waals attraction forces (see text). [c] Contribution for the *inter*-molecular hydrogen bonding network in alkoxyamines (see text). [d] Strength of the *intra*-molecular hydrogen bonding calculated from Equation (6).

As it can be seen from this table, the *intra*-HB strength in alkoxy-amines of -7.0 kJ mol<sup>-1</sup> represents the general level in series discussed in Figures 4–6.

## Conclusion

In this work, the intramolecular NH...O hydrogen bond strength was determined in three series of aminoalcohols characterized by branching, monoalkylation of the amino group, or increased chain length between the functional groups.

It was observed that moderate tertiary branching at the H-acceptor or at the H-donor side has only a marginal effect on the NH...O hydrogen bond strength in 2-amino-ethanol and 2-methoxy-ethylamine, so that their strength remains in the range of -4 kJ mol<sup>-1</sup> to -6 kJ mol<sup>-1</sup>. This also applies to chain length extension of the branching point up to the butyl rest in 2-amino-1-ethanols (-6 kJ mol<sup>-1</sup>) and their methoxy analogs (-4 kJ mol<sup>-1</sup>). The lower *intra*-HB strength of the methoxy analogs could be explained by the restricted rotational freedom due to the CH<sub>3</sub>-substituent in proximity of the space required for H-bond formation. In the series of branched aminoethanols and 2-methoxy-ethylamines, only quaternary branching leads to a notable reduction to roughly -2 kJ mol<sup>-1</sup> *intra*-HB strength. A decrease in bond strength also occurs in N-methylated aminoethanol and 2-methoxy-ethylamine derivatives, whereas NH...O bonding in these compounds still leads to stabilization of the molecule of -2 kJ mol<sup>-1</sup>.

In the case of 3-amino-1-propanol and 3-methoxy-1-propylamine, it has been shown that the NH...O bond strength is barely strong enough to stabilize the necessary twisting of the alkyl chain. The same conclusion applies to their N-monomethylated derivatives. With increasing chain length in linear  $\alpha,\omega$ -amino alcohols and linear  $\alpha,\omega$ -methoxyalkylamines, destabilization due to alkyl chain twisting increases and cannot be compensated by NH...O hydrogen bonding, so this bonding is also unlikely to occur in these molecules.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that supports the findings of this study are available within the article and its Supporting material.

**Keywords:** enthalpy of formation · enthalpy of vaporization · *intra*-molecular hydrogen bonding · quantum-chemical calculations · structure-property relationships

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