

Studying Etherification Mechanism of Primary Alcohols in Acidic Condition with *ab initio* Quantum Chemistry Methods

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Abstract: This paper establishes the etherification mechanism of primary alcohols R-CH₂OH in acidic condition using *ab initio* quantum chemistry methods, through surveying the effect of the substituent -R (-R = -H, -CH₃, -CH₂CH₃, -Vinyl, -Phenyl, -CH₂NHCH₃, -CH₂OCH₃, -CH₂F) and water solvent on the mechanism, at the same time assessing the effect of basis set (6-31g(d,p), 6-311g(d,p), 6-311++g(d,p)) on computational results. The results indicate that the etherification reaction follows dual-molecule nucleophilic substitution (S_N2) mechanism. Reactants and products form reactive intermediates with H⁺ and water, in this state H⁺ is occupied by both alcohol and water or ether and water. This state has lower energy level compared to both of the following cases: H⁺ is fully occupied by water, and H⁺ is fully occupied by the product/reactant. The substituent -R has a significant impact on activation energy and the amount of energy needed to convert the reactive intermediate into ether, while the effects of water solvent and basis set are negligible.

Keywords: Etherification Reaction Mechanism, Primary Alcohol, Effect of H⁺.

Introduction:

Williamson (1850) ether synthesis is currently the most common method to synthesize ether from an organohalide and an alkali metal alkoxide due to its high efficiency, high selectivity, and mild condition for reaction; in several cases, however, when simplicity, economy, and environmentally friendliness are required, ether may also be synthesized from primary alcohols with acid catalyst at 130°C - 140°C [1,2,3]. For example, Marshall *et al.*

(2005) modified hydroxyl groups on lignocellulosic materials using choline chloride and cross-linking agent 4,5-dihydroxy-1,3-bis (hydroxymethyl) imidazolidin-2-one (DMDHEU) in acidic condition to form a material possessing great ability to adsorb and exchange anions such as chromate, arsenate, and selenate [4]; another simple example is the cross-link formation in fabric for crease-proofing [5].

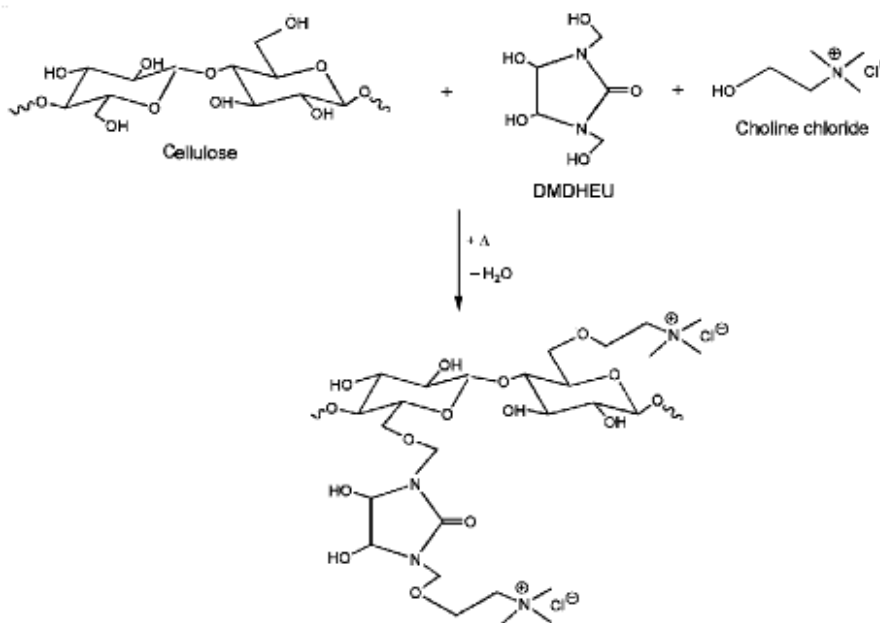


Figure 1. Modification of cellulose using DMDHEU and choline chloride

Up until today, the widely accepted mechanism for etherification of primary alcohols in acidic condition is made of three steps: first is the protonation of -OH understand this matter more thoroughly, Gaussian software was used in this study to calculate and establish a mechanism of reaction, using density functional theory. One of the advantages of density functional theory over other *ab initio* quantum

in alcohol, second is the dual-molecule nucleophilic substitution S_N2, and last is deprotonation of the final product assisted by water or alcohol [1,2,3]. To chemistry methods is that the properties of a system comprising N electrons can be determined by an electron density that depends on 3 spatial coordinates, instead of a wave function that depends on 3N spatial coordinates; therefore density

functional theory has become popular in recent years, especially hybrid functional B3LYP (Becke, 3-parameter, Lee-Yang-Parr exchange). In 1998, Walter Kohn received Nobel Prize in Chemistry for his development of the density functional theory, along with John A. Pople, one of the developers of the first Gaussian program (Gaussian 70) in 1970 at Carnegie-Mellon University [6,7,8,9,10,11].

Calculation Methods:

Calculation methods and basis sets used for the initial guess were HF/ 3-21g and B3LYP/ 6-31g(d,p); calculation method and basis set used to get the result was B3LYP/ 6-311g(d,p). Exclusively for evaluating the effect of different basis sets on the results,

calculation method and basis set used for the initial guess was HF/ 3-21g; calculation methods and basis sets used to get the result were B3LYP/ 6-31g(d,p), B3LYP/ 6-311g(d,p), and B3LYP/ 6-311++g(d,p).

The software used in this study for calculations was Gaussian 03; reagents, products, and transition states were built with GaussView 03.

Results and Discussion

Etherification mechanism of methanol in acidic condition

The energy levels of substances, ions, and transition states were calculated using the calculation methods and basis sets mentioned in Section 2, the results are as presented in Table 1.

Table 1. Energy level of substances, ions, and transition states

Substance, ion, transition state	E SCF (Hartree)	0.98ZPE (Kcal/mol)	E ₀ (Kcal/mol)
Methanol	-115.7573949	31.4	-72607.4
Dimethyl ether	-155.071921	48.8	-97260.3
Water	-76.447448	13.1	-47958.4
Oxonium Ion	-76.7280691	20.2	-48127.4
Methanol...H ⁺	-116.0612573	39.4	-72790.2
Methanol...H ⁺ ...H ₂ O	-192.5609342	53.1	-120780.7
Dimethyl ether...H ⁺	-155.3882482	57.0	-97450.6
Dimethyl ether...H ⁺ ...H ₂ O	-231.8815370	70.9	-145437.0
TS_Methanol--> Dimethyl ether	-231.8329520	70.9	-145406.5

Note:

E SFC: Energy resulted from solving Schrodinger equation (in Hartree); is equal and opposite to the energy required to completely break up the molecule.

0.98ZPE: Energy level of the ground state, adjusted by 0.98 (for using B3LYP method).

E₀: Total energy of the molecule at 0 K, including E SFC and the adjusted ground state energy (in Kcal/mol).

From these results, an energy level diagram was established by setting the energy level of the transition state Methanol...H⁺...H₂O (when H⁺ is shared between methanol and water) as basepoint, the energy levels of the reactants, products, intermediates, and transition states are determined in relation to the basepoint.

Table 2. Energy levels of reactants, products, intermediates, and transition states

Reactant, product, intermediate, transition state	Relative energy level (Kcal/mol)
Methanol...H ⁺ ...H ₂ O	0.0
Methanol + H ₃ O ⁺	45.8
Methanol...H ⁺ + H ₂ O	32.1
Dimethyl ether...H ⁺ ...H ₂ O	-7.3
Dimethyl ether...H ⁺ + H ₂ O	20.7
Dimethyl ether + H ₃ O ⁺	41.9
TS_Methanol--> Dimethyl ether	23.3

As shown in Figure 2, in acidic condition, H⁺ ions can form reactive intermediates with methanol and water, in this state H⁺ is shared between methanol and water. This state has a lower energy level compared to the states where H⁺ is occupied by water or by methanol. Although the formation of the transition state is exothermic, the number of H⁺ ions present in the solution is low; therefore the released heat is completely absorbed by the surroundings. Consequently, for the S_N2 reaction to start, an activation energy E_a=23.3 Kcal/mol is required. Another transition state is then formed, where H⁺ is shared between water and dimethylether. In order to convert this state into the final product, it is required to provide the system with a minimum amount of energy E_c=49.2 Kcal/mol.

Effect of basis sets:

The effect of basis sets on the results was assessed by changing the basic sets used for each calculation, from valence double-zeta polarized basis set 6-31g(d,p), to valence triple-zeta basis set 6-311g(d,p), and valence triple-zeta basis set with additional diffuse functions 6-311++g(d,p). The results for activation energy E_a and conversion energy E_c are presented in Table 3.

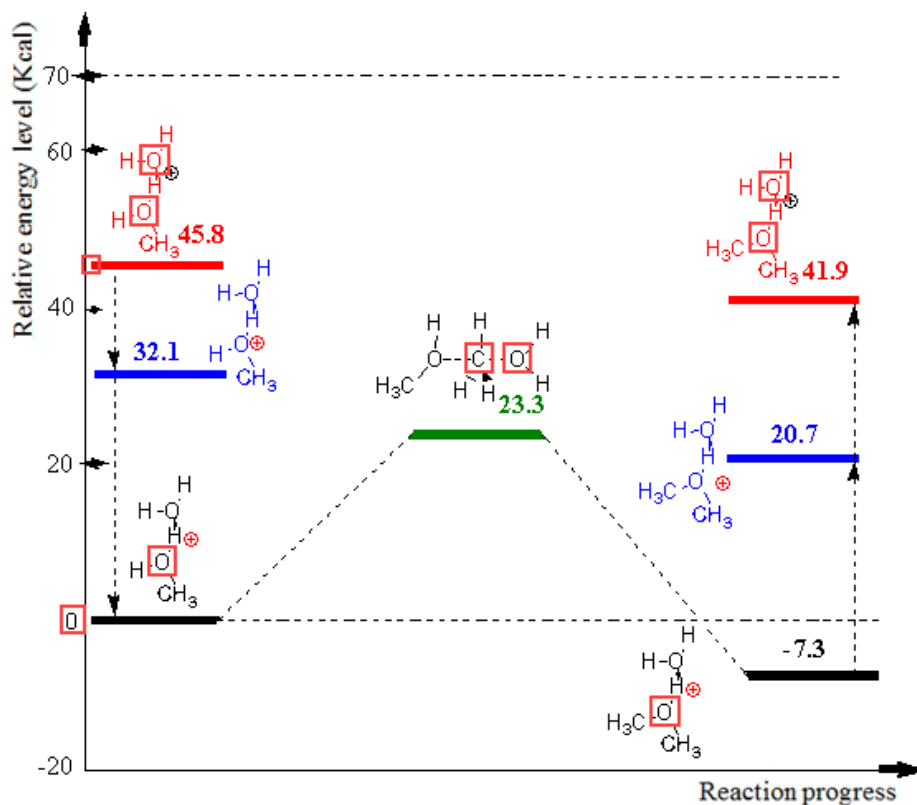


Figure 2. Energy level diagram for reactants, products, intermediates, and transition states

Table 3. Activation energy and conversion energy calculated using different basis sets

Basis set	Activation energy E_a (Kcal/mol)	Conversion energy E_c (Kcal/mol)
6-31g(d,p)	23.9	49.1
6-311g(d,p)	23.3	49.2
6-311++g(d,p)	20.8	48.8

As shown in Table 3, when the basis set was switched from 6-31g(d,p) to 6-311g(d,p), there was no significant change in the values of activation energy and conversion energy. When the basis set was switched from 6-311g(d,p) to 6-311++g(d,p), activation energy dropped by 2.5 Kcal/mol, and conversion energy increased by 0.4 Kcal/mol. The 6-311++g(d,p) is a more shallow basis set than 6-311g(d,p), taking the diffusion of electrons into account, however 6-311++g(d,p) is mostly applied in calculation for molecules containing large atoms (electrons distant from the atomic nuclei). In this study, 6-311g(d,p) was chosen for the following steps.

Effect of water solvent:

The change in activation energy and conversion energy was examined when the reaction medium was changed from gas-phase to water solvent using Onsager model. The results are shown in Table 4.

Table 4. Activation energy and conversion energy in water solvent

Solvent model	Activation energy E_a (Kcal/mol)	Conversion energy E_c (Kcal/mol)
Gas-phase	23.3	49.2
Onsager	21.1	49.7

As can be seen from Table 4, the activation energy for the reaction in water solvent dropped by 2.2 Kcal/mol, the reason can be that the positive charge density on carbon atom of the $-C-O-H$ group in transition state was relieved by surrounding water molecules, making it easier for the substitution reaction to occur. A small increase in conversion energy was also present, only 0.5 Kcal/mol; conversion energy is related to the negative charge density on oxygen atom of the $-C-O-C-$ group in the second reactive intermediate, therefore it is rarely affected by surrounding water molecules; the small increase could be the result of hydrogen bond and van der Waals attraction.

Effect of substituent $-R$

The change in activation energy and conversion energy was examined when the substituent $-R$ in $R-CH_2OH$ was altered between different electron donating groups based on inductive effect +I ($-CH_3$, $-CH_2CH_3$) and mesomeric effect $n-\pi +C$ ($-Vinyl$, $-CH_2NHCH_3$, $-CH_2OCH_3$, $-CH_2F$). The results are shown in Table 5.

Table 5. Activation energy and conversion energy according to different substituents

Substituent -R in R-CH ₂ OH	Activation energy E _a (Kcal/mol)	Conversion energy E _c (Kcal/mol)
-H	23.3	49.2
-CH ₃	20.6	52.3
-CH ₂ CH ₃	19.9	53.7
-Vinyl	13.8	51.2
-CH ₂ NHCH ₃	14.8	53.8
-CH ₂ OCH ₃	16.4	49.9
-CH ₂ F	22.0	37.8

From Table 5 it can be seen that the presence of electron donating group decreased the activation energy; and the drop in activation energy increased as the strength of polar effect got stronger. This can be explained as follows, when the positive charge density on carbon atom of the -C-O-H group is relieved, the transition state is made stable, making the reaction easier to occur. It is also indicated that the polar effect is stronger in n-π +C mesomeric effect compared to +I inductive effect, with the exception being -CH₂F group (greatly affected by -I effect). Among the mesomeric effect groups, vinyl is the strongest, and the strength of the effect decreases as the electronegativity increases, from N, O, to F. As opposed to activation energy, conversion energy is in relation to negative charge density on oxygen atom of the -C-O-C- group, the ability to hold on to H⁺ is strengthened when the negative charge density is increased, leading to a rise in conversion energy. Thus, the conversion energy is higher when an electron donating group is present. Conversion energy rose from 49.2 Kcal/mol (-R being -H) to 53.7 Kcal/mol (-R being -CH₂CH₃); the groups that caused mesomeric effect on carbon atom only caused inductive effect on oxygen atom, therefore conversion energy decreased and reached minimum of 37.8 Kcal/mol when -R is -CH₂F.

Conclusion:

From the results of this study, a new and clearer view of etherification mechanism of primary alcohols in acidic condition was opened up. During the reaction, reactive intermediates are formed; they are transition states where H⁺ is occupied by both alcohol and water or by both ether and water; the amount of energy needed to convert the intermediate to the final product is significantly larger than the activation

energy of reaction; the effect of substituent -R on the reactivity is noticeable; mesomeric effect n-π +C produces a stronger electron pushing than inductive effect +I. Based on the results, the etherification mechanism of primary alcohols in acidic condition can be remodeled as follows:

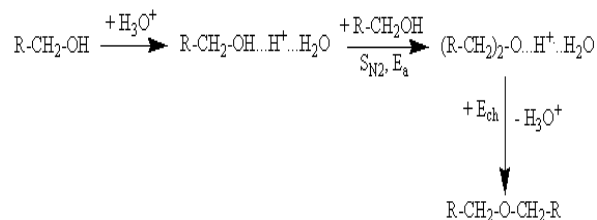


Figure 3. Etherification mechanism of primary alcohols in acidic condition

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