

## COMMUNICATIONS

Chemistry

CHEMOSELECTIVITY OF AMINOMETHYLATION OF  
AMINO- AND ALKOXYETHANOLS IN CHARGE UNITS  
OF GENERAL THEORY OF ACIDS AND BASES

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The evidence on the violation of chemoselectivity of aminomethylation of dimethyl- and diethylaminoethanol, which occurs under the influence of hydrogen bond was received. The same hydrogen bond occurs in the oxygen analogues of aminoethanols and  $\beta$ -alkoxyethanols, but contrary to expectations, it is not accompanied by a change in the chemoselectivity of the reaction. We propose a rationale to explain the differences in the properties of these molecules, using charge units of the ionic character of the bond.

**Keywords:** chemoselectivity, aminomethylation, acid of Pauling, base of Pauling.

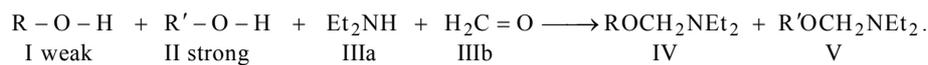
Recently was observed [1] that the aminomethylation of a mixture of dimethyl- (1) and diethylaminoethanols (2) according to Mannich reactions occurs by violation of the laws observed in the homologous series of alkanols [2], i.e. contrary to expectations, the main reaction product is the conversion of the lowest and not the highest member of the pair of alcohols.

Consequently, it is necessary to establish the cause of this change of the reaction direction. Since the solution of this problem based on the principles of modern chemistry is impossible [3–6], we were forced to turn to new views of the generalized theory of acids and bases [7, 8]. The conventional approach proposes that such a drastic change in the properties of molecules 1 and 2 could be caused only by a change in the donor strength of amine nitrogen. For example, it could be due to the emergence of intra- and intermolecular hydrogen bonds as proposed in [1]. If this version adequately describes the real balance of forces, we should expect the same dependence in methoxy, ethoxy and butoxyethanols (3–5), which are oxygen analogues of 1 and 2. However, contrary to expectations, in these esters we find only chemoselectivity of alkanols [2] and not of aminoethanols [1], as if in the row of alkoxyethanols the formation of hydrogen bonds, which explained the change in the reactivity of molecules 1 and 2, does not happen. It has become clear that either the reasoning for the cause of inversion of the chemoselectivity of molecules 1 and 2 is not true, or there is another point of view, which has eluded the attention [1].

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However, further experiments completely eliminate this doubt (Sch. 1). They show that the formation of hydrogen bonds also occurs with alkoxyethanols, although not with the same chemical effects (the selectivity inversion), as observed in molecules 1 and 2.



Scheme 1.

*Regiochemistry of aminomethylation of the mixture of alkoxy- and dialkylaminoethanols*

Serial number of alcohol ROH, I (weak acid of Pauling)*	Serial number of alcohol R'OH, II (strong acid of Pauling)	Ratio IV:V (yield in %)
1. Me <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> OH	2. Et <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> OH	55:45 (73)
3. CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	4. C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	**
3. CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	5. C <sub>4</sub> H <sub>9</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	20:80 (73.5)
3. CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	6. CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH	31:69 (65)
2. Et <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> OH	3. CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	79:21 (56)
2. Et <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> OH	4. C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	**
1. Me <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> OH	3. CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	68:32 (82.6)
1. Me <sub>2</sub> NCH <sub>2</sub> CH <sub>2</sub> OH	7. Me <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> OH	33:67 (54)
4. C <sub>2</sub> H <sub>5</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	8. C <sub>3</sub> H <sub>7</sub> CH <sub>2</sub> CH <sub>2</sub> OH	36:64 (56)

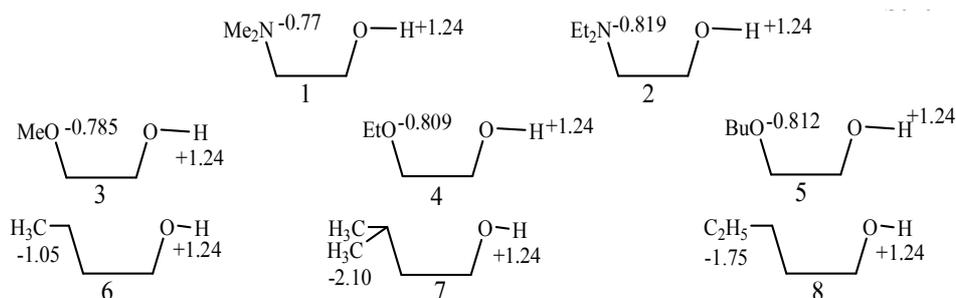
\* For the quantitative characterization of the charge of atoms of these molecules (see Sch. 2).

\*\* Reaction does not happen, intra- and intermolecular hydrogen bonds are formed.

If the molecules 1–5 for some reason do not form hydrogen bonds or lose them during the reaction, then this should have reflected the ratios of formed esters. For example, in competitive reactions, involving alkanols: butanol (6), iso-pentanol (7) and pentanol (8), they should lead to nearly equal mixture of Mannich, bases IV and V. However, as can be seen from the Sch. 1, this does not occur, and apparently not without a reason. Most likely, the reason of this is the emergence of a hydrogen bond, which stays until the moment of conversion of the starting molecules into Mannich bases. The problem is further complicated by the fact that under these conditions the mixture of methoxy and ethoxyethanols (3 and 4) and diethylaminoethanol (2 and 4) are not involved in the reaction of aminomethylation. More precisely, they react individually or in a mixture with other alcohols, but not together in the reaction mixture.

In order to find an electronic cause of this phenomenon, we have once again turned to the evaluation of the charging power of the atoms β-dialkylamino and β-alkoxyethanols 1–5 [7, 8], simplifying it significantly. The essence of it is the evaluation of the charging powers of the atoms only in fragments which contain the atoms of the proposed hydrogen bond. These are the hydrogen atoms of hydroxyl groups (with a charge equal to +1.24 in charge units of ionic character, u.i.c.) and atoms of nitrogen and oxygen in β-dialkylamino and alkoxy groups (in Sch. 2, they are provided with values of the charges, also in u.i.c.). In other words, in hydroxy groups fragments of molecules only the ionic nature of O–H is taken into account and in the fragments of amino and alkoxy groups only the charge powers (values of negative charges) of nitrogen in β-dialkylamino (R<sub>2</sub>N) and oxygen in (RO) groups are taken into account (Sch. 2). The approach is based on the assumption,

according to which the atoms two-carbon system, which links two “peripheral” fragments of molecules 1–8, plays the role of a conductor (or semiconductor) of charging powers of atoms.



Scheme 2.

1.  $AF(N)_{Me} = +0.77$ ;  $DF(N)_{Me} = -0.77$ ; 2.  $AF(N)_{Et} = +0.819$ ;  $D\ 1-2\ DF(N)_{Me/Et} = 0.049$ ; 3.  $AF(O)_{Me} = +0.785$ ;  $DF(O)_{Me} = -0.785$ ; 4.  $AF(O)_{Et} = +0.8095$ ;  $DF(O)_{Et} = -0.8095$ ;  $D\ 3-4\ DF(O)_{Me/Et} = -0.0245$ ; 5.  $AF(O)_{Bu} = +0.812195$ ;  $DF(O)_{Bu} = -0.812195$ ;  $D\ 3-5\ DF(O)_{Me/Bu} = -0.027195$ ;  $D\ 4-5\ DF(O)_{Et/Bu} = -0.002695$ ;  $AF(O)_H = +1.24$ ;  $DF(O)_{OH} = -1.24$ ; 6.  $DF(C)_{Me} = -1.05$ ; 7.  $DF(C)_{2Me} = -2.10$ ; 8.  $DF(C)_{Et} = -1.75$  (u.i.c.).

The task is more simplified, if we note that the same role of a conductor (or semiconductor) of charging power of the peripheral carbon atoms plays the amine nitrogen and ester oxygen in molecules 1–5. At the same time we observe that the atoms of nitrogen and oxygen, although they are conductors of charging power, they conduct not the negative but the positive charges, which arise on  $\alpha$ -carbon atoms of the “peripheral” alkyl group under the influence of the same heteroatoms of the fragment. In addition, it should be said that a heteroatom on the associated carbon atom induces positive charges and decreases the strength of the donor substituent compared with the same groups in their hydrocarbon analogs.

After this clarification it becomes apparent (Sch. 2) that the greater the donor force (amount of charge) of amine nitrogen and ester oxygen (i.e., magnitude of positive charges on the “peripheral”  $\alpha$ -methyl and  $\alpha$ -ethyl carbon atoms), the stronger Pauling acid (in this case a proton acid of Pauling) molecule becomes. Therefore, the compounds 1–8, as O–H Pauling acids, constitute an acidity series ( $1 < 3 < 4 < 5 < 2 < 6 < 8 < 7$ ), wherein the superiority of acid 7 is undeniable.

Comparison of the charging power of molecule fragments 1–8 with the data of chemoselectivity of aminomethylation of their mixtures revealed facts (Sch. 2), which shed light both on the relative reactivity of aminoethanols 1 and 2, and alkoxyethanols 3–5. It became clear after detecting differences in charging powers of key atoms of methyl and ethyl fragments of molecules 1 and 2 (0.049 u.i.c.) and their oxygen analogues (0.0245 u.i.c.). Such a contrast of atoms suggests not just a certain difference in the strength of donor forces of heteroatoms, but also an effective response to the behavior of molecules of two series [7, 8]. As a result, there was a need to look at another aspect of the generalized theory of acids and bases. According to this theory, any donor-acceptor interaction is also a redox process, and the extent of the transfer of the electron density depends on the values of charging power of contacting atoms.

**Experimental Part.** PMR spectrum was recorded on the spectrometer Mercury-300 Varian with a 300 MHz operating frequency on protons in solution DMSO-*d*<sub>4</sub>-CCl<sub>4</sub> (1: 3), internal standard is TMS.

**Diethylaminomethylation of 2-Metoxyethanol by Mannich.** A mixture of 1.5 g (0.05 mol) of paraformaldehyde, 3.8 g (0.05 mol) of 2-metoxyethanol and 3.7 g (0.05 mol) of diethylamine was left to stand at a temperature of 14°C overnight and heated on a steam bath for 1.5 h. After distilling off low-boiling fractions by distillation of 4.8 g (60%) of product was isolated with b.p. 55–56°C at 6 mm Hg column, *n*<sub>D</sub><sup>20</sup> 1.4265. <sup>1</sup>H NMR, δ, ppm (DMSO-*d*<sub>6</sub>): 1.08 t (6H, CH<sub>3</sub>, *J* = 7.6 Hz); 2.32 k (4H, NCH<sub>2</sub>, *J* = 7.6 Hz); 3.28 s (3H, OCH<sub>3</sub>); 3.42t (4H, OCH<sub>2</sub>, *J* = 7.6 Hz); 4.12 c (2H, OCH<sub>2</sub>N).

**Diethylaminomethylation of 2-Etoxyethanol by Mannich.** A mixture of 1.5 g (0.05 mol) of paraformaldehyde, 3.8 g (0.05 mol) of 2-etoxyethanol and 3.7 g (0.05 mol) of diethylamine was left to stand at a temperature of 14°C overnight and heated on a steam bath for 1.5 h. After distilling off low-boiling fractions by distillation of 42.1 g (48.3%) of product was isolated with b.p. 85–88°C at 16 mm Hg column, *n*<sub>D</sub><sup>20</sup> 1.4294. <sup>1</sup>H NMR, δ, ppm (DMSO-*d*<sub>6</sub>): 1.08 t (6H, CH<sub>3</sub>, *J* = 7.6 Hz); 2.32 k (4H, NCH<sub>2</sub>, *J* = 7.6 Hz); 3.28 s (3H, OCH<sub>3</sub>); 3.42 t (4H, OCH<sub>2</sub>, *J* = 7.6 Hz); 4.12 c (2H, OCH<sub>2</sub>N).

**Diethylaminomethylation of the Mixture of 2-Alkoxyethanols and Alkanols by Mannich.** The reaction and isolation of the transformation products was carried out similarly as described above. A mixture of 0.9 g (0.03 mol) of paraformaldehyde and 0.03 mol of 2-dialkylaminoethanols (2-alkanol or alkoxyethanol) was added to 2.2 g (0.03 mol) of diethylamine and left to stand at a temperature of 14°C overnight and heated on a steam bath for 1.5 h. After distillation of low-boiling fractions by vacuum distillation the high-boiling fraction was isolated, without separating it into fractions. The overall yield is 49–83%. The ratios of reaction products were determined by distinctive signs of integrals PMR protons of mixtures of molecules.

Yields of mixtures of amines and their ratios are recorded in Table.

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