



Alkylation of potassium ethyl acetoacetate: HSAB versus Marcus theory



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ABSTRACT

Investigation of the reactions of potassium ethyl acetoacetate (**KEAE**) with C_2H_5X ($X = Cl, Br, \text{ and } I$) in the gas-phase, tetrahydrofuran, and hexamethylphosphoramide was conducted at the B3LYP/6-311+G(d,p) level of theory. The C3- and O2-ethylations were examined to find out whether the Marcus or HSAB theory can explain the ambident reactivity of this nucleophile. It was found that the O2-ethylation of **KEAE** with all three halides is both kinetically and thermodynamically unfavourable in all media. Higher activation energy (as well as intrinsic activation barrier) in the O2 position is a consequence of the attractive forces between the oxygens and potassium, which are often unjustifiably neglected. This finding demonstrates that the Marcus theory is not applicable to the investigated reaction. On the other hand, the reaction is highly dependable on charge distribution and HOMO–LUMO gap in the reactant complexes, thus confirming the applicability of the HSAB rationale. The following conclusion was made: the smaller atomic number of the halogen in ethyl halide and more polar reaction medium, the more favourable charge distribution for the O2-ethylation of **KEAE**; the larger atomic number of the halogen and less polar reaction medium, the smaller HOMO–LUMO gap and more favourable the C3-ethylation.

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1. Introduction

Depending on the reaction conditions, ambident nucleophiles can perform nucleophilic attack in two (or more) different ways, and, thus, yield two (or more) different reaction products. Such behaviour of the ambident nucleophiles has been usually explained by the HSAB (hard – soft – acid – base) theory [1,2]. According to this theory hard-hard and soft-soft interactions are favourable whereas hard-soft interactions are unfavourable, implying that nucleophilic substitution reactions of the S_N2 type occur best when the nucleophile and leaving group are either both hard or both soft [1–4]. The HSAB rationale is complemented with the Klopman-Salem theory of charge and orbital control of organic reactions which states that interactions between hard species are charge-controlled, whereas interactions between soft species are orbital-controlled [5–7]. Redistribution of electron density in orbital-controlled reactions can be understood as electron transfer from electron donor to electron acceptor orbital (from HOMO to LUMO) [8].

Such a concept has been widely accepted by many researchers, but has also been criticised [9–11]. It was put forward that, in spite of the fact that different reaction conditions dictate different reaction products, the HSAB theory does not make difference between

thermodynamic and kinetic control [9,10]. In addition, the HSAB theory can only explain the obtained results, and makes poor predictions on possible charge or orbital control [9]. Mayr et al. reconsidered the papers where the alkylation reactions of typical ambident nucleophiles: NCS^- , NC^- , NO_2^- , NCO^- , $RCHNO_2^-$, amide anions, and benzene sulfinate have been investigated. They concluded that not even the site of alkylation is correctly predicted by the HSAB theory, and suggested another approach to ambident reactivity [11]. This approach differentiates between thermodynamically and kinetically controlled reactions. If an examined reaction is kinetically controlled, it has to be revealed whether the reaction is diffusion-controlled or occurs via a transition state. The regioselectivity of the latter reaction can be predicted by the Marcus theory [12].

The ethyl acetoacetate anion (**EAE**[−]) is a typical ambident nucleophile, as the alkylation reaction of this anion with ethyl halides takes place at either O2 or C3 [13] (Fig. 1). It has been demonstrated that the yield of the C-product increases, whereas the yield of the O-product decreases with the increasing atomic number of the halogen involved.

It was pointed out [11] that, unlike many other enolate anions, the alkylation of **EAE**[−] cannot be elucidated on the basis of the qualitative Marcus analysis. On the other hand, the HSAB theory explains the above reaction in the following way: Ethyl chloride, with the hard leaving group, reacts preferentially with the harder oxygen, whereas ethyl iodide, with the soft leaving group, reacts

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