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Ab Initio Study of the S_N2 and E2 Mechanisms in the Reaction between the Cyanide Ion and Ethyl Chloride in Dimethyl Sulfoxide Solution

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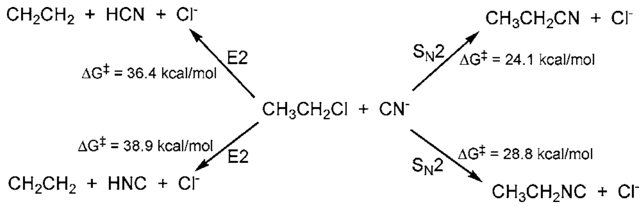
ABSTRACT



Reliable theoretical calculations predict a free energy barrier for nitrile formation from the reaction between the cyanide ion and ethyl chloride in DMSO solvent of 24.1 kcal/mol, close to the experimental value of 22.6 kcal/mol. We have also predicted that the isonitrile formation is less favorable by 4.7 kcal/mol, while the elimination mechanism is less favorable by more than 10 kcal/mol. These results indicate that isonitrile formation and bimolecular elimination are not significant side reactions for primary alkyl chloride reactions.

Bimolecular nucleophilic substitution (S_N2) reactions are widely used in organic chemistry and the fine chemical industry. However, it is known that S_N2 reactions are usually accomplished by bimolecular elimination (E2), which can lead to low yields. Therefore, it is relevant to know how important side reactions are when planning synthetic routes, and theoretical ab initio calculations are an interesting tool for investigating these competitive reactions. Indeed, reliable predictions could be very useful in organic synthesis, and fundamental investigations of these reactions have recently received considerable attention.[1−12]

Among the many nucleophilic species, the cyanide ion is a very interesting one because of the possibility of forming a carbon−carbon bond. Experimental studies indicate that reactions of cyanide ion with alkyl halides are slow in protic solvents such as alcohols but are considerably accelerated in dipolar aprotic solvents such as dimethyl sulfoxide (DMSO).[13−15] In the case of primary halides, a high yield of the corresponding nitrile was obtained.[13,14] However, it is not clear how important the E2 pathway is. Furthermore, the cyanide ion is an ambident nucleophile, and both the carbon and nitrogen atoms of this ion can act as the reactive site. In the second case, the S_N2 reaction would lead to the isonitrile structure R−NC. The relative activation free energy

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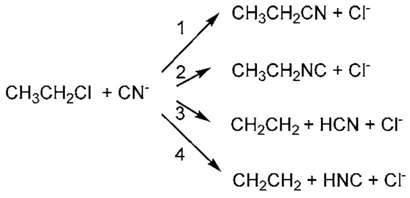
of these pathways is not known, and just one theoretical study of the S_N2 pathway leading to the nitrile has been reported to date.[3]

The aim of the present work is to provide a complete theoretical study of the possible reaction pathways, and free energy barriers, of the reaction between the cyanide ion and ethyl chloride in DMSO solution. This can be regarded as a model system for the interaction of the cyanide ion with alkyl chlorides.

There are four possible reaction pathways for this system, presented in Scheme 1. Reaction 1 is the S_N2 pathway leading to the ethyl cyanide. Reaction 2 is also an S_N2 pathway, but producing the respective isonitrile. Reactions 3 and 4 are bimolecular elimination reactions, taking place through the carbon and nitrogen atoms, respectively.

Scheme 1



The ab initio calculations were performed at the B3LYP/6-31G(d) level of theory for geometry optimization and harmonic frequency analysis. To obtain reliable activation energies, single-point calculations were done at MP2/6-311+G(2df,2p) and CCSD(T)/6-31+G(d) levels. The additivity approximation was used to obtain effective CCSD(T)/6-311+G(2df,2p) energies.

The solvent effect was included through the polarizable continuum model (PCM)[16−18] with the integral equation formalism routines and using the Pliego and Riveros parametrization[19,20] developed for modeling solvation in DMSO. It was recently shown that this parametrization is very reliable for predicting pK_a values in DMSO,[21] which supports its use for anion−molecule reactions. Indeed, a recent theoretical study of the reaction between the acetate ion and ethyl halides[1] provides further support for this methodology. Therefore, the present study should be able to make accurate predictions for this system. All of the ab initio calculations were done using the Gaussian 98 program[22] for the gas-phase calculations, and for the PCM computations, we have used the Gamess program.[23]

The optimized transition-state structures are depicted in Figure 1, and the calculated activation ($\Delta G^\ddagger$) and reaction (ΔG) free energy contributions are presented in Table 1. As it can be seen, the relative reactivity order predicted in the gas phase ($\Delta G_g^\ddagger$) is the same as that determined in solution ($\Delta G_{sol}^\ddagger$). Indeed, the solvent contribution ($\Delta\Delta G_{solv}^\ddagger$) increases the activation barrier by 14 to 18 kcal/mol for every step, and the effect is greater for the elimination reaction. On the other hand, for the reaction free energy, the solvent has a minor effect, decreasing the free energy by less than 5 kcal/mol. Analysis of Table 1 shows that reaction 1, which forms the nitrile, is the most important, with an activation free energy barrier of 24.1 kcal/mol. The product is thermodynamically favorable by 30.3 kcal/mol.

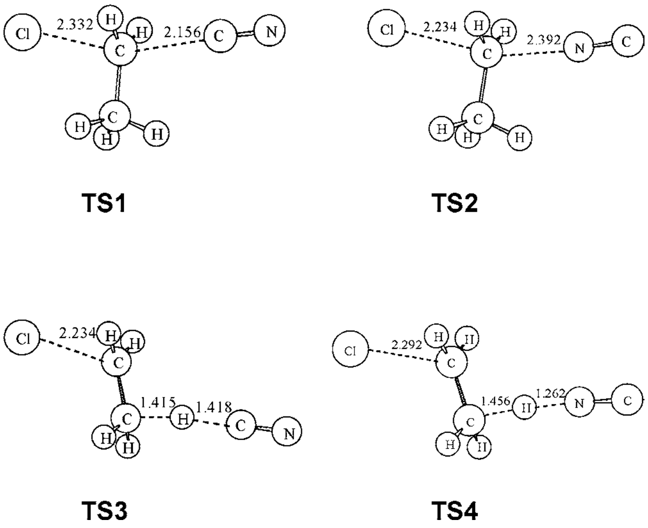


Figure 1. Transition states for the reaction between the cyanide ion and ethyl chloride.

The next lowest barrier occurs for reaction 2, leading to the isonitrile. The free energy barrier of 28.8 kcal/mol makes this pathway less favorable by 4.7 kcal/mol in relation to reaction 1. In addition, the reaction free energy is only qj−5.7 kcal/mol, indicating the reversibility of this reaction. It is interesting to note that the solvent stabilizes the TS1 structure more than the TS2 one. As a consequence, in the solution phase, nitrile formation is even more favorable than isonitrile formation in comparison to the gas phase.

Reactions 3 and 4, corresponding to the elimination mechanisms, have very high $\Delta G^\ddagger$ values of 36.4 and

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Table 1. Activation and Reaction Properties for the EtCl + CN^- Reaction[a]

	activation properties			
	$\Delta E^{\ddagger b}$	$\Delta G_g^{\ddagger c}$	$\Delta\Delta G_{solv}^{\ddagger d}$	$\Delta G_{sol}^{\ddagger e}$
TS1	3.6	10.3	13.9	24.1
TS2	7.1	13.3	15.5	28.8
TS3	15.6	18.6	17.8	36.4
TS4	18.7	20.4	18.5	38.9

	reaction properties			
	ΔE^{b}	ΔG_g^{c}	$\Delta\Delta G_{solv}^{d}$	ΔG_{sol}^{e}
1	−30.2	−26.2	−4.1	−30.3
2	−7.3	−3.6	−2.1	−5.7
3	2.9	−4.2	−4.7	−8.9
4	18.2	10.5	−3.6	7.0

[a] Units of kcal/mol, 298.15 K, standard state of 1 mol/L. [b] Activation and reaction energy obtained at the CCSD(T)/6-311+G(2df,2p) level on the B3LYP/6-31G(d)-optimized structure (see text). [c] Gas-phase free energy. [d] Solvent contribution (DMSO). [e] Liquid-phase free energy.

38.9 kcal/mol, respectively. In addition, reaction 4 is thermodynamically unfavorable, with a reaction ΔG of 7.0 kcal/mol. Thus, only the elimination through TS3 is possible.

There are experimental data for the kinetics measured for this reaction by Fang et al.[3] These authors have determined that the $\Delta G^{\ddagger}$ at room temperature is 22.6 kcal/mol, in excellent agreement with our calculated value of 24.1 kcal/mol. The deviation of only 1.5 kcal/mol shows the high reliability of our calculations.

The present study is representative for the reaction of the cyanide ion with primary alkyl chlorides. Our results suggest that primary chlorides form cyanides quantitatively and that E2 reactions will not be important even at high temperatures. Furthermore, the isonitrile formation, the main side reaction investigated, should also be unimportant at room temperature, and even at temperatures as high as 140 °C, corresponding to the experimental conditions used in synthesis, this reaction should contribute less than 1% to the products. These are very important fundamental results, because they show that the E2 reaction, usually thought to be the main side reaction, does not take place at all.

Although our calculations were performed for a primary alkyl chloride, they are relevant for reactions involving secondary alkyl chlorides. In fact, it seems improbable that elimination becomes much more favorable in this case, and experimental studies show that good yields of nitriles are also obtained.[13,14] Nevertheless, the yields are not as high as that observed for primary chlorides, suggesting that side reactions could be more important. On the basis of the present results, we could analyze the possible source of side products or low yields experimentally observed. Under experimental conditions adequate for synthetic applications, a very high concentration of the reactants is used, and ion-pair formation should take place. In this case, it is reasonable to suppose that the isonitrile formation could be favored due the interaction of the counterion with the carbon side of the cyanide ion. A calculation of the atomic charges by the CHELPG method using the MP2/6-311+G(2df) wave function predicts a charge of −0.41 on the N atom and of −0.59 on the C atom, suggesting that the counterion would favor the isonitrile formation. It should be noted that in a recenty theoretical study, Luque et al.[24] has concluded that the tautomeric equilibrium involving 2-aminopyrroles is influenced by the counterion. Therefore, the influence of the counterion on the formation of products of organic reactions is a question that deserves more investigation. Furthermore, it is interesting to speculate if the dark product observed in some cases could have its origin in the isonitrile formation.

In summary, the bare cyanide ion reacts with primary alkyl chlorides in DMSO, forming alkyl cyanides, and the isonitrile formation and elimination reactions are not important side reactions.

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