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Theoretical study of azido *gauche* effect and its origin

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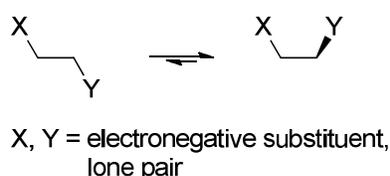
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Abstract

The strength of the azido *gauche* effect in 1,2-diazidoethane, *N*-(2-azidoethyl)ethanamide, (protonated) 2-azidoethanamine and (protonated) 2-azidoethanol, and its origin were studied theoretically at the MP2/6-311++G(d,p) level of theory. The results show that the azido *gauche* effect in amine and alcohol can perform a control over molecular conformation to the similar extent as the fluorine *gauche* effect, but to greater extent in charged species, amide and vicinal diazido-fragment. A quantitative partitioning of isomerization energy into contributions from electrostatic, orbital, dispersion and Pauli interactions, and energy spent on structural changes revealed that electrostatic forces play important role in *gauche* isomer stabilization in two charged species and alcohol. Electrostatic interactions and dispersion are main contributors to the *gauche* effect in amide, while dispersion and orbital interactions can be considered as the two most important stabilizing effects of *gauche* forms in vicinal diazido fragment. The interplay of all three stabilizing interactions determines *gauche* preference in amine. Stereoelectronic effects, involved in orbital interactions, contribute to the *gauche* effect in all molecules except 2-azidoethylammonium ion and protonated 2-azidoethanol. Hydrogen-bonding interaction was found only in protonated alcohol.

Introduction

The *gauche* effect is a counterintuitive preference for *gauche* over the *anti* form when two electronegative substituents, or lone pairs, occupy vicinal position (Scheme 1).¹ It is well known for 1,2-difluoroethane ($X = Y = F$)² and other organofluorine compounds containing the second row elements such as oxygen and nitrogen ($X = F, Y = O, N$),³ and is recently reported for the third row element such as sulfur ($X = F, Y = S$).⁴ The fluorine *gauche* effect determines the conformation of small molecules,¹⁻⁵ drugs⁶ and large molecules such as 9,10-difluorostearic acid,⁷ peptides and proteins.⁸ This fluorine conformational bias has also found useful synthetic applications.⁹



Scheme 1. The *gauche* effect.

The origin of fluorine *gauche* effect has been extensively studied by theoretical chemists and has been ascribed to $\sigma_{C-H} \rightarrow \sigma_{C-F}^*$ hyperconjugative stabilization,^{2a,d-f,3d,e,5,10} the C–C bond bending caused by fluorine's high electronegativity^{2c} and electrostatic stabilization involving fluorine and positively, or partially positively charged groups.^{3c,d,f,4,5} Even in 1,2-difluoroethane, electrostatic forces were found to act against our chemical intuition and stabilize *gauche* form more than the *anti* one.^{2g}

A recent work has showed that, apart from fluorine, an azido group, too, tends to orient itself *gauche* to an electronegative substituent in the fragment $N_3-C-C-Y$ ($Y = N, O$).¹¹ This azido *gauche* effect was shown to influence peptide conformation^{11a,b,d,e} and was predicted to be comparable or even stronger than the fluorine *gauche* effect in amides.^{11a} Since azido *gauche* effect is conformation-directing element, understanding its origin is important. To our knowledge, there is only one study on

the origin of *gauche* effect in 1-azido-2-fluoroethane, combining both fluorine and azido *gauche* preferences. It was ascribed to electrostatic attraction between fluorine and the central nitrogen of N_3 group and to stabilizing $\sigma_{C-H} \rightarrow \sigma_{C-F}^*$ and $\sigma_{C-H} \rightarrow \sigma_{C-N}^*$ interactions in *gauche* form.^{3d} Apart from this work, there are only a few reports on conformational behaviour of azido-substituted compounds, and all discuss conformation around the N_3-C bond,¹² not around the $C-C$ bond.

Molecular conformation plays a decisive role in reactivity of molecules and function of biomolecules. Understanding the forces that drive flexible (bio)molecules toward a particular conformation is thus at the heart of chemistry. Such knowledge, in turn, allows one to predict and, therefore, to control molecular conformation. The recent studies disclosing that the azido group can serve as a conformation-directing element, along with a little knowledge about its origin, have prompted us to explore the factors responsible for the azido *gauche* effect. We have theoretically studied 2-azido-1-substituted ethanes (Scheme 1, $X = N_3$, $Y = N_3$, NH_2 , NH_3^+ , OH , OH_2^+ and $NHCOCH_3$) as simple model systems to get an insight into the nature of the effect. The N_3C-CN_3 and $N_3C-CNHCO$ fragments appeared in experimentally studied peptides,^{11a,b,d,e} while the N_3C-CO *gauche* form was found by X-ray analysis for 1-azidoethoxy-2,3,4,6-tetra-*O*-acetyl- β -D-glucoside.^{11c} To our knowledge, there are no reports on conformational behavior of N_3C-CNH_2 containing compounds and we were also intrigued to see the effect of nitrogen and oxygen protonation on conformational preferences (the strong electrostatic F/N^+ *gauche* effect has been found in various acyclic and cyclic compounds^{3c,f,13}). An azido group also presents a function that can be exploited in a variety of chemical transformations.¹⁴

Computational Details

General Remarks

All structures were optimized in the gas-phase at the MP2(full)/6-311++G(d,p) level of theory¹⁵ by using the Gaussian 09 programme package.¹⁶ The gas-phase obtained structures were re-optimized in a solvent (CH₂Cl₂, $\epsilon = 8.9$; DMSO, $\epsilon = 46.8$; H₂O, $\epsilon = 78.4$) by using the integral equation formalism polarizable continuum model (IEFPCM).¹⁷ The nature of a stationary point was confirmed as minima (no imaginary frequency), transition structure (one imaginary frequency), or higher order saddle point (two or more imaginary frequencies) by frequency calculations at the same level. These calculations also provided thermodynamic data such as enthalpy, entropy and Gibbs free energy. When necessary, relative free energies were corrected for entropy of symmetry ($\Delta S_{\text{sym}} = -R \ln \sigma$, where σ is the symmetry number characteristic of the symmetry point group of conformer in question) and for entropy of mixing of an enantiomeric pair in case of chiral conformers ($\Delta S_{\text{mix}} = -R(0.5 \ln 0.5 + 0.5 \ln 0.5) = -R \ln 0.5 = R \ln 2$).

In the case of enantiomeric conformers, only one form was optimized and its data were used, when needed, in place of its enantiomer.

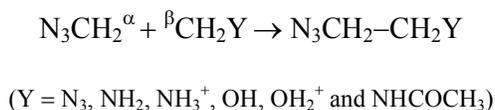
Energy Decomposition Analysis

The importance of various factors to conformational energy was assessed on the basis of energy decomposition analysis (EDA). Thus, isomerization energy (ΔE_{iso}), corresponding to energy change when one conformer rotates into another one, can be decomposed into two main parts, interaction energy change ($\Delta \Delta E_{\text{int}}$) and deformation energy change ($\Delta \Delta E_{\text{def}}$) (Eq. 1).

$$\Delta E_{\text{iso}} = \Delta \Delta E_{\text{int}} + \Delta \Delta E_{\text{def}} \quad (1)$$

The $\Delta \Delta E_{\text{int}}$ corresponds to energy change due to changes in bonding nature coming from electrostatic and orbital interactions, while $\Delta \Delta E_{\text{def}}$ reflects energy change due to structural changes accompanying isomerization. To perform EDA, we have built the studied molecules from two radical fragments,

$\text{N}_3\text{H}_2\text{C}\cdot$ and $\cdot\text{CH}_2\text{Y}$ having opposite spins (α and β superscripts in Scheme 2), so that they can form a molecule.



Scheme 2. Formation of studied compounds from two radicals.

A quantitative decomposition of $\Delta\Delta E_{\text{int}}$ between these two fragments into contributions from various energy terms (Eq. 2) was done by employing the localized molecular orbital energy decomposition analysis (LMOEDA), developed by Su and Li,¹⁸ and implemented in the Gamess progame package.¹⁹

$$\Delta E_{\text{int}} = \Delta E_{\text{elstat}} + \Delta E_{\text{ex}} + \Delta E_{\text{rep}} + \Delta E_{\text{pol}} + \Delta E_{\text{disp}} \quad (2)$$

In the equation, electrostatic energy (ΔE_{elstat}) involves all attractive (nucleus-electron) and repulsive (nucleus-nucleus, electron-electron) electrostatic interactions between the two fragments having geometry and position as in conformer in question. This energy is usually stabilizing (negative energy contribution), because attractive electrostatic forces overcome the repulsive ones. The exchange energy (ΔE_{ex}) refers to the quantum-mechanical exchange between the same-spin electrons and is simultaneously counteracted by the repulsion energy (ΔE_{rep}). Taken together, they form the exchange repulsion²⁰ or Pauli repulsion²¹ of other EDA schemes, which is a destabilizing interaction (positive energy contribution). Herein, we use the sum of ΔE_{ex} and ΔE_{rep} to represent the Pauli repulsion and refer to it as ΔE_{Pauli} . The polarization energy (ΔE_{pol}) is an orbital relaxation energy that account for the bond formation, charge transfer (donor-acceptor interactions between occupied orbitals on one fragment with empty orbitals on the other) and polarization (empty-occupied orbital mixing within one fragment due to the presence of another fragment). Herein, we change the original labeling ΔE_{pol} ¹⁸ into ΔE_{oi} to refer to the all orbital interactions. Dispersion energy (ΔE_{disp}) is available at the DFT and post-HF levels and is associated with electron correlation. Both ΔE_{oi} and ΔE_{disp} are stabilizing

interactions. In the performed conformational analysis, the individual energy changes occurring during the conformational isomerization are expressed as a difference between the corresponding energies of final and starting conformations, and are denoted as $\Delta\Delta E$ values.

The second energy term in Eq. 1 ($\Delta\Delta E_{\text{def}}$) shows energy change due to structural changes within the two fragments that accompany the conformational isomerization. This energy is calculated as a difference between the two fragment ($\text{N}_3\text{H}_2\text{C}\cdot$ and $\cdot\text{CH}_2\text{Y}$) deformation energy in final and starting conformations (Eq 3), where ΔE_{def} represents an energy required to deform an isolated radical fragment from its equilibrium geometry into geometry it has in a conformer in question.

$$\Delta\Delta E_{\text{def}} = [\Delta E_{\text{def}}(\text{CH}_2\text{N}_3) + \Delta E_{\text{def}}(\text{CH}_2\text{Y})]_{\text{final}} - [\Delta E_{\text{def}}(\text{CH}_2\text{N}_3) + \Delta E_{\text{def}}(\text{CH}_2\text{Y})]_{\text{starting}} \quad (3)$$

It should be mentioned that structural changes have an effect on all interaction energy components. They take place in order to achieve a balance between repulsive (Pauli interactions) and attractive (electrostatic, orbital and dispersion) forces such that a molecule attains an energy minimum structure.

The LMOEDA was done in the gas-phase at the same theory level as geometry optimizations, MP2(full)/6-311++G(d,p), by employing the Gamess program package.¹⁹ The LMOEDA was also done with inclusion of solvent (H_2O) in the case of the most stable CC_{anti} and $\text{CC}_{\text{gauche}}$ forms.

Analysis of the interaction energy between two or more radical fragments constituting a molecule has been applied before to study the torsional potential of ethane,^{18,22} butane²³ and group 13-elements ($E = \text{B} - \text{Ti}$),²⁴ *gauche* effect in 1,2-difluoroethane,^{2g} conformational preferences in 1-chloro-2-fluoroethane and (protonated) 2-haloethanol and 2-haloethylamine ($X = \text{F}, \text{Cl}$),^{3f} distortion to the trans-bent geometry in heavier ethylene homologues,²⁵ the isomerization energy of heterocyclic²⁶ and polycyclic²⁷ compounds, the strength of conjugation and hyperconjugation,²⁸ and the nature of covalent bonds.²⁹

Hyperconjugation

Hyperconjugation, that is the stabilizing $\sigma \rightarrow \sigma^*$ orbital interaction, is usually invoked to explain the *gauche* effect.^{2a,d-f,3d,e,5,10} Thus, to extract this kind of interaction from all orbital interactions (ΔE_{oi}) discussed above we have used the second-order perturbation approach in the natural bond orbital (NBO) analysis,³⁰ which offers a way to evaluate energies of all individual delocalizations in a molecule. The second-order interaction energies ($E(2)$) are calculated according to Eq. 4, where q_i represents electron occupancy of bonding orbital, F_{ij} is the Fock matrix element between interacting orbitals and ΔE_{ij} is energy difference between the orbitals.

$$E(2) = -q_i(F_{ij})^2/\Delta E_{ij} \quad (4)$$

We have considered only vicinal hyperconjugative interactions between N_3CH_2 and CH_2Y fragments, because this type of electron delocalization is used as an explanation of *gauche* effect as a stereoelectronic phenomenon. The hyperconjugative energies denoted in tables as "total_{anti}" and "total_{gauche}" were obtained as the sum of six hyperconjugations between the *anti*-related σ -bonds for the former, and as the sum of twelve hyperconjugations between the *gauche*-related σ -bonds for the latter. The hyperconjugative energies denoted as "total" were obtained as the sum of these two.

The hyperconjugation analysis was done at the HF/6-311++G(d,p) level by using the NBO 6.0 version.³¹ The NBO data provided a quantitative measure of hyperconjugative energies, but they are not directly related to ΔE_{oi} obtained from EDA. A note should also be given that the NBO method tends to overestimate delocalization energies.^{22a}

Results and Discussion

In the following analysis, the azido *gauche* effect was studied in two ways: (1) as an energy difference between the $N_3CH_2-CH_2Y_{gauche}$ and the $N_3CH_2-CH_2Y_{anti}$ arrangement while conformations around the N_3-C and $C-Y$ bonds did not change, in the fully optimized structures (for example, *aaa*

→ *aga* conformational isomerization), and (2) as an energy difference between the most stable $\text{N}_3\text{CH}_2\text{-CH}_2\text{Y}_{gauche}$ and the most stable $\text{N}_3\text{CH}_2\text{-CH}_2\text{Y}_{anti}$ forms, involving paths that connect them (for example, *aaa* → *aag* and *aag* → *agg*, or *aaa* → *aga* and *aga* → *agg*, if *aaa* and *agg* were the most stable $\text{N}_3\text{CH}_2\text{-CH}_2\text{Y}_{anti}$ and $\text{N}_3\text{CH}_2\text{-CH}_2\text{Y}_{gauche}$ forms). The names of the compounds are abbreviated as following: DAE (1,2-diazidoethane), 2AEA (2-azidoethanamine), 2AEAH (2-azidoethylammonium cation), 2AE (2-azidoethanol), 2AEH (protonated 2-azidoethanol) and N2AEEA (*N*-(2-Azidoethyl)ethanamide).

Conformations and conformational preferences. The magnitude of the *gauche* effect.

Stable conformations of DAE, 2AEA, 2AEAH, 2AE, 2AEH and N2AEEA are denoted by three letters, where the first one refers to the conformation around the $\text{N}_3\text{-C}$ bond, the middle one describes conformation around the C-C bond and the third letter refers to the conformation around the C-N/O bond (with respect to CC-N/O-: orientation in the case of 2AEA and 2AEH, and with respect to CC-NAc orientation in the case of N2AEEA). For 2AEAH two letters are used, the first one referring to the conformation around the C-C bond and the second one to the conformation around the $\text{N}_3\text{-C}$ bond. The gas-phase stable forms of all compounds are shown in Figures 1, 3, 5, 7, 9 and 11, along with their relative energies and isomerization energies, while structures viable only in solvents are presented in Figure S1. The calculated relative energies (ΔE), enthalpies (ΔH), free energies (ΔG) and free energies corrected for entropy of symmetry and entropy of mixing (ΔG_{corr}) for all compounds, in the gas-phase and in solvents (CH_2Cl_2 , DMSO and H_2O), are given in Tables S1, S4, S7, S10, S13 and S16.

1,2-Diazidoethane ($\text{N}_3\text{CH}_2\text{CH}_2\text{N}_3$)

At the theory level employed, DAE exists as ten energetically distinguishable conformers in all mediums examined (Figure 1). The most stable form in the gas-phase is *gg*⁻*g*, followed by *ag*⁻*g*

($\Delta E/\Delta H/\Delta G = 0.13/0.22/0.39$ kcal/mol) and ggg^- ($\Delta E/\Delta H/\Delta G = 0.26/0.42/1.32$ kcal/mol, Table S1 and Figure 1). In all three forms two azido groups point into the same direction with respect to a C–C–N plane and at least one $C^{\delta+}-N^{\delta-}$ bond dipole is parallel with the oppositely oriented $C-N^{\delta-}=N^{\delta+}=N$ dipole (two such interactions in the most stable gg^-g isomer), as is also shown by the wedge formulas given in Figure 2. In the three less stable CC_{gauche} forms two azido groups point into different (aga), or opposite directions (ggg and agg) relative to a C–C–N plane. In polar solvents such as DMSO and water, gg^-g and ggg^- isomers become almost isoenergetic with respect to ΔE and ΔH , and more stable than ag^-g by up to 0.15 kcal/mol (Table S1). In all solvents, free energy favours ag^-g form, followed by gg^-g (~ 0.3 kcal/mol) and ggg^- (0.83 kcal/mol in CH_2Cl_2 and ~ 0.5 kcal/mol in DMSO and water).

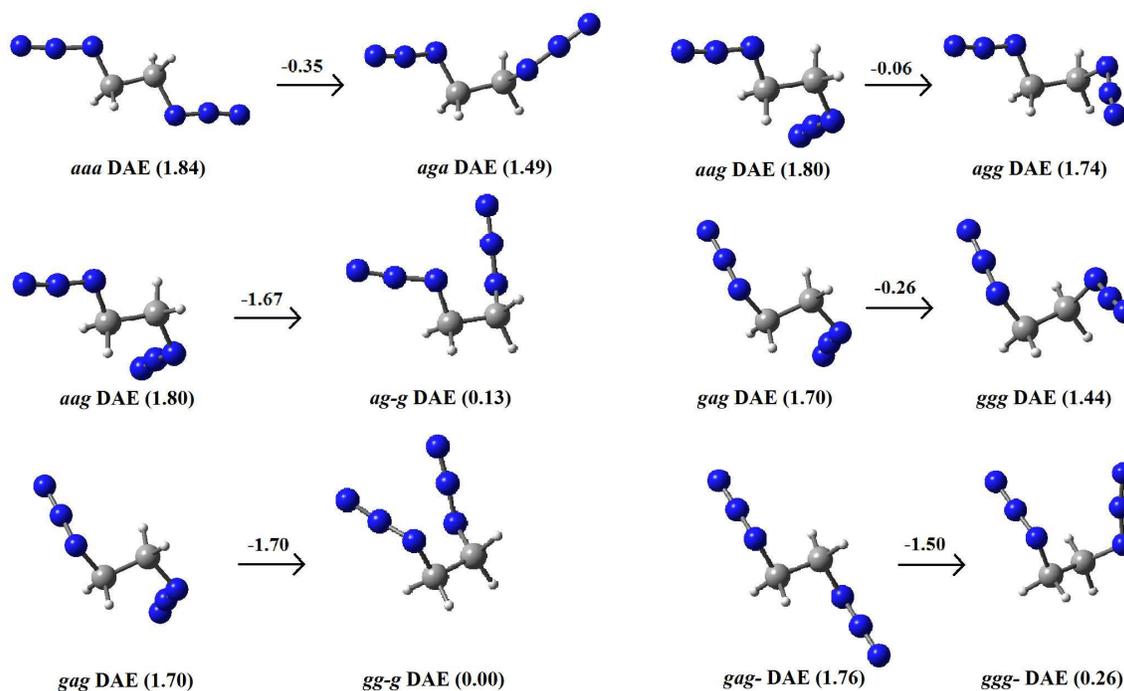


Figure 1. Optimized structures of 1,2-diazidoethane (DAE), their relative energies (ΔE , kcal/mol) in the gas-phase and isomerization energies, calculated at the MP2/6-311++G(d,p) level of theory.

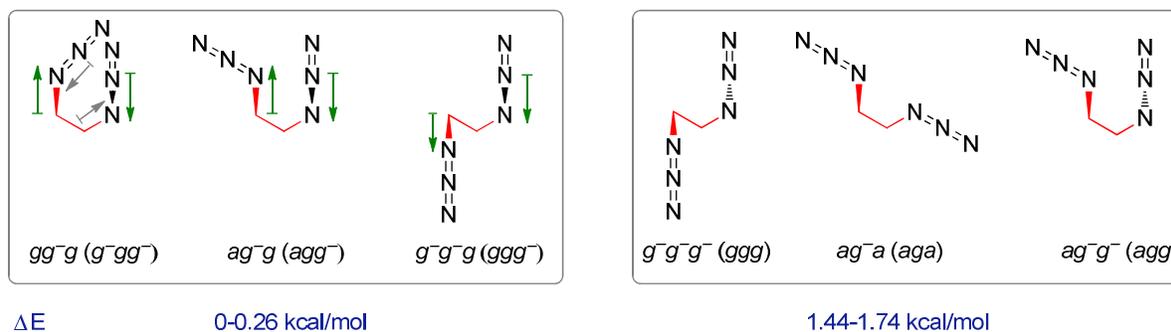


Figure 2. Wedge formulas of CC_{gauche} conformers of 1,2-diazidoethane (enantiomeric forms, which are not shown, are given in brackets), showing that two N_3 groups point into the same direction in the three most stable forms.

As data in Table S1 show, all $CC_{anti} \rightarrow CC_{gauche}$ conformational isomerizations result in the *gauche* effect which ranges from $\Delta E = -0.06$ to -1.70 kcal/mol and $\Delta H = -0.09$ to -1.93 kcal/mol, in the gas-phase. Increasing medium polarity strengthens the effect which reaches values of $\Delta E/\Delta H = -2.08/-2.16$ kcal/mol in water, in the case of $aag \rightarrow ag^-g$ isomerization. Free energies also drop when CC_{anti} form rotates into the CC_{gauche} isomer (except for $aaa \rightarrow aga$ and $aag \rightarrow agg$ in the gas-phase), and their change with increasing medium polarity is not as regular as for ΔE and ΔH .

The *gauche* effect of DAE, calculated as energy difference between the most stable CC_{gauche} and the most stable CC_{anti} forms amounts $\Delta E = -1.70$ kcal/mol in the gas-phase and increases with solvent polarity to $\Delta E = -1.92$ kcal/mol in water. The value in the gas-phase compares with the previously calculated ZPE-corrected value of -1.32 kcal/mol.^{11a} The strength of the *gauche* effect in DAE is more than twice as large as its strength in 1,2-difluoroethane, $\Delta E = -0.77$ kcal/mol, calculated by us at the same theory level.^{3f} As for enthalpy, it amounts $\Delta H = -1.91$ kcal/mol in the gas-phase and is almost the same in all solvents having a value of $\Delta H = \sim 2.04$ kcal/mol. The ΔG_{corr} favours the CC_{gauche} arrangement by $\Delta G_{corr} = -2.06$ kcal/mol in the gas-phase, then increases to $\Delta G_{corr} = -2.20$ kcal/mol in CH_2Cl_2 , but drops to $\Delta G_{corr} = -2.04$ kcal/mol in DMSO and water (Table S1).

2-Azidoethanamine ($\text{N}_3\text{CH}_2\text{CH}_2\text{NH}_2$)

2AEA could be optimized as thirteen forms in the gas-phase and in CH_2Cl_2 , and as fourteen in DMSO and H_2O (Figures 3 and S1). In the first two mediums, optimization of ag^-g form, having lone pair of NH_2 group oriented only toward the partially negatively charged nitrogen of N_3 ($\text{N}=\text{N}=\text{N}^{\delta-}-\text{C}$), converged into the gg^-g conformation, where the same lone pair becomes also near to the partially positively charged middle nitrogen of N_3 ($\text{N}=\text{N}^{\delta+}=\text{N}-\text{C}$).

Data in Table S4 show that, in the gas-phase, relative energies (ΔE) and enthalpies (ΔH) of all CC_{gauche} forms, except ggg^- , fall within 1 kcal/mol (ΔG within 1.4 kcal/mol), which is followed by all CC_{anti} forms, the energies of which range from 1.49-1.93 kcal/mol (ΔE), 1.61-1.87 kcal/mol (ΔH) and 1.49-1.95 kcal/mol (ΔG). The least stable isomer is ggg^- with conformational energy of ≥ 1.99 kcal/mol. The wedge formulas of all nine CC_{gauche} forms are depicted in Figure 4. Thus, the structures in Figure 3 and in Figure 4 show that in CC_{gauche} forms where either H or lone pair from NH_2 group can come in the vicinity of *only one* partially negatively charged nitrogen of N_3 ($\text{N}=\text{N}=\text{N}^{\delta-}-\text{C}$), it is the hydrogen and not the lone pair (aga , agg , Figure 3 and Figure 4a, gga and ggg , Figure 3 and Figure 4b). In all these isomers, the $\text{C}^{\delta+}-\text{N}^{\delta-}=\text{N}=\text{N}$ and $\text{N}^{\delta-}-\text{H}^{\delta+}$ bond dipoles are in an antiparallel orientation, with dihedral angles ranging from 2.3° to 4.8° . In case of gg^-a , gg^-g and gg^-g^- (Figure 3 and Figure 4c), where H or lone pair from NH_2 group come in the vicinity of two nitrogens from N_3 group ($\text{N}=\text{N}^{\delta+}=\text{N}^{\delta-}-\text{C}$), all three forms are stable conformers, the one having lone pair oriented toward the N_3 (gg^-g) is of lowest energy among the three ($\Delta E \sim \Delta H = 0.48$ kcal/mol vs $\Delta E/\Delta H = 0.52/0.57$ kcal/mol for gg^-g^- and $\Delta E \sim \Delta H = 1$ kcal/mol for gg^-a). In this structure, the $\text{C}^{\delta+}-\text{N}^{\delta-}-\text{H}_2$ and $\text{C}-\text{N}^{\delta-}=\text{N}^{\delta+}=\text{N}$ bond dipoles are aligned in an antiparallel fashion, with dihedral angle of 1.8° . The global minimum structure of 2AEA in the gas-phase is agg form. All solvents favour gg^-g structure as the most stable with respect to ΔE and ΔH , while agg is thermodynamically most favoured in all mediums examined.

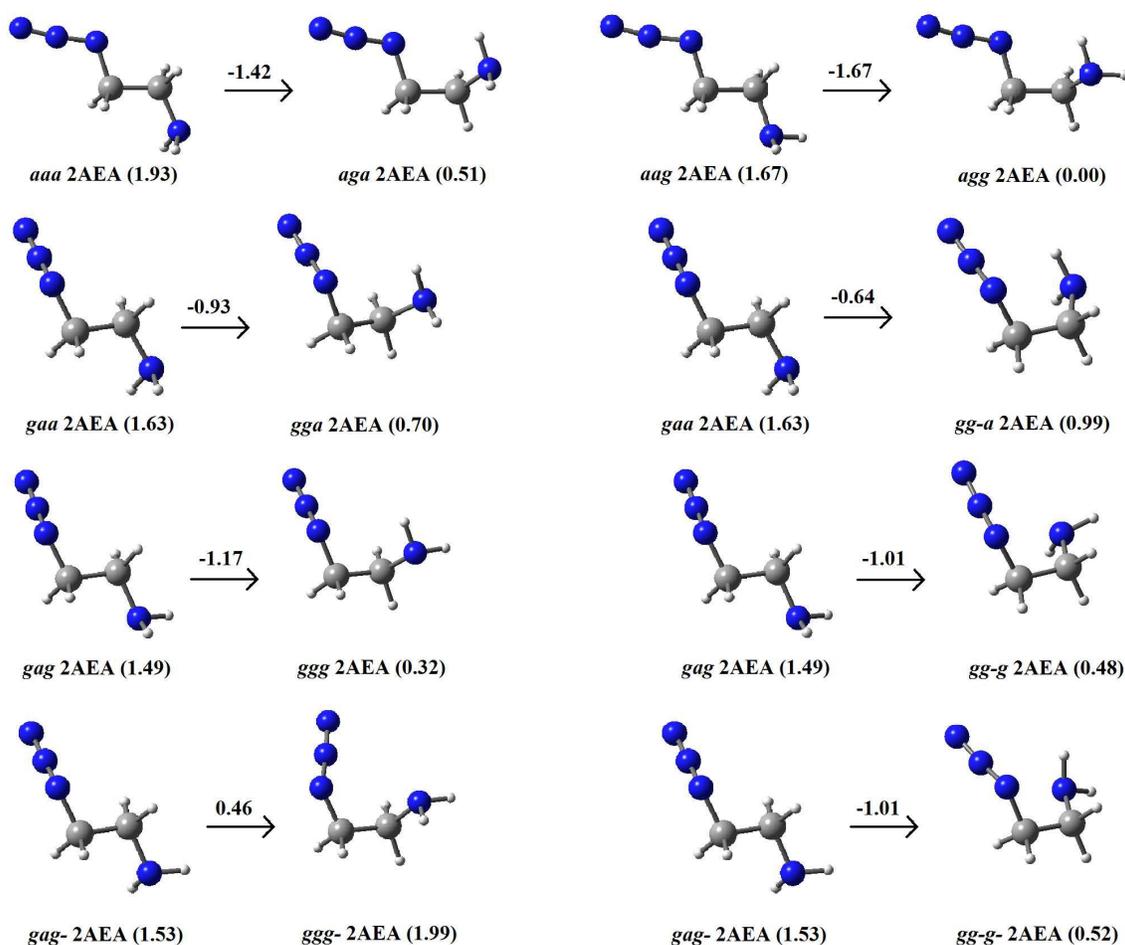


Figure 3. Optimized structures of 2-azidoethanamine (2AEA), their relative energies (ΔE , kcal/mol) in the gas-phase and isomerization energies, calculated at the MP2/6-311++G(d,p) level of theory.

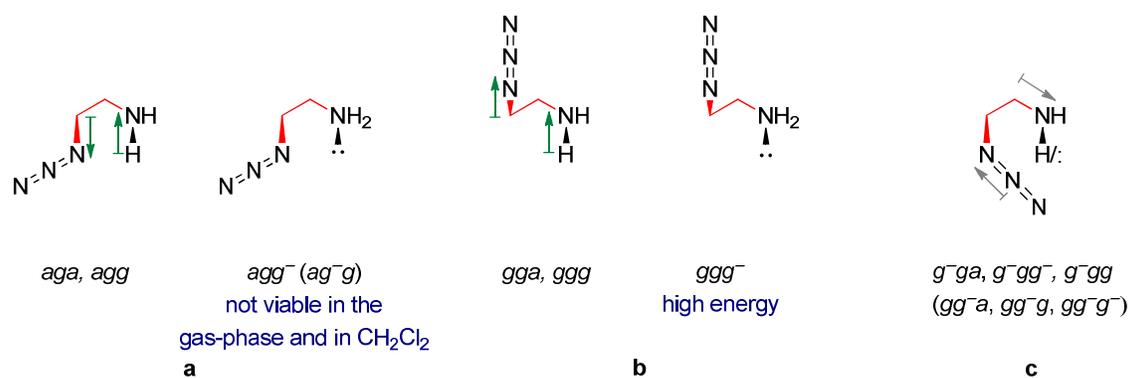


Figure 4. Wedge formulas of CC_{gauche} conformers of 2-azidoethanamine (enantiomeric forms of those shown are given in brackets).

An inspection of Table S4 shows that, in the gas-phase, all conformational isomerizations except one ($gag^- \rightarrow ggg^-$) exhibit *gauche* effect ranging from $\Delta E/\Delta H/\Delta G = -0.64/-0.70/-0.52$ to $-1.67/-1.69/-1.49$ kcal/mol. Calculated as an energy difference between the most stable CC_{gauche} (agg) and CC_{anti} (gag) forms, the 2AEA *gauche* effect amounts $\Delta E/\Delta H/\Delta G_{corr} = -1.49/-1.61/-1.49$ kcal/mol, and is thus slightly weaker than the *gauche* effect in 1,2-diazidoethane, $\Delta E/\Delta H/\Delta G_{corr} = -1.70/-1.91/-2.06$ kcal/mol.

Inclusion of solvents makes all $CC_{anti} \rightarrow CC_{gauche}$ isomerizations energetically favourable, the energies of majority of them weaken with increasing solvent polarity. In case of the most stable CC_{gauche} and CC_{anti} structures, the *gauche* effect amounts $\Delta E/\Delta H/\Delta G_{corr} = -0.86/-0.93/-1.10$ kcal/mol in CH_2Cl_2 , $\Delta E/\Delta H/\Delta G_{corr} = -0.82/-0.89/-0.93$ kcal/mol in DMSO and $\Delta E/\Delta H/\Delta G_{corr} = -0.82/-0.89/-0.91$ kcal/mol in water. According to our previous calculations on *gauche* effect in 2-fluoroethanamine (2FEA) at the same theory level,^{3f} substitution of fluorine by azido group has a little influence on the magnitude of the *gauche* effect ($\Delta E = -1.40/-1.49$ kcal/mol for 2FEA/2AEA, in the gas-phase). We are unaware of any previous experimental or theoretical evaluation of the strength of the N_3/NH_2 *gauche* effect.

2-Azidoethylammonium ion ($N_3CH_2CH_2NH_3^+$)

In the case of 2AEA^H, only three forms (out of five) are viable in the gas-phase and four in solvents, while optimization of gg^- structure ended in *ga* one, in all mediums (Figures 5 and S1). The most stable form of 2AEA^H is *ga* in which the $C^{\delta+}-N^{\delta-}=N=N$ and $H_2N^{\delta-}-H^{\delta+}$ bond dipoles attain an antiparallel orientation with dihedral angle of 1.2° , while the partially positive middle nitrogen of N_3 stays away (N_3-C *anti* conformation, Figures 5 and 6).

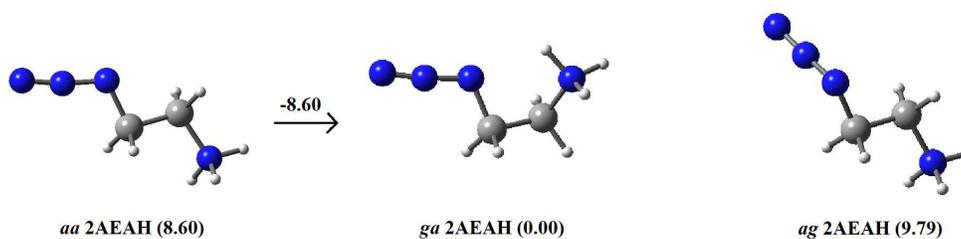


Figure 5. Optimized structures of 2-azidoethylammonium cation (2AEAH), their relative energies (ΔE , kcal/mol) in the gas-phase and isomerization energy, calculated at the MP2/6-311++G(d,p) level of theory.

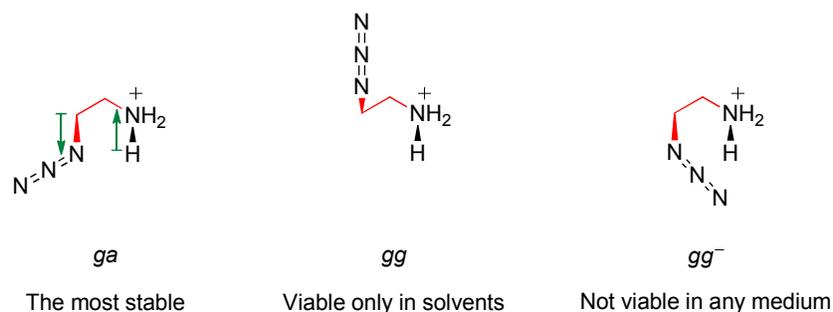


Figure 6. Wedge formulas of CC_{gauche} conformers of 2-azidoethylammonium cation.

The most stable CC_{anti} form, aa , is by as much as 8.60 kcal/mol higher in energy, in the gas-phase. This gas-phase *gauche* effect is significantly stronger than in neutral amine, where it amounts $\Delta E = -1.49$ kcal/mol, and is even larger than that in 2-fluoroethylammonium cation (2FEAH) by 1.76 kcal/mol ($\Delta E = -6.84$ kcal/mol for 2FEAH).^{3f} Thus, while protonation of 2-fluoroethanamine increases the strength of the *gauche* effect by 5.44 kcal/mol, protonation of 2-azidoethanamine leads to an increase in the *gauche* effect by 7.11 kcal/mol. An increasing medium polarity reduces the magnitude of the N_3/NH_3^+ *gauche* effect to $\Delta E/\Delta H/\Delta G = -3.58/-3.38/-3.24$ in CH_2Cl_2 , $\Delta E/\Delta H/\Delta G = -2.97/-3.21/-3.11$ in DMSO and $\Delta E/\Delta H/\Delta G = -2.91/-3.14/-3.08$ in water, but renders it still quite large.

2-Azidoethanol ($N_3CH_2CH_2OH$)

Among fourteen possible forms of 2AE, thirteen are viable in both gas-phase and in solvents (Figures 7 and S1). The *aga* form, not viable in the gas-phase, could be optimized in all solvents

considered, while optimization of gg^-g form in solvents converged into the more stable gg^-a isomer. As data in Figure 7 and Table S10 show, the three most stable forms of 2AE (ag^-g , ggg^- and gg^-a) all have *gauche* conformation around the CC bond and differ in energy by ≤ 0.7 kcal/mol (ΔE and ΔH) and ≤ 1 kcal/mol (ΔG), in the gas-phase (the free energy actually slightly favours gg^-g with respect to ggg^-). The first two isomers have an almost antiparallel orientation of the two $C^{\delta+}-N^{\delta-}=N=N$ and $O^{\delta-}-H^{\delta+}$ bond dipoles, with dihedral angles of 5.1° and 6.6° , respectively (Figure 7 and Figure 8a,b). In the third one, the $C^{\delta+}-O^{\delta-}$ and $N^{\delta-}=N^{\delta+}=N$ dipoles are positioned in an antiparallel way (dihedral angle = 1.2°), while oxygen lone pair and N_3 group are *syn*-oriented with respect to the C–C–O plane (Figure 7 and Figure 8c). As EDA data in Table S11 show, this orientation is favoured by larger dispersion interactions and weaker Pauli repulsion compared with gg^-g (hydrogen *syn* with N_3 , Figure 7 and Figure 8c) and gg^-g^- (lone pair *syn* with N_3 , Figure 7 and Figure 8c). Other CC_{gauche} forms are by 1.4-3.4 kcal/mol (ΔE), 1.3-3.3 kcal/mol (ΔH) and 1.9-3 kcal/mol (ΔG) higher in energy.

The conformational energy of the most stable CC_{anti} isomer is $\Delta E/\Delta H/\Delta G = 2.39/2.36/1.24$ kcal/mol, which represents the amount of the gas-phase *gauche* effect in 2-azidoethanol. It is larger than the *gauche* effect in 2-azidoethanamine ($\Delta E/\Delta H = -1.49/-1.61$ kcal/mol), but slightly weaker with respect to $\Delta G_{corr} = -1.49$ kcal/mol. In addition, it is similar in magnitude to the *gauche* effect in 2-fluoroethanol ($\Delta E = -2.30$ kcal/mol).^{3f} Data in Table S10 also show that those isomerizations leading to high energy CC_{gauche} forms (≥ 2.7 kcal/mol, *agg*, *gga* and *ggg*) do not result in *gauche* effect.

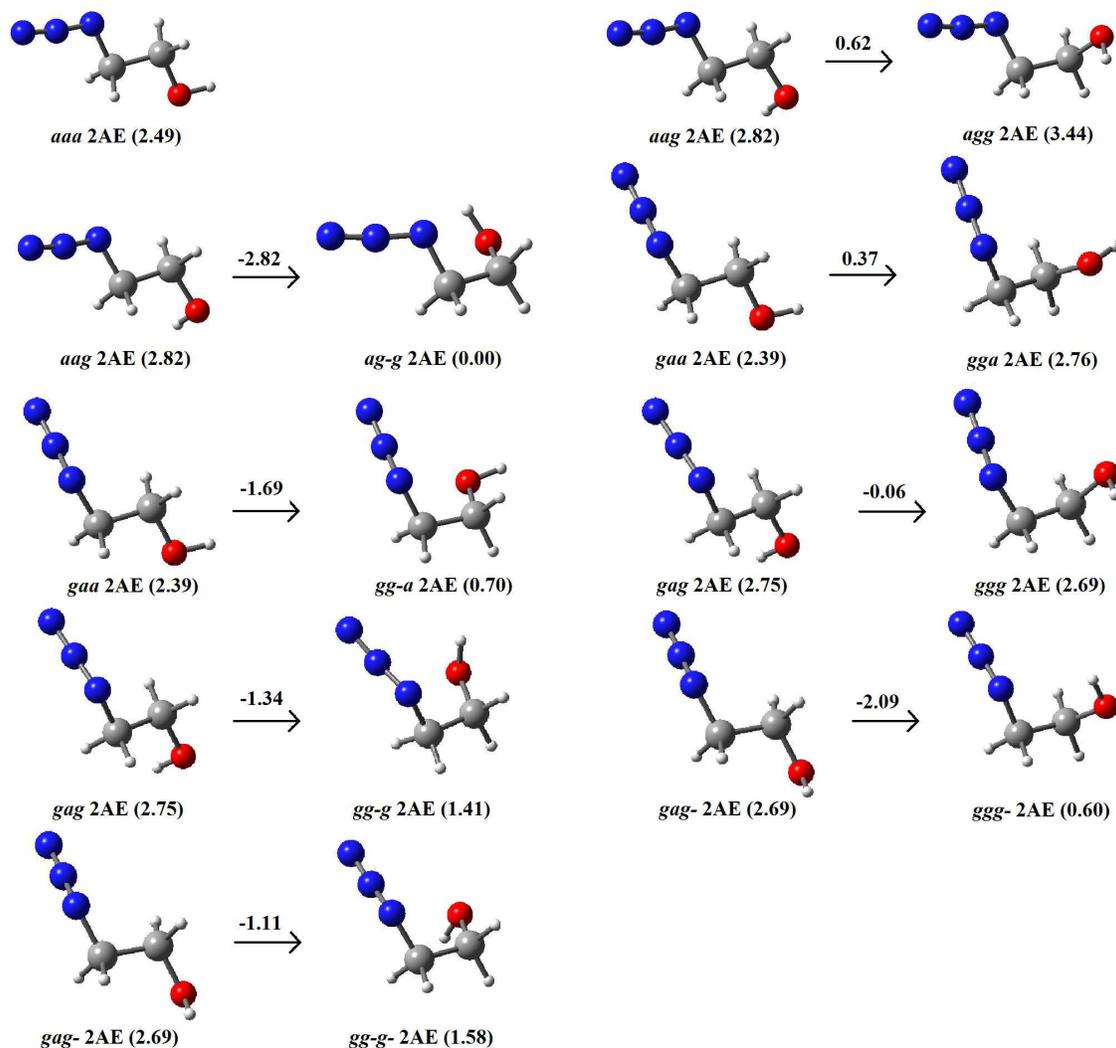


Figure 7. Optimized structures of 2-azidoethanol (2AE), their relative energies (ΔE , kcal/mol) in the gas-phase and isomerization energies, calculated at the MP2/6-311++G(d,p) level of theory.

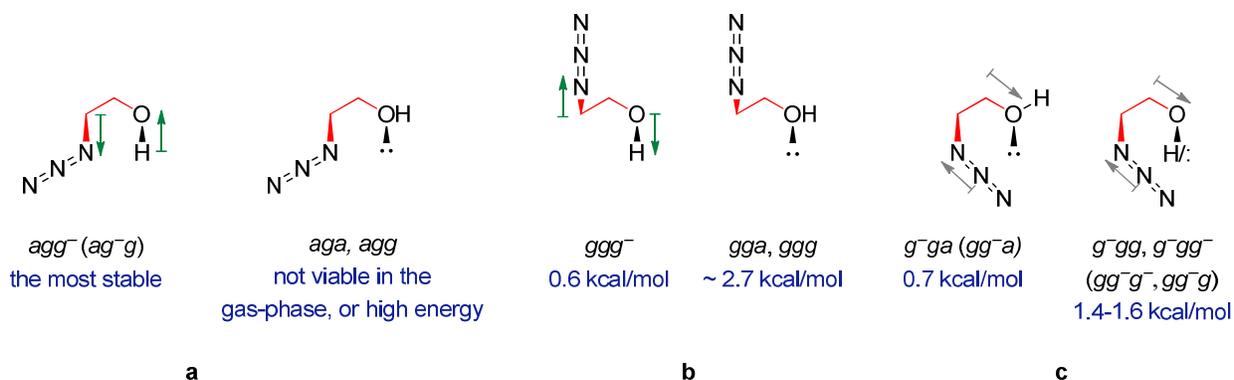


Figure 8. Wedge formulas of CC_{gauche} conformers of 2-azidoethanol (enantiomeric forms of those shown are given in brackets) and their respective ΔE values.

Transferring of the two most stable CC_{gauche} and CC_{anti} forms into solvent conditions slightly reduces the strength of *gauche* preference, from $\Delta E = -2.39$ kcal/mol to $\Delta E = -1.93/-1.85/-1.84$ kcal/mol in CH_2Cl_2 /DMSO/water, from $\Delta H = -2.36$ kcal/mol to $\Delta H \sim 2$ kcal/mol in all solvents, and from $\Delta G = -1.24$ kcal/mol to $\Delta G = -1.13$ kcal/mol in CH_2Cl_2 , while it is similar in polar DMSO and water, $\Delta G = -1.20$ kcal/mol. In solvent conditions, all individual $CC_{anti} \rightarrow CC_{gauche}$ rotations show *gauche* effect which can increase or decrease with increasing solvent polarity, depending on a particular isomerization. It ranges from $\Delta E/\Delta H/\Delta G = -0.46/-0.58/-0.37$ to $-2.13/-2.21/-1.78$ in CH_2Cl_2 , $\Delta E/\Delta H/\Delta G = -0.72/-0.74/-0.56$ to $-2.03/-2.07/-1.62$ in DMSO and $\Delta E/\Delta H/\Delta G = -0.75/-0.76/-0.59$ to $-2.04/-2.06/-1.60$ in water. To the best of our knowledge this is the first estimation of the strength of N_3/OH *gauche* effect.

Protonated 2-azidoethanol ($N_3CH_2CH_2OH_2^+$)

2AEH could be optimized as only four conformers in the gas-phase (two CC_{anti} and two CC_{gauche}) and as twelve, under the solvent conditions (Figures 9 and S1). As can be seen in Figure 9, the two most stable forms of 2AEH (*aga* and *agg*) have one of OH_2^+ hydrogens oriented toward partially negatively charged nitrogen of N_3 group ($N=N=N^{\delta-}-C$), with *anti* conformation around the C–N bond. The CC_{anti} isomers are significantly higher in energy, showing an enormous gas-phase *gauche* effect of 12.73 kcal/mol (energy difference between the most stable CC_{gauche} and CC_{anti} forms). As a comparison, the *gauche* effect in protonated 2-fluoroethanol (2FEH), considered as the largest calculated value, amounts 7.2 kcal/mol^{3c} and 8.23 kcal/mol.^{3f} Thus, the effect of protonation of oxygen beta to an azido group enhances *gauche* preference by as much as 10.34 kcal/mol, which is

almost double than the increase of the *gauche* preference when oxygen beta to fluorine is protonated (5.93 kcal/mol).^{3f}

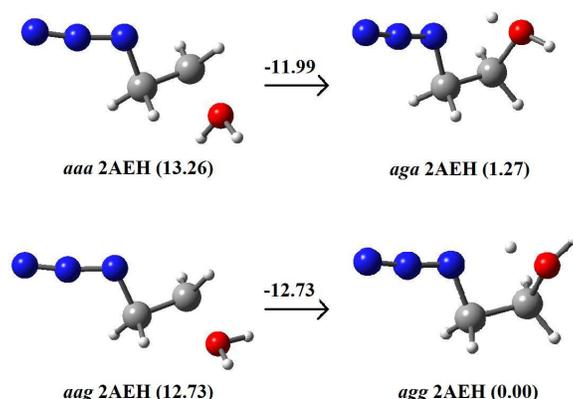


Figure 9. Optimized structures of protonated 2-azidoethanol (2AEH), their relative energies (ΔE , kcal/mol) in the gas-phase and isomerization energies, calculated at the MP2/6-311++G(d,p) level of theory.

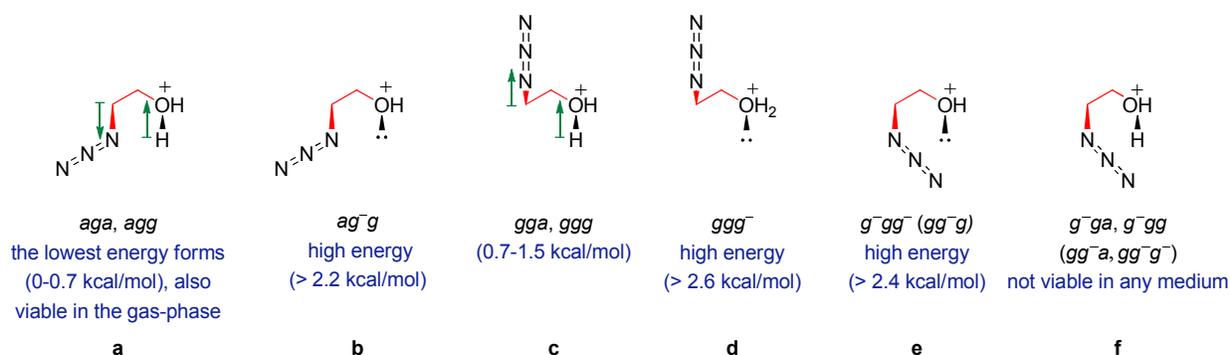


Figure 10. Wedge formulas of CC_{gauche} forms of protonated 2-azidoethanol (enantiomeric forms of those shown are given in brackets) and their respective ΔE values under solvent conditions (the lowest energy value refers to water and the highest energy value refers to CH_2Cl_2).

In solvent conditions, all but two CC_{gauche} forms (gg^-a and gg^-g^- , having O-H and N_3 too close to each other) could be optimized (Figure S1). Increasing solvent polarity decreases relative energy of all isomers of 2AEH (Table S13). The wedge formulas of all possible CC_{gauche} forms are shown in Figure 10, along with the range of their relative energies (ΔE) calculated in solvents (the lowest and the highest energy values for all solvents are given, that is, water for the former and CH_2Cl_2 for the latter). With respect to ΔE and ΔH (Table S13), the most stable structure of 2AEH is *agg* in all

mediums, followed by *aga* (0.6-1.4 kcal/mol, in all mediums), *ggg* (0.7-1 kcal/mol, in all mediums) and *gga* (1.3-1.7 kcal/mol, in all mediums). Free energy, however, favours *ggg* over *aga*. The common feature of all four structures is OH_2^+ hydrogen oriented only toward the negatively charged nitrogen of N_3 ($\text{N}=\text{N}=\text{N}^{\delta-}-\text{C}$), as depicted in Figure 10, structures **a** and **c** (dihedral angles between the two oppositely oriented O–H and C–N bond dipoles vary from 2° to 13°). All forms having oxygen lone pair oriented toward the azido group are of high energy (> 2.2 kcal/mol, structures **b**, **d** and **e**), while those in which hydrogen points toward two nitrogens of azido group (gg^-a and gg^-g^- , structure **f**) are not viable in any medium.

All CC_{anti} forms are, by at least 4 kcal/mol higher in energy (ΔE , ΔH and ΔG) in solvents. Thus, inclusion of solvents into calculations reduces the magnitude of the *gauche* effect from $\Delta E/\Delta H/\Delta G = -12.73/-13.60/-12.16$ kcal/mol in the gas-phase to $\Delta E/\Delta H/\Delta G = -5.48/-5.95/-5.29$ kcal/mol in CH_2Cl_2 , $\Delta E/\Delta H/\Delta G = -4.43/-4.83/-4.17$ kcal/mol in DMSO and $\Delta E/\Delta H/\Delta G = -4.33/-4.71/-4.12$ kcal/mol in water. Even though, it is still quite large and larger than that in 2-azidoethylammonium cation ($\Delta E/\Delta H/\Delta G = -2.91/-3.14/-3.08$ kcal/mol in water). In addition, all kinds of conformational isomerizations are followed by the *gauche* effect, the strength of which ranges from $\Delta E/\Delta H/\Delta G = -4.28/-4.67/-4.30$ to $-5.48/-5.95/-5.54$ kcal/mol in CH_2Cl_2 , $\Delta E/\Delta H/\Delta G = -3.40/-3.61/-3.48$ to $-4.57/-4.97/-4.39$ kcal/mol in DMSO and $\Delta E/\Delta H/\Delta G = -3.31/-3.56/-3.06$ to $-4.48/-4.89/-4.33$ kcal/mol in water, taking into account only those isomerizations that lead to low energy conformers (< 2 kcal/mol).

***N*-(2-Azidoethyl)ethanamide ($\text{N}_3\text{CH}_2\text{CH}_2\text{NHAc}$)**

The amide-containing N2AEEA exists as nine stable forms, at the theory level employed. Figures 11 and 12, the latter containing wedge formulas of CC_{gauche} forms of N2AEEA, show that in the most stable form the N_3 and NHAc point into the same direction, with N_3 and H *syn*-oriented (gg^-g^- and its enantiomer g^-gg). The other two isomers having N_3 and H *syn*-positioned, but with N_3

away from NHAc (*agg* and *ggg*) are by 0.91 kcal/mol and 1.59 kcal/mol higher in energy. The *gg⁻g* conformer (and its enantiomeric *g⁻gg⁻* form) having N₃ and Ac in *syn* orientation, while both substituents point into the same direction, come next with relative energy of 1.70 kcal/mol. The other two isomers with N₃ and Ac in *syn* orientation (*ggg⁻* and *ag⁻g*) are of much higher energy, > 2.2 kcal/mol.

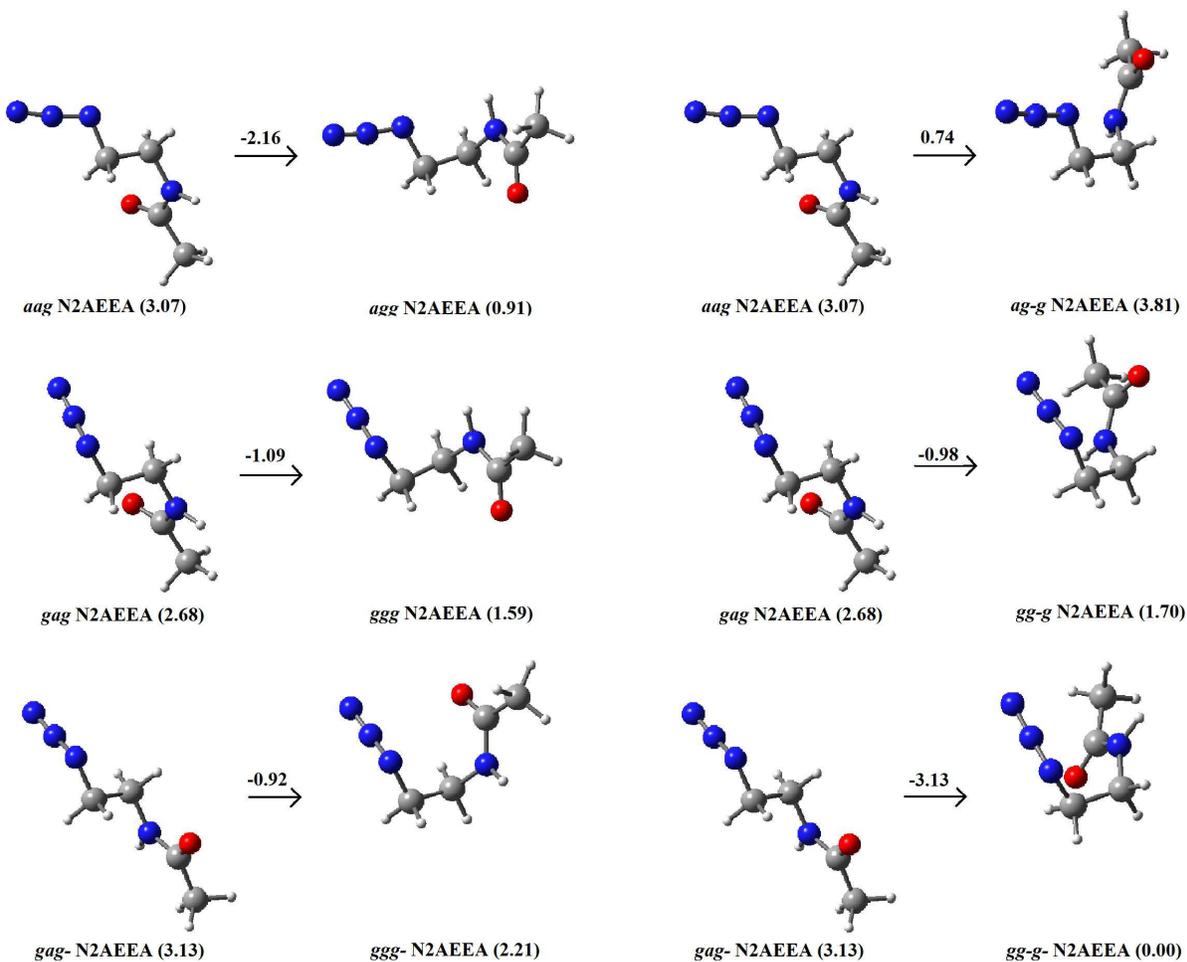


Figure 11. Optimized structures of *N*-(2-azidoethyl)ethanamide (N2AEEA), their relative energies (ΔE , kcal/mol) in the gas-phase and isomerization energies, calculated at the MP2/6-311++G(d,p) level of theory.

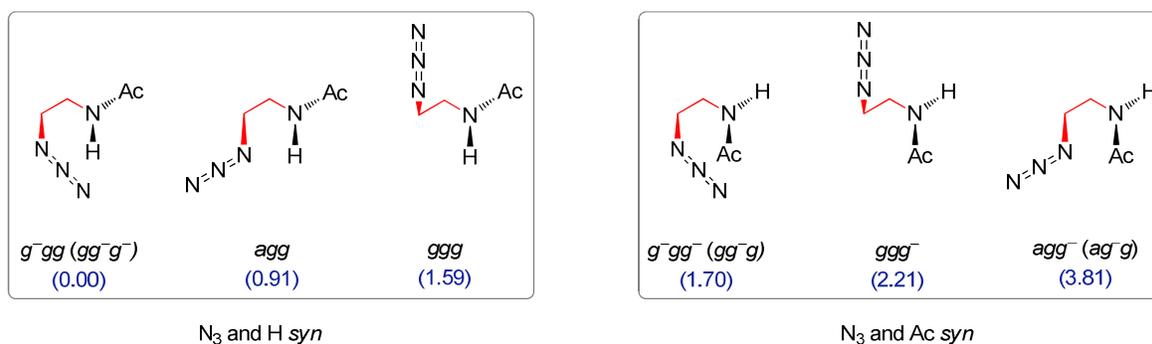


Figure 12. Wedge formulas of CC_{gauche} forms of *N*-(2-azidoethyl)ethanamide (enantiomeric forms of those shown are given in brackets) and their relative gas-phase energies (ΔE).

All CC_{anti} forms are by > 2.6 kcal/mol less stable and the gas-phase *gauche* effect of N2AEEA amounts $\Delta E/\Delta H/\Delta G = -2.68/-2.70/-1.34$ kcal/mol (gg^-g^- and gag isomers, Table S16). The magnitude of the *gauche* effect of N2AEEA obtained in this work is larger than that previously calculated for the same molecule ($\Delta E = -1.63$ kcal/mol),^{11a} because in the previous study it was estimated on the basis of *agg* and *gag* forms. In that case, our calculated energy difference $\Delta E_{agg-gag} = -1.77$ kcal/mol agrees with the previous work. Our results also agree with previous experimental and theoretical work on β -azidoalanine peptides showing *syn* orientation of N_3 and H in the most stable structure of dipeptide.^{11d} The data in Table S16 show that all conformational isomerizations leading to CC_{gauche} forms, with conformational energy of < 1.7 kcal/mol, result in *gauche* effect which ranges from $\Delta E/\Delta H/\Delta G = -1.09/-1.05/-0.62$ to $-3.13/-3.13/-1.74$ kcal/mol.

Inclusion of solvents into calculations reduces conformational energies of all isomers of N2AEEA so that relative energies of all CC_{gauche} forms are within ~ 1.50 kcal/mol (ΔE and ΔH) and ~ 1 kcal/mol (ΔG) in DMSO and water (gg^-g^- and gg^-g are isoenergetic, with respect to ΔE and ΔH). Only in CH_2Cl_2 the ag^-g form remains with high energy ($\Delta E/\Delta H \sim 2$ kcal/mol, $\Delta G = 1.6$ kcal/mol).

The *gauche* effect, measured as difference in energy between the most stable CC_{gauche} and CC_{anti} forms, amounts $\Delta E/\Delta H/\Delta G = -1.90/-1.99/-0.99$ kcal/mol in CH_2Cl_2 , $\Delta E/\Delta H/\Delta G =$

-1.75/-1.85/-1.10 kcal/mol in DMSO and $\Delta E/\Delta H/\Delta G = -1.74/-1.88/-1.08$ kcal/mol in water. These values agree with experimental data that the azido *gauche* effect can control conformation of peptides.^{11a,b,d} Under solvent conditions, all kinds of $CC_{anti} \rightarrow CC_{gauche}$ isomerizations occur with energy lowering which can increase or decrease with increasing solvent polarity. The magnitude of the *gauche* effect amounts $\Delta E/\Delta H/\Delta G = -0.35/-0.35/-0.41$ to $-2.21/-2.28/-1.63$ kcal/mol in CH_2Cl_2 , $\Delta E/\Delta H/\Delta G = -0.64/-0.70/-0.75$ to $-1.97/-2.04/-1.52$ kcal/mol in DMSO and $\Delta E/\Delta H/\Delta G = -0.67/-0.73/-0.79$ to $-1.94/-2.02/-1.51$ kcal/mol in water (only $aag \rightarrow ag^-g$ isomerization goes with no or weak *gauche* effect with respect to ΔG , in all solvents).

Origin of conformational preferences

Analysis of contributing effects

Results of EDA for all compounds are shown in Tables S2, S5, S8, S11, S14 and S17, along with the data for fluorine analogues, which are included for comparison.

1,2-Diazidoethane ($N_3CH_2CH_2N_3$)

The $aaa \rightarrow aga$, $aag \rightarrow agg$ and $gag \rightarrow ggg$ conformational isomerizations of DAE go with small *gauche* effect ($\Delta G_{iso} \leq -0.35$ kcal/mol), which only for the latter comes from an increase in interaction energy component ($\Delta\Delta E_{int}$). In addition, the aga , agg and ggg forms have $\Delta G_{corr} > 2$ kcal/mol (Table S1), so that these three isomerizations would have an insignificant contribution to the overall *gauche* effect of DAE. The other three conformational changes leading to the three most stable forms of DAE, $aag \rightarrow ag^-g$, $gag \rightarrow gg^-g$ and $gag^- \rightarrow ggg^-$, have $\Delta E_{iso} \leq -1.5$ kcal/mol (Table S2) and can be considered as a source of DAE *gauche* effect. The second one also corresponds to the energy difference between the most stable CC_{gauche} and the most stable CC_{anti} forms, in the gas-phase.

In the case of $aag \rightarrow ag^-g$ rotation the *gauche* effect $\Delta E_{iso} = -1.67$ kcal/mol originates from both $\Delta\Delta E_{def} = -0.90$ kcal/mol and $\Delta\Delta E_{int} = -0.77$ kcal/mol. The first energy term reflects structural relaxation upon $CC_{anti} \rightarrow CC_{gauche}$ rotation, while the second shows bonding strengthening mainly due

to enhanced electrostatic and orbital interactions, contributing almost equally (44.1% and 45.8%, respectively) to the higher stability of ag^-g form with respect to aag one. In the case of $gag^- \rightarrow ggg^-$ and $gag \rightarrow gg^-g$ isomerizations, *gauche* effect $\Delta E_{\text{iso}} = -1.50$ kcal/mol and $\Delta E_{\text{iso}} = -1.70$ kcal/mol, respectively, arises solely from $\Delta\Delta E_{\text{int}} = -2.19$ kcal/mol and $\Delta\Delta E_{\text{int}} = -1.72$ kcal/mol, respectively. Structural changes are energetically costly for the former, $\Delta\Delta E_{\text{def}} = 0.69$ kcal/mol, and have almost no influence on the *gauche* effect strength for the latter, $\Delta\Delta E_{\text{def}} = 0.02$ kcal/mol. In the case of $gag^- \rightarrow ggg^-$ conformational isomerization, contributions of $\Delta\Delta E_{\text{elstat}}$ and $\Delta\Delta E_{\text{oi}}$ are reduced (29.8% and 22.9%, respectively) in favour of dispersion, which appears as the main contributor to the *gauche* effect of this rotation (47.3% of all attractive interactions). The *gauche* effect in DAE, measured as an energy difference between the most stable CC_{gauche} and the most stable CC_{anti} forms ($gag \rightarrow gg^-g$ isomerization) is equally contributed by $\Delta\Delta E_{\text{oi}}$ and $\Delta\Delta E_{\text{disp}}$ (45.7% for both), while electrostatic energy contribution is only 8.6%. The attraction between local dipoles in the three most stable isomers of DAE, mentioned in the previous section, is a partial contributor to all-charge electrostatic interactions, and is not a dominant force for *gauche* preference in any of the three isomerizations.

On the basis of the preceding discussion, it is not possible to generalize the origin of DAE *gauche* effect, because it depends on the type of conformational isomerization, though, roughly speaking, it is contributed by orbital and dispersion interactions more than by electrostatic interactions and structural relaxation. When compared to 1,2-difluoroethane (DFE), the magnitude of attractive electrostatic and orbital energy components is smaller ($\Delta\Delta E_{\text{elstat}} = -0.55$ to -2.6 kcal/mol and $\Delta\Delta E_{\text{oi}} = -1.32$ to -2.89 kcal/mol, compared with $\Delta\Delta E_{\text{elstat}} = -3.38$ kcal/mol and $\Delta\Delta E_{\text{oi}} = -4.53$ kcal/mol for DFE), while dispersion interactions are larger ($\Delta\Delta E_{\text{disp}} = -0.60$ to -2.89 kcal/mol compared with $\Delta\Delta E_{\text{disp}} = -0.61$ kcal/mol for DFE), that is the DAE *gauche* effect is more dispersion-guided than the DFE *gauche* effect (10.1-47.3% for DAE compared with 7.1% for DFE). But, overall, larger $\Delta\Delta E_{\text{int}}$ for DAE ($gag^- \rightarrow ggg^-$ and $gag \rightarrow gg^-g$ isomerizations) compared with DFE does not stem from an

increase in attractive energy components, but from a decrease in Pauli repulsion that follow $CC_{anti} \rightarrow CC_{gauche}$ isomerization ($\Delta\Delta E_{Pauli} = 3.58-5.13$ kcal/mol for DAE and $\Delta\Delta E_{Pauli} = 7.57$ kcal/mol for DFE).

Inclusion of H_2O into calculations strengthens the *gauche* effect of the $gag \rightarrow gg^-g$ isomerization by 0.17 kcal/mol, due to increase in all three stabilizing interactions, $\Delta\Delta E_{elstat}$, $\Delta\Delta E_{oi}$ and $\Delta\Delta E_{disp}$, while $\Delta\Delta E_{Pauli}$ and $\Delta\Delta E_{def}$ become more destabilizing. It is interesting that electrostatic energy contribution increases from 8.6% in the gas-phase to 22.6% in water, as a results of the larger drop in electrostatic stabilization of *gag* than of gg^-g . In water, the effect is still dominated by $\Delta\Delta E_{oi}$ (37.1%) and $\Delta\Delta E_{disp}$ (40.3%).

2-Azidoethanamine ($N_3CH_2CH_2NH_2$)

The observed *anti* preference of 0.46 kcal/mol in the case of $gag^- \rightarrow ggg^-$ is due to energetically costly structural changes, $\Delta\Delta E_{def} = 2.09$ kcal/mol, while $\Delta\Delta E_{int}$ decreases by 1.63 kcal/mol solely due to the relief of all-electron Pauli repulsion. The *gauche* effect of all other isomerizations benefit from $\Delta\Delta E_{int}$, and in two cases from $\Delta\Delta E_{def}$, as well (for $gag^- \rightarrow gg^-g^-$ rotation $\Delta\Delta E_{def}$ dominates). All isomerizations showing *gauche* effect are followed by more or less increase in the Pauli repulsion, so that the *gauche* preference comes from increase in electrostatic, orbital and dispersion stabilizing energies. As in the case of DAE, the source of the *gauche* effect depends on the type of conformational isomerization and is dominated by $\Delta\Delta E_{elstat}$ for $aaa \rightarrow aga$ (72.6% of all attractive interactions), $gaa \rightarrow gga$ (64.6%) and $gag \rightarrow gg^-g$ (45.8%), involving the previously mentioned antiparallel dipole attraction. Orbital interactions play dominant role in the case of two isomerizations, $gaa \rightarrow gg^-a$ (47.7%) and $gag^- \rightarrow gg^-g^-$ (50.5%), while dispersion attraction dominates for $gag \rightarrow ggg$ rotation (51%). Percent contributions from all three attractive interactions are similar for $aag \rightarrow agg$ isomerization (36%/32%/32% for $\Delta\Delta E_{elstat}/\Delta\Delta E_{oi}/\Delta\Delta E_{disp}$), leading to the most stable isomer of 2AEA.

The origin of *gauche* effect in 2AEA, taken as an energy change when going from the most stable CC_{anti} to the most stable CC_{gauche} form ($gag \rightarrow agg$), can be viewed as two paths, each consisting from two isomerizations: 1) $gag \rightarrow ggg$ followed by $ggg \rightarrow agg$, and 2) $gag \rightarrow aag$ followed by $aag \rightarrow agg$ (Table S5). 1) The $CC_{anti} \rightarrow CC_{gauche}$ $gag \rightarrow ggg$ rotation decreases energy by 1.17 kcal/mol and is dominated by dispersion forces. Further rotation around the N_3-C bond to agg form decreases energy further by -0.32 kcal/mol solely due to the relief in Pauli repulsion. This sums up to total $\Delta E_{iso} = -1.49$ kcal/mol. 2) This alternative way first increases the energy of the system slightly (0.18 kcal/mol) due to structural changes occurring upon rotation around the N_3-C bond ($\Delta \Delta E_{def} = 7.99$ kcal/mol), while interaction energy drops by 7.81 kcal/mol due to the relief in Pauli repulsion. A driving force to the CC_{gauche} arrangement, now, comes almost equally from all three attractive interactions ($\Delta \Delta E_{elstat}$, $\Delta \Delta E_{oi}$ and $\Delta \Delta E_{disp}$).

Overall, the most stable $CC_{anti} \rightarrow CC_{gauche}$ isomerization, that is $gag \rightarrow agg$, benefits from the Pauli repulsion relief ($\Delta \Delta E_{Pauli} = -11.99$ kcal/mol), and just slightly from dispersion energy change ($\Delta \Delta E_{disp} = -0.64$ kcal/mol). Electrostatic attraction is smaller in agg than in gag form, while orbital interactions have a negligible effect (Table S5). A driving force for the *gauche* effect, viewed as a combination of two rotations, $gag \rightarrow ggg$ followed by $ggg \rightarrow agg$ (where both lead to energy decrease), can be considered to be dispersion forces (51%), electrostatic (27.3%) and orbital (21.7%) interactions, further enhanced by Pauli energy relief. For comparison, *gauche* effect in 2-fluoroethanamine results from orbital interactions (37.2%), electrostatic (33.5%) and dispersion forces (20.3%), and is of similar magnitude (Table S5). As in the case of DAE, local dipoles attraction, shown in Figure 4, is not a dominant conformation-controlling element.

Under solvent conditions (H_2O), the most stable CC_{gauche} form (gg^-g) is by 0.82 kcal/mol lower in energy than the most stable CC_{anti} form (gaa), the interconversion of which also involves gg^-a isomer (Table S5). The first step, that is $gaa \rightarrow gg^-a$ isomerization, decreases the energy by 0.31

kcal/mol and is almost equally contributed by the three attractive interactions, $\Delta\Delta E_{\text{elstat}}$ (31.9%), $\Delta\Delta E_{\text{oi}}$ (35.7%) and $\Delta\Delta E_{\text{disp}}$ (32.4%). Additional conformational change around the C–NH₂ bond lowers the energy by 0.51 kcal/mol mainly due to the relief in Pauli repulsion (80.7%) and the rest of 19.3% comes from an increase in dispersion interactions.

2-Azidoethylammonium ion (N₃CH₂CH₂NH₃⁺)

The very strong *gauche* effect of 2AEAH results mainly from $\Delta\Delta E_{\text{int}} = -7.82$ kcal/mol and less from $\Delta\Delta E_{\text{def}} = -0.75$ kcal/mol (Table S8). Major contributor to the *gauche* preference is strong electrostatic attraction (69.3%), involving the already mentioned C^{δ+}–N^{δ-}=N=N and H₂N^{δ-}–H^{δ+} bond dipoles attraction. This is followed by orbital stabilization (30.7%), while dispersion forces do not play a stabilizing role. Percent contributions of $\Delta\Delta E_{\text{elstat}}$ and $\Delta\Delta E_{\text{oi}}$ to the *gauche* effect are very similar as in fluoro analogue (FEAH), 71.9% and 27%, respectively. The larger magnitude of N₃/NH₃⁺ *gauche* preference with respect to F/NH₃⁺ one stems almost equally from three energy contributors, $\Delta\Delta E_{\text{elstat}}$, $\Delta\Delta E_{\text{oi}}$ and $\Delta\Delta E_{\text{def}}$, which are all by ~1.1 kcal/mol more favourable in 2AEAH ($\Delta\Delta E_{\text{def}}$ is a destabilizing effect in 2FEAH). The Pauli repulsion is more pronounced in the case of 2AEAH.

In H₂O as a solvent, the magnitude of the *gauche* effect decreases to 2.91 kcal/mol, which, interestingly, mainly comes from positive contribution of $\Delta\Delta E_{\text{oi}}$ (orbital interactions are less stabilizing in *ga* than in *aa*; see Hyperconjugation section for additional details). Under these conditions, the effect is dominated by $\Delta\Delta E_{\text{elstat}}$ term (94%), followed by $\Delta\Delta E_{\text{def}}$ (3.1%) and $\Delta\Delta E_{\text{disp}}$ (2.9%). Although intramolecular electrostatic interactions are significantly attenuated in the solvent, their decrease is similar in both isomers (~69 kcal/mol) resulting in the still much more favoured interactions in the CC_{*gauche*} form (Table S8).

2-Azidoethanol (N₃CH₂CH₂OH)

The EDA results are shown in Table S11. The *aag* → *agg* and *gag* → *ggg* isomerizations involve high energy conformers (≥ 2.7 kcal/mol), the contribution of which to the overall

conformational energy of 2AE is negligible. Rotation of the most stable *anti* form into the corresponding *gauche* form, that is *gaa* \rightarrow *gga* isomerization, increases the energy by 0.37 kcal/mol due to energy consuming structural changes and, thus, does not contribute to the overall *gauche* effect in 2AE (it also involves high energy *gga* form). All other isomerizations occur with *gauche* preference, ranging from 1.11-2.82 kcal/mol and its main contribution comes from strengthening of bonding mechanism ($\geq 80\%$, in few cases $\Delta\Delta E_{\text{def}}$ contributes to the effect, as well). The main role in *gauche* form stabilization is played by electrostatic forces (45.1-62.2%), which is followed by orbital interactions (26.5-47.6%) and dispersion interactions (7.4-15.7%). In just one case, *gag* \rightarrow *gg⁻g*, $\Delta\Delta E_{\text{elstat}}$ and $\Delta\Delta E_{\text{oi}}$ are almost equally important (46.4% and 47.6%, respectively). The all-charge electrostatic interactions involve local dipole/dipole attraction shown in Figure 8 ($\text{C}^{\delta+}-\text{N}^{\delta-}=\text{N}=\text{N}$ and $\text{O}^{\delta-}-\text{H}^{\delta+}$ in *ag⁻g* and *ggg⁻*, with $\varphi = 5.1^\circ$ and 6.6° , $\text{C}^{\delta+}-\text{O}^{\delta-}$ and $\text{N}^{\delta-}=\text{N}^{\delta+}=\text{N}$ in *gg⁻a*, *gg⁻g⁻* and *gg⁻g*, with $\varphi = 1.2^\circ$, 3.2° and 12.1°), which plays more important stabilizing role than in 2AEA, where $\Delta\Delta E_{\text{elstat}}$ energy component is not dominant in all isomerizations.

The two most stable isomers of 2AE and 2-fluoroethanol (2FE) have a common feature that the two CF/N and OH bond dipoles attain an antiparallel orientation (Figure 13). The corresponding attraction must be larger in fluoro-compound due to stronger C–F dipole than the C–N one. This is reflected in weaker all-charge electrostatic stabilization of *ag⁻g* 2AE ($\Delta\Delta E_{\text{elstat}} = -4.36$ kcal/mol for *aag* \rightarrow *ag⁻g* isomerization compared with $\Delta\Delta E_{\text{elstat}} = -5.34$ kcal/mol in case of *ag⁻* 2FE \rightarrow *gg⁻* 2FE isomerization). Orbital energy component is also weaker in 2AE ($\Delta\Delta E_{\text{oi}} = -2.13/-3.03$ kcal/mol for 2AE/2FE), while the magnitude of dispersion interactions is almost the same ($\Delta\Delta E_{\text{disp}} = -0.52/-0.51$ kcal/mol for 2AE/2FE). Thus, the slightly larger *gauche* preference in 2AE ($\Delta E_{\text{iso}} = -2.82/-2.54$ kcal/mol for 2AE/2FE) originates from weaker Pauli repulsion and $\Delta\Delta E_{\text{def}} \sim 0$ in 2AE (Table S11).

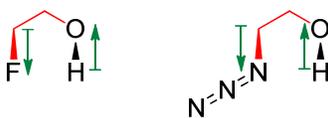


Figure 13. The two most stable forms of 2-fluoroethanol and 2-azidoethanol having an antiparallel orientation of OH and CF/N bond dipoles.

Isomerization from the most stable CC_{anti} isomer to the most stable CC_{gauche} isomer ($gaa \rightarrow ag^-g$) can proceed via two mechanisms, each consisting of two steps: 1) $gaa \rightarrow gg^-a$ and $gg^-a \rightarrow ag^-g$, involving $CC_{anti} \rightarrow CC_{gauche}$ rotation as the first step, followed by conformational changes around the N_3-C and $C-OH$ bonds, and 2) $gaa \rightarrow aag$ and $aag \rightarrow ag^-g$, having conformational changes around the N_3-C and $C-OH$ bonds as the first step, followed by $CC_{anti} \rightarrow CC_{gauche}$ rotation. Energy changes associated with these two mechanisms are given in Table S11. In the first case, the $CC_{anti} \rightarrow CC_{gauche}$ isomerization ($gaa \rightarrow gg^-a$) lowers the energy by 1.69 kcal/mol, primarily due to the enhancement of electrostatic attraction (47%), followed by larger orbital (38.5%) and dispersion interactions (10%), and structural relaxation, the contribution of which is the smallest (4.5%). Subsequent conformational changes ($gg^-a \rightarrow ag^-g$) additionally lowers the energy by 0.7 kcal/mol, primarily due to the relief of Pauli repulsion (71.8%) and secondly due to an increase in electrostatic attraction (28.2%). The second isomerization mechanism firstly increases the energy by 0.43 kcal/mol ($gaa \rightarrow aag$ rotation), which comes solely from an energy needed for structural changes that accompany conformational isomerization around the N_3-C and $C-OH$ bonds. Now, the $CC_{anti} \rightarrow CC_{gauche}$ rotation ($aag \rightarrow ag^-g$) significantly lowers the energy by 2.82 kcal/mol, primarily because of an increased electrostatic attraction (62%), followed by an enhancement in orbital interactions (30.3%) and larger dispersion interactions (7.4%). Contribution of structural relaxation is negligible (0.3%). Thus, in both mechanisms, the major stabilizing role is played by electrostatic forces, which is followed by orbital interactions. Later, we discuss if hyperconjugation is important for the *gauche* effect of 2AE.

In water, the most stable CC_{anti} to CC_{gauche} isomerization, $gag \rightarrow gg^-a$, goes with a drop in energy by 1.84 kcal/mol, mainly coming from an enhancement of dispersion interactions (42.8%) and

lowering in Pauli repulsion (42.0%, in this case, the intermediate isomer gg^-g could not be optimized), followed by electrostatic (12.8%) and orbital energy term (2.4%). Thus, under solvent conditions, the roles played by $\Delta\Delta E_{\text{elstat}}$ and $\Delta\Delta E_{\text{oi}}$ in the gas-phase are taken up by $\Delta\Delta E_{\text{disp}}$ and $\Delta\Delta E_{\text{Pauli}}$.

Protonated 2-azidoethanol ($\text{N}_3\text{CH}_2\text{CH}_2\text{OH}_2^+$)

The huge gas-phase *gauche* effect of 2AEH ($\Delta E_{\text{iso}} = -12.73$ kcal/mol) originates solely from strengthening of bonding interactions ($\Delta\Delta E_{\text{int}} = -22.10$ kcal/mol), while structural changes occurring upon going to *gauche* isomer are energetically costly ($\Delta\Delta E_{\text{def}} = 9.37$ kcal/mol, Table S14). The main contribution to bonding strengthening comes from electrostatic attractive interactions (45.1%), followed by orbital interactions (39.2%) and dispersion interactions (15.7%). Compared to the fluoro analogue 2FEH ($\Delta\Delta E_{\text{elstat}}/\Delta\Delta E_{\text{oi}}/\Delta\Delta E_{\text{disp}} = 66.4\%/29.1\%/4.5\%$), the percent contribution of electrostatic energy is reduced on account of increased orbital and dispersion energy stabilization. The magnitude of all interactions, attractive and repulsive, is significantly larger than in 2FEH.

In H_2O , energetically most favourable pathway between the most stable CC_{anti} and $\text{CC}_{\text{gauche}}$ forms involves $gag^- \rightarrow ggg^-$ isomerization, changing the CC bond conformation, followed by $ggg^- \rightarrow agg$ isomerization, changing conformations around the $\text{N}_3\text{-C}$ and C-OH_2^+ bonds. The first isomerization, lowering the energy by 1.65 kcal/mol, is dominated by an enhancement of electrostatic attraction (79.4%), while percent contribution of orbital and dispersion energy stabilization is almost the same (~10%). The subsequent conformational changes, going with a decrease in energy by 2.68 kcal/mol, further enhance electrostatic stabilization and lowers the Pauli repulsion. Hence, the *gauche* effect of protonated 2-azidoethanol in water is mainly electrostatic.

N-(2-Azidoethyl)ethanamide ($\text{N}_3\text{CH}_2\text{CH}_2\text{NHAc}$)

In the gas-phase, there is just one conformational isomerization $aag \rightarrow ag^-g$ having CC_{anti} preference by 0.74 kcal/mol. The EDA data in Table S17 point to $\Delta\Delta E_{\text{def}}$ as the only reason for this observation. Both conformers involved in this isomerization have high energies, > 3 kcal/mol, and

thus their contribution to the gas-phase conformational preferences of N2AEEA can be neglected. As for other isomerizations, the *gauche* preference of 0.92-3.13 kcal/mol comes solely from bonding strengthening, in all but one case, that is, $gag^- \rightarrow ggg^-$ isomerization in which $\Delta\Delta E_{\text{def}}$ dominates ($\Delta\Delta E_{\text{def}} = -0.78$ kcal/mol vs $\Delta\Delta E_{\text{int}} = -0.14$ kcal/mol). The origin of bonding strengthening upon $CC_{\text{anti}} \rightarrow CC_{\text{gauche}}$ rotations depends on a particular isomerization. For $aag \rightarrow agg$, $gag \rightarrow ggg$ and $gag^- \rightarrow ggg^-$ conformational changes electrostatic energy is dominant contribution (60-65% vs 20-24% and 12-21% found for $\Delta\Delta E_{\text{oi}}$ and $\Delta\Delta E_{\text{disp}}$, respectively, Table S17). A part of total electrostatic stabilization of *gauche* forms involved in the mentioned isomerizations comes from electrostatic $NH^{\delta+}/N^{\delta-}=N=N$ attraction in *agg* and *ggg* with N_3 and NH *syn*-oriented, and from $C^{\delta+}=O^{\delta-}/N^{\delta-}=N^{\delta+}=N$ bond dipoles attraction in ggg^- (*syn*- N_3 /Ac) which are positioned in an antiparallel orientation (the dihedral angle between the two local dipoles is 1.4° , Figure 12). For $gag \rightarrow gg^-g$ isomerization the dominant force is dispersion (54.7%), while orbital and electrostatic interactions have similar percent contribution to all attractive interactions that stabilize the CC_{gauche} arrangement (23.4% and 21.9%, respectively). The remaining $gag^- \rightarrow gg^-g^-$ isomerization benefits from electrostatic and dispersion stabilization to the same extent (38.1%), which is followed by orbital interactions (23.8%). The gg^-g^- conformer possess *syn*-oriented N_3 and H, so that a part of its electrostatic stabilization comes from $NH^{\delta+}/N^{\delta-}=N=N$ attraction.

An analysis of the origin of N2AEEA *gauche* effect considering the most stable CC_{anti} and CC_{gauche} forms involves two cases, each consisting from two isomerizations: 1) $gag \rightarrow gg^-g$, which changes the CC conformation from *anti* to *gauche*, followed by $gg^-g \rightarrow gg^-g^-$ rotation during which the molecule rotates around the C–NHAc bond, thus changing *syn*- N_3 /Ac to *syn*- N_3 /H orientation, and 2) $gag \rightarrow gag^-$ that involves conformational change around the C–NHAc bond as the first step, followed by $gag^- \rightarrow gg^-g^-$ isomerization that changes conformation around the CC bond. In the first case, there is an energy lowering of 0.98 kcal/mol that results mainly from dispersion interactions,

followed by orbital and electrostatic energies, contributing almost equally, as already discussed. The next step, the conformational change around the C–NHAc bond lowers the energy to the greater extent (by 1.7 kcal/mol), thus giving a total of $\Delta E_{\text{iso}} = -2.68$ kcal/mol. The rotation around the C–NHAc bond results in structure relaxation, $\Delta\Delta E_{\text{def}} = -0.44$ kcal/mol, and more importantly in bonding strengthening, $\Delta\Delta E_{\text{int}} = -1.26$ kcal/mol, primarily due to the relief in Pauli repulsion (59.0%), followed by an enhancement of electrostatic attraction (41.0%). In the second case, there is an initial energy rise of 0.45 kcal/mol during the $gag \rightarrow gag^-$ isomerization which comes from energetically costly structural changes ($\Delta\Delta E_{\text{def}} = 0.16$ kcal/mol) and interaction energy weakening ($\Delta\Delta E_{\text{int}} = 0.29$ kcal/mol), which is due to the loss of electrostatic and orbital stabilization (0.63 kcal/mol and 0.19 kcal/mol, respectively, Table S17). The next step leading to conformational change around the CC bond decreases energy significantly ($\Delta E_{\text{iso}} = -3.13$ kcal/mol), which is solely due to interaction energy lowering coming from electrostatic and dispersion interactions (38.1% for both), and orbital interactions, the contribution of which is smaller (23.8%), as already discussed.

On the total, the N2AEEA *gauche* effect, measured on the basis of the most stable CC_{anti} and CC_{gauche} forms, benefits exclusively from interaction energy, primarily from dispersion interactions (44.3%), which is followed by electrostatic interactions (32.7%) and finally from orbital interactions (23.0%).

In water, the *gauche* effect, measured as an energy difference between the most stable CC_{anti} and CC_{gauche} forms, the $gag \rightarrow gg^-g$ isomerization ($\Delta E_{\text{iso}} = -1.74$ kcal/mol), is contributed almost equally by $\Delta\Delta E_{\text{oi}}$ and $\Delta\Delta E_{\text{disp}}$, 51.8% and 48.1%, respectively, while electrostatic energy contribution is negligible (0.1%).

Stereoelectronic control

Calculated energies of vicinal hyperconjugative interactions between the CH_2N_3 and CH_2Y fragments of forms involved in isomerizations that result in *gauche* effect, along with energy changes occurring during the $\text{CC}_{anti} \rightarrow \text{CC}_{gauche}$ rotation are listed in Tables S3, S6, S9, S12, S15 and S18.

1,2-Diazidoethane ($\text{N}_3\text{CH}_2\text{CH}_2\text{N}_3$)

All three isomerizations of DAE, $aag \rightarrow ag^-g$, $gag \rightarrow gg^-g$ and $gag^- \rightarrow ggg^-$, go with an enhanced total hyperconjugation by 1.19-1.71 kcal/mol, involving almost entirely *anti*-interactions (changes in *gauche*-interaction energies are less than 0.1 kcal/mol and they can stabilize CC_{anti} forms slightly more than the CC_{gauche} ones). Magnitude of individual $\sigma_{\text{CH}} \rightarrow \sigma^*_{\text{CH}}$ interactions is similar in CC_{anti} (2.82-3.34 kcal/mol) and CC_{gauche} forms (2.97-3.49 kcal/mol), meaning that this type of hyperconjugation favours CC_{anti} arrangement (four in CC_{anti} vs two in CC_{gauche}). What goes in favour of CC_{gauche} form is $\sigma_{\text{CH}} \rightarrow \sigma^*_{\text{CN}}$ hyperconjugation (3.88-4.59 kcal/mol) vs $\sigma_{\text{CN}} \rightarrow \sigma^*_{\text{CN}}$ (1.77-2.09 kcal/mol) in CC_{anti} orientation. Thus, it can be said that the DAE *gauche* effect also has a stereoelectronic origin. However, the magnitude of hyperconjugative stabilization is less than in DFE, where total vicinal hyperconjugation increases by 5.48 kcal/mol upon *anti* \rightarrow *gauche* rotation, due to the strong $\sigma_{\text{CH}} \rightarrow \sigma^*_{\text{CF}}$ interaction in *gauche* form (5.81 kcal/mol) and weaker $\sigma_{\text{CH}} \rightarrow \sigma^*_{\text{CH}}$ interactions in both isomers.^{3f} This is obviously reflected in smaller total orbital interaction energy contribution ($\Delta\Delta E_{oi}$, Table S2), which is affected mostly by hyperconjugation and polarization. The strength of the CC bond, also involved in $\Delta\Delta E_{oi}$, does not differ much between the isomers, since the CC bond length changes negligibly upon isomerization ($< 0.004 \text{ \AA}$) and bond bending is also insignificant ($< 2.7^\circ$, being even somewhat larger in *gauche* forms).

2-Azidoethanamine ($\text{N}_3\text{CH}_2\text{CH}_2\text{NH}_2$)

Data in Table S6 show that all conformational isomerizations, resulting in the *gauche* effect, have stereoelectronic origin, as well, the magnitude of which ranges from 1.03-1.99 kcal/mol. A

change in total vicinal hyperconjugation originates mainly from *anti*-interactions. Contributions from *gauche*-interactions do not exceed 0.2 kcal/mol and are either stronger or weaker upon isomerization. All CC_{gauche} forms are particularly stabilized by $\sigma_{CH} \rightarrow \sigma_{CN_3}^*$ and $\sigma_{CH} \rightarrow \sigma_{CNH_2}^*$ interactions, the former being stronger by 0.12-0.79 kcal/mol, except in *aga* form.

The magnitude of hyperconjugation contribution to the *gauche* effect of 2AEA is smaller compared to 2FEA, where it amounts 2.64-3.36 kcal/mol, at the same level of theory.^{3f} This is due to the weaker $\sigma_{CH} \rightarrow \sigma_{CN_3}^*$ interaction (4.34-5.10 kcal/mol) vs $\sigma_{CH} \rightarrow \sigma_{CF}^*$ interaction (5.93-6.17 kcal/mol) in 2FEA, while magnitude of $\sigma_{CH} \rightarrow \sigma_{CNH_2}^*$ interactions in both compounds is similar (3.94-4.98/4.06-4.92 kcal/mol in 2AEA/ FEA).

As for DAE, the $CC_{anti} \rightarrow CC_{gauche}$ isomerizations affect CC bond lengths by < 0.005 Å and bond bending is small, so that the strength of CC bond differs negligibly between the isomers. Thus, the hyperconjugation and polarization are main contributors to overall orbital interaction energy ($\Delta\Delta E_{oi}$ in Table S5).

2-Azidoethylammonium ion ($N_3CH_2CH_2NH_3^+$)

Data given in Table S9 reveal that hyperconjugative interactions do not contribute to the *gauche* effect of 2AEAH, that is, the change in total, as well as *anti* hyperconjugative interactions are negligible, 0.01 and 0.04 kcal/mol, respectively. Main reasons for this are: 1) weak $\sigma_{CH} \rightarrow \sigma_{CN_3}^*$ interaction in CC_{gauche} form of 2.6 kcal/mol, which is significantly weaker than the corresponding interaction in neutral amine (4.3-5.1 kcal/mol), and 2) strong $\sigma_{CN_3} \rightarrow \sigma_{CNH_3}^*$ interaction of 3.55 kcal/mol that stabilizes the CC_{anti} form (the corresponding $\sigma_{CN_3} \rightarrow \sigma_{CNH_2}^*$ interaction in amine ranges from 1.79 kcal/mol to 2.26 kcal/mol). The decrease in the magnitude of $\sigma_{CH} \rightarrow \sigma_{CN_3}^*$ interaction occurring in CC_{gauche} form is caused by an increased electronegativity of nitrogen geminal to the C–H bond, which makes the C–H bond as poorer electron donor compared to C–H bond which is geminal to neutral NH_2 group. In the case of fluorine compound, 2FEAH, there is a hyperconjugative

stabilization of *gauche* form by 2.45 kcal/mol relative to the *anti* one, coming from stronger $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CF}}^*$ interaction, 3.97 kcal/mol (magnitudes of $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CNH}_3}^*$ interactions are similar in both 2AEAH, 5.34 kcal/mol, and 2FEAH, 5.31 kcal/mol) and weaker $\sigma_{\text{CF}} \rightarrow \sigma_{\text{CNH}_3}^*$ interaction in *anti* form, 2.42 kcal/mol (magnitudes of $\sigma_{\text{CNH}_3} \rightarrow \sigma_{\text{CN}_3/\text{F}}^*$ interactions are similar in both azido- and fluoro-compounds, 1.18 kcal/mol and 1.43 kcal/mol, respectively).^{3f}

In addition, the NBO analysis reveals a charge transfer from the sp-lone pair orbital of the azido nitrogen ($\text{N}=\text{N}=\text{N}^{\delta-}-\text{C}$) into the antibonding orbital of N^+-H bond that points toward the N_3 group in *ga* conformer. This interaction stabilizes *ga* form by 4.47 kcal/mol and is reminiscent of hydrogen-bonding interaction, though geometry in such a small system is far from an optimal one needed for a good hydrogen bond (an $\text{N}^{\delta-}-\text{H}-\text{N}$ angle of 180° compared to 109.8° in *ga*-2AEAH). The N^+-H bond involved in this interaction is by 0.009 Å longer than the other two N^+-H bonds of NH_3^+ group, which can result from both electrostatic and orbital interactions. The distance between hydrogen of NH_3^+ and nitrogen of N_3 (2.1 Å) is by 0.65 Å smaller than the sum of van der Waals radii of H and N (2.75 Å). In the case of neutral amine, this distance is longer (2.5-2.6 Å), charge transfer interaction energy is small (~ 0.2 kcal/mol for sp-lone pair and 0.1-0.5 kcal/mol for p-lone pair) and the two N-H bonds have similar lengths (difference is ≤ 0.001 Å).

Hence, on the basis of the discussion in this section, the $\Delta\Delta E_{\text{oi}} = -4.64$ kcal/mol energy change given in Table S8 involves mainly $n_{\text{N}} \rightarrow \sigma_{\text{NH}^+}^*$ interaction and polarization,³² which are also responsible for larger $\Delta\Delta E_{\text{oi}}$ compared with that of 2FEAH. Although, there is a stereoelectronic *gauche* effect in the fluoro-compound, the corresponding $n_{\text{F}} \rightarrow \sigma_{\text{NH}^+}^*$ charge transfer is weak (0.84 kcal/mol). In water, total hyperconjugative stabilization increases to 1.54 kcal/mol (Table S9), but $n_{\text{N}} \rightarrow \sigma_{\text{NH}^+}^*$ decreases to 1.41 kcal/mol. Thus, the less stabilizing orbital interactions in *ga* with respect to *aa*, as obtained from EDA, stem from weaker hydrogen-bonding and less favourable polarization.

2-Azidoethanol ($\text{N}_3\text{CH}_2\text{CH}_2\text{OH}$)

Data in Table S12 show that all isomerizations are followed by an increase in total hyperconjugative interactions resulting mainly from *anti*-interactions. Contributions from *gauche*-interactions are either negligible (≤ 0.1 kcal/mol) or stabilize *anti* form more than the *gauche* form (-0.23 kcal/mol for $gag \rightarrow gg^-g$ isomerization). Thus, the stereoelectronic control of *gauche* effect in 2AE comes from *anti* vicinal hyperconjugation, that is, $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CN}_3}^*$ and $\sigma_{\text{CH}} \rightarrow \sigma_{\text{COH}}^*$ interactions, the relative strength of which depends on the type of isomerization. They both range from 4.1-5.1 kcal/mol and their relative strength in a particular isomerization differs by less than 0.65 kcal/mol.

The contribution from hyperconjugation to the *gauche* effect in 2AE is weaker than in 2FE (1.6-2.3 kcal/mol for the former and 3.2-4.62 kcal/mol for the latter),^{3f} originating mainly from weaker $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CN}_3}^*$ interaction in 2AE (4.11-4.82 kcal/mol) compared to $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CF}}^*$ interaction in 2FE (5.79-6.15 kcal/mol).^{3f}

Protonated 2-azidoethanol ($\text{N}_3\text{CH}_2\text{CH}_2\text{OH}_2^+$)

Data presented in Table S15 reveal that, surprisingly, while there is a large hyperconjugative stabilization of *gauche* forms in fluoro-compound (2FEH, 3.33-6.42 kcal/mol),^{3f} the *gauche* effect of 2AEH does not benefit from this kind of interactions. On the contrary, total vicinal hyperconjugation stabilizes CC_{anti} forms by 2.22-3.05 kcal/mol more than the $\text{CC}_{\text{gauche}}$ ones, which results solely from *anti*-interactions (upon $\text{CC}_{\text{anti}} \rightarrow \text{CC}_{\text{gauche}}$ isomerization, stabilizing energy from *anti*-interactions decreases by 2.61-3.52 kcal/mol, while stabilizing energy from *gauche* interactions increases by 0.39-0.47 kcal/mol). The absence of stereoelectronic control of *gauche* effect in 2AEH stems mainly from small energy of $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CN}_3}^*$ interaction in *gauche* form (1.81-1.85 kcal/mol vs 4.11-4.82 kcal/mol in 2AE, Tables S12 and S15) and large energy of $\sigma_{\text{CN}_3} \rightarrow \sigma_{\text{COH}_2}^*$ interaction that stabilizes *anti* forms (4.82-5.32 kcal/mol vs 1.87-2.18 kcal/mol in 2AE, Tables S12 and S15). As a comparison, in fluoro-analogue $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CF}}^*$ and $\sigma_{\text{CH}} \rightarrow \sigma_{\text{COH}_2}^*$ interactions in $\text{CC}_{\text{gauche}}$ isomers are both larger (3.53-4.08

kcal/mol and 6.37-8.97 kcal/mol, respectively, vs 1.81-1.85 kcal/mol and 4.59-4.91 kcal/mol in 2AEH), while $\sigma_{CF} \rightarrow \sigma_{COH_2}^*$ hyperconjugation in CC_{anti} isomers is weaker (3.20-3.44 kcal/mol).^{3f}

Additionally, upon $CC_{anti} \rightarrow CC_{gauche}$ rotation there is an increase in the CC bond length of 0.011 Å, which decreases its strength. Hence, to search for an origin of the large $\Delta\Delta E_{oi}$ in Table S14 we examined all charge transfer interactions between N_3CH_2 and $CH_2OH_2^+$ fragments of 2AEH and found a significant stabilization that comes from delocalization of lone pair of azido nitrogen $N=N=N^{\delta-}-C$ into the antibonding orbital of H–O bond, which is oriented toward the N_3 group (Figure 10). The delocalization energies amount 41.82 kcal/mol in *aga* isomer, and 39.39 kcal/mol and 22.59 kcal/mol in *agg* isomer. The H–O bond is elongated (~1.04 Å) and is by 0.06-0.07 Å longer than the other O–H bond of OH_2^+ group. The distance between H and azido nitrogen of 1.603 Å and 1.572 Å for *aga* and *agg*, respectively, is significantly shorter than the sum of Van der Waals radii (2.75 Å). The $N^{\delta-}H-O$ angle is widened to 129°-130°, compared to ~108° in 2-azidoethanol and ~110° in 2-azidoethylammonium ion. All these data point to a hydrogen-bonding stabilization, despite geometric constraints encountered in a formation of a 5-membered chelate structure in such a small system. Thus, the large $\Delta\Delta E_{oi}$ energy component in Table S14 originates primarily from intramolecular hydrogen bond. The same interaction affects $\Delta\Delta E_{elstat}$ energy, as well.

***N*-(2-Azidoethyl)ethanamide ($N_3CH_2CH_2NHAc$)**

As can be seen from data in Table S18, all isomerizations benefit from hyperconjugative interactions, the energies of which span a range from 1.09-1.94 kcal/mol. This stabilization comes exclusively from *anti*-interactions, while *gauche* ones are weak (≤ 0.33 kcal/mol) and stabilize CC_{anti} forms more than the CC_{gauche} conformers. The most important hyperconjugative stabilization of CC_{gauche} isomers comes from $\sigma_{CH} \rightarrow \sigma_{CN_3}^*$ and $\sigma_{CH} \rightarrow \sigma_{CNHAc}^*$, the energies of which are quite similar (differ by at most 0.43 kcal/mol) and range from 4.01-4.68 kcal/mol. No charge transfer

corresponding to hydrogen-bonding interaction was found in any of *gauche* isomers, which is expected on the basis of molecular geometry, shown in Figure 12.

Conclusions

In this work, we have theoretically estimated magnitude of the gas-phase and solution-state azido *gauche* effect in 1,2-diazidoethane, (protonated) 2-azidoethanamine, (protonated) 2-azidoethanol and *N*(2-azidoethyl)ethanamide, which were chosen as model systems for molecules which contain vicinal N_3/N_3 , N_3/NH_2 , N_3/NH_3^+ , N_3/OH , N_3/OH_2^+ and $N_3/NHAc$ groups. A comparative analysis of the gas-phase energy values, summarized in Table 1, shows that the strength of the azido *gauche* effect compares with the strength of the fluoro *gauche* effect in amine and alcohol, but exceeds the magnitude of the fluoro *gauche* effect in amide, protonated amine and protonated alcohol. In addition, it is more than doubled in 1,2-diazidoethane compared with 1,2-difluoroethane. Inclusion of solvents decreases the azido *gauche* effect (as a difference in energy between the most stable CC_{anti} and CC_{gauche} forms) in all but one case (1,2-diazidoethane), while its magnitude is still enough to allow the use of an azido substituent as a conformation-controlling element. From stereochemical and synthetic point of view, the N_3 group is sterically not demanding and allow for further chemical transformations.

Table 1. Comparison of the gas-phase *gauche* effect (ΔE in kcal/mol) of fluoro- and azido-ethane derivatives, considering the most stable CC_{gauche} and CC_{anti} isomers, estimated at the MP2/6-311++G(d,p) level of theory.

Y	$YCH_2CH_2NH_2$	$YCH_2CH_2NH_3^+$	YCH_2CH_2OH	$YCH_2CH_2OH_2^+$	YCH_2CH_2NHAc	FCH_2CH_2F $N_3CH_2CH_2N_3$
F	1.40 ^a	6.84 ^a	2.30 ^a	8.23 ^a	1.78 ^b	0.77 ^a
N_3 ^c	1.49	8.60	2.39	12.73	2.68	1.70

^a From ref. 3f. ^b From ref. 3a, the ZPE-corrected value obtained at the B3LYP/6-31+G(d,p) level. ^c This work.

The azido *gauche* effect comes from a balance of attractive interactions, (electrostatic, orbital and dispersion), repulsive interactions (Pauli repulsion) and energy loss or gain due to structural changes that accompany conformational isomerizations. Its origin is mostly electrostatic in 2-azidoethylammonium ion, that is, larger electrostatic attraction in *gauche* form contributes approximately two thirds of total *gauche* form stabilizing energy. Slightly less than one third comes from orbital interactions involving polarization and $n_N \rightarrow \sigma_{NH^+}^*$ charge transfer, the rest of 5% goes to structural relaxation. The large *gauche* effect in protonated 2-azidoethanol comes primarily from all-charge electrostatic interactions and $N^{\cdots}H-O$ hydrogen-bonding, also seen as $n_N \rightarrow \sigma_{OH^+}^*$ orbital interaction. No stereoelectronic *gauche* effect was found in both charged species. In water as a solvent the *gauche* effect is primarily of electrostatic origin, for both systems.

Electrostatic interactions are the main contributor to *gauche* preference in 2-azidoethanol (45-62%), followed by orbital interactions (26-40%) involving $\sigma_{CH} \rightarrow \sigma_{CN}^*$ and $\sigma_{CH} \rightarrow \sigma_{CO}^*$ hyperconjugation and polarization, and dispersion which contributes no more than 16% to all attractive interactions. With inclusion of water, dispersion attraction and decrease in Pauli repulsion are main contributors to the *gauche* effect, taking into consideration most stable CC_{anti} and CC_{gauche} forms.

Although the exact source of the *gauche* effect in *N*-(2-azidoethyl)ethanamide, 1,2-diazidoethane and 2-azidoethanamine depends on a particular isomerization, the following conclusions can be extracted. In the case of amide, the most important interactions are dispersion and electrostatic, followed by orbital interactions. Dispersion and orbital interactions are main factors contributing to the *gauche* effect in 1,2-diazidoethane, 46-47% and 40-46%, respectively, followed by electrostatic interactions, the percent contribution of which does not exceed 38%. All three stabilizing interactions are important in the case of amine: electrostatic (36-73%), orbital (18-48%) and dispersion (10-51%). In isomerizations accompanied by structural relaxation, its contribution is at

most 16%. For all three systems, the $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CN}}^*$ hyperconjugation in *gauche* isomers contributes to the *gauche* effect. The relative importance of various interactions is similar for diazidoethane and amine in water, but changes to orbital and dispersion with negligible contribution of electrostatic interactions in amide.

We hope that results and discussion presented in this paper can give an idea about the strength of the azido *gauche* effect to those tending to perform a control over molecular conformation for medical, material and synthetic purposes, and also to help understanding its origin.

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Supplementary Information: Tables S1-S18, Figure S1. showing optimized structures of isomers which are viable only in solvents, absolute energies and x, y, z coordinates of optimized structures in the gas-phase and in all three solvents (CH₂Cl₂, DMSO, water).

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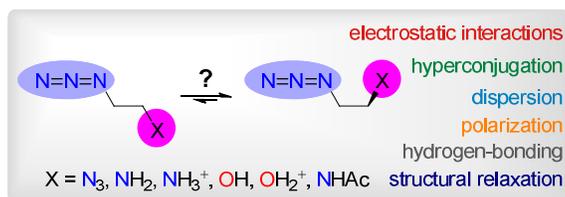
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32. As in the case of previously discussed compounds, the $CC_{anti} \rightarrow CC_{gauche}$ rotation almost does not affect the CC bond length and bond bending is $< 3.5^\circ$, so that the strength of the CC bond remains similar in both isomers.

TOC Graphic



The strength and the origin of azido *gauche* effect were studied by *ab initio* calculations and compared to the well known fluorine *gauche* effect.