# Influence of Alkylating Reagent Softness on the Regioselectivity in Enolate Ion Alkylation: A Theoretical Local Hard and Soft Acids and Bases Study

**S. Damoun, G. Van de Woude, K. Choho, and P. Geerlings***

*Eenheid Algemene Chemie, Faculteit Wetenschappen, Vrije Universiteit Brussel, Pleinlaan 2,*
*1050 Brussels, Belgium*

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C-Alkylation and O-alkylation of ethyl acetoacetate by a series of alkylating agents is investigated, in the gas phase as well as in the solvent, within a local viewpoint of the hard and soft acids and bases (HSAB) principle at the Hartree−Fock level using a 3-21+G* basis set. The Gázquez and Méndez formula for calculating the interaction energy is used to reveal the influence of the alkylating agent softness on the two possible orientations in the ethyl acetoacetate alkylation. O-Alkylation was found to be favored by a hard alkylating agent, whereas C-alkylation becomes less and less disfavored upon increasing softness.

## 1. Introduction

The keto−enol tautomerism in ketones or esters presents one of the oldest known forms of ambident reactivity, the overall reactivity of such compounds being localized in two connected reactive sites.[1] The carbonyl group, together with the nitro and the nitrile groups, is one of the groups to show the highest effectiveness to acidify a hydrogen atom bonded to an α-carbon, due to the combination of its inductive electron-withdrawing activity and its ability to delocalize the negative charge remaining when the proton is removed.[2]

The extent of enolization in 1,3-dicarbonyl compounds, such as *β*-keto esters, and the structure and stereochemistry of the enols are dependent on the structure of the dicarbonyl compound but also on the solvent. Nonpolar, aprotic solvents usually favor the enol form, which normally exists as a monomer with an intramolecular bond, while, in more polar solvents and especially in protic solvents, the amount of keto form is usually enhanced, since this tautomer is more prone to solvation or intermolecular hydrogen bonding with solvent molecules. The mesomerism in these anionic ambident nucleophiles involves sites of quite a different nature, implying an unequal negative charge distribution between both reactive sites of the system. This is for instance reflected in the concurrent formation of both C-alkylated and O-alkylated products, as either the carbon or the oxygen could acquire more negative charge (carbanionic nucleophilicity and oxyanionic nucleophilicity). The two possible orientations are elucidated in Scheme 1.

From the huge amount of data existing on the subject of alkylation of enolate ambidents, it appears that the regioisomer ratio proves very sensitive to the nature of reagents and the reaction conditions, in particular the solvent. The factors influencing the dual reactivity of enolates and ultimately the kinetic product ratio are usually interrelated, but under appropriate conditions, one factor can become dominant and determines the direction of attack. Factors to be considered are (for a comprehensive review, see ref 3): (1) the nature of the metallic cation, whose effect is greater in nonpolar solvents; so O-alkylation of ethyl acetoacetate varies from 47 to 23% in the K, Na, and Li salt series, in the same solvent, DMSO;[4] (2) the nature of the solventl; and (3) the nature of the electrophile, important factors being, for example, branching (the O-alkylation of sodioacetoacetonate increases from 3 to 27% on using either *n*-propyl bromide or isopropyl bromide) as well as the nature of the leaving group. The greater the degree of carbonium ion character at the site of the carbon being substituted in the electrophile, the greater its tendency to react with the anionic site in the enolate ion of largest electron density. The hardness of the leaving group ($I < Br < Cl < OSO_2R$, sulfate) thus favors O-alkylation (vide infra).

When considering factors responsible for regioselectivity, it should be remembered that the vast majority of alkylations of ambident enolates are kinetically controlled; i.e., the C- vs O-alkylation is determined by the ratio of the reaction rates with respect to each site. More generally, the mechanism of substitution of ambident nucleophilic enolates is thought to involve a second-order kinetics ($S_N2$ process), although the transition state can be closer to the $S_N1$ or to the $S_N2$ type, according to the site which undergoes the attack.

Ambident reactivity has already been accounted for on theoretical grounds by G. Klopman at the end of the 1960s in terms of a perturbational treatment in a molecular orbital context.[5] The simplified treatment of the reactivity of ambident nucleophiles in terms of frontier molecular orbitals (FMO) has been beatifully summarized by Fleming.[6]

A major breakthrough in this field has been the introduction of Pearson's hard and soft acids and bases (HSAB) theory[7] offering a more intuitive approach, free from an orbital context, as used extensively by, for example Reutov's group.[8]

Within the context of modern conceptual density functional theory (DFT),[9,10] Pearson's hard and soft acids and bases principle, however, found a sound basis[11] both for sharp definitions of the concepts (hardness/softness) and the rules they should obey upon molecular interaction.

The foundation of the HSAB principle is an important example of the impact conceptual DFT in recent years when rationalizing chemical reactivity using reactivity descriptors (for reviews, see refs 10, 12, and 13). Many studies performed until now are essentially "one reactant" studies in which a given reactivity index of one reactant, say A, is explored without

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* Corresponding author. E-mail: pgeerlin @ vub.ac.be. Tel: 00 33 2 629 3314. Fax: 0033 2 629 33 17.

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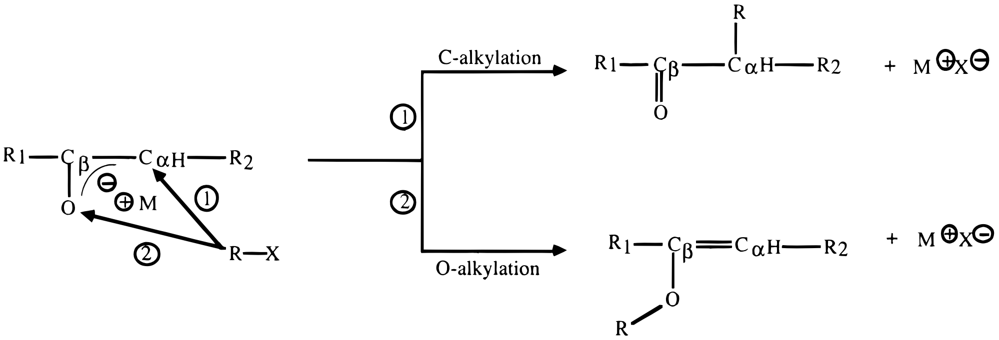
**SCHEME 1**



explicitly considering the properties of the other reactant B or the solvent. This approach is obviously doomed to fail when considering the implementation of the HSAB concept and in view of the regioselectivity aspect that one should even work at a local (i.e., atomic) rather than at a global (i.e., molecular) level.

The local HSAB principle, formulated by Gázquez and Méndez,[14] and successfully applied by them and the present authors in studies of regioselectivity of Diels−Alder reactions,[15] 1,3-dipolar cycloadditions,[16] and [2+1]-cycloadditions,[17] is a proper way to tackle the ambident reactivity problem, even permitting incorporation of the effect of solvent. These authors presented a general formulation and, using some typical values for the atomic properties involved (softnesses, fukui functions, ....), pointed out some general features of the regioselectivity problem.[18] They essentially concentrated on the role of the total softness of the reaction partner B when comparing two possible reaction sites, k and l, of partner A, characterized by their local softnesses, without referring to a particular series of experimental data or considering the role of the solvent in an explicit way. They, however, remarked that all values invoked in the interaction energy (vide infra), like local softness and chemical potential, are influenced by the solvent. A critical study of the local HSAB principle was also performed by Krishnamurty et al.[19] in the investigation of interactions between reagents largely differring in global softness.

In the present work, the ansatz is different. We selected from the literature three well-documented series of data showing, for a given enolate—in this case, the enolate from ethyl acetoacetate—a variation of the total softness of the reactant, all data referring to experiments in DMF carried out at room temperature. We thereby hoped to gain a realistic view of the local HSAB at work, including the effect of the solvent, the latter aspect being also related to our recent studies on the evaluation of solvent effect on DFT reactivity descriptors.[21,22]

## 2. Methodology

**2.1. Systems Chosen.** The C- and O-alkylation of ethyl acetoacetate (**A**) ($C_2H_5OCOCHCOCH_3^-$) by a given alkylating reagent **B** (R−X) are considered; the systems chosen are summarized in Table 1, each time mentioning the alkylating agent B, and the O-/C-alkylation ratio is grouped according to the experimental references. In all these groups a marked change of the softness can be expected on an intuitive basis. Indeed, the softness increases systematically when going down in a column in the periodic table (O → S in series II, Br → I in series I, with F added as a reference) and upon introducing unsaturations (in series III).[22,23]

**TABLE 1: Experimental Data on O- and C-Alkylation Percentages for Ethyl Acetoacetate Enolate $CH_3COCHCHCOOC_2H_5$ (=A)[a]**

| series | alkylating agent B | reaction number | O-alkylation % | C-alkylation % | refs |
|---|---|---|---|---|---|
| I | $CH_3F$[b] | 1 | | | |
| | $CH_3OTs$[c] | 2 | 89 | 7 | 8b |
| | $CH_3Br$ | 3 | 14 | 42 | 8b |
| | $CH_3I$ | 4 | 5 | 31 | 24 |
| II | $CH_3OCH_2Cl$ | 5 | 100 | 0 | 25 |
| | $CH_3SCH_2Cl$ | 6 | 0 | 100 | 26 |
| III | $CH_3CH_2CH_2Cl$ | 7 | 100 | 0 | 4a,b,24 |
| | $CH_2{=}CHCH_2Cl$ | 8 | 25 | 45 | 4a,b,24,8b |

[a] All data from measurements in HMPT. [b] No experimental data available, included as a reference (see text). [c] Ts = tosylate (=$CH_3$-$C_6H_4SO_3^-$).

**2.2. Basic Formula.** Upon interaction of a reactant B with a given atom k on reactant A, the interaction energy can be decomposed in two terms, as pointed out by Méndez and Gázquez:[18] a first term, $\Delta E_v$, representing the energy change at constant external potential and corresponding to the charge transfer process between A and B at constant external potential, and the second term, an energy change at constant chemical potential, $\Delta E_\mu$, equivalent to a reshuffling of the charge distribution at constant chemical potential. This finally leads to an interaction energy of the form

$$\Delta E_{\mathrm{A,k}} = -\frac{1}{2}\frac{(\mu_{\mathrm{A}}-\mu_{\mathrm{B}})^2}{s_{\mathrm{A,k}}+S_{\mathrm{B}}}S_{\mathrm{B}}s_{\mathrm{A,k}} - \frac{1}{2}\frac{\lambda}{s_{\mathrm{A,k}}+S_{\mathrm{B}}} \qquad (1)$$

where $\mu_A$ and $\mu_B$ represent the electronic chemical potential of A and B, respectively, $S_B$ the total softness of B, $s_{A,k}$, the condensed local softness on atom k of A, equal to the product of the total softness of A and the fukui function $f_{A,k}$. Further details about the introduction and definition of these quantities can be found in ref 9.

The positive factor $\lambda$ has been shown to be proportional to an effective number of valence electrons involved in the reaction step considered.[14,27,28]

It should be noted that the analysis of the influence of the alkylating reagent softness $S_B$ on the regioselectivity in enolate ion A alkylation on the basis of formula 1 may be considered as a global (B)−local (A) application of the HSAB principle. Within the context of a local−local application of this approach in which the regioselectivity is rationalized on the basis of equal condensed local softnesses of the two reactive sites of the two reaction partners, Méndez and Gázquez[14] have shown that a minimization of the grand potential for an interaction of atom k (on A) and l (on B) with respect to $S_A$ and $S_B$ respectively leads to the condition of $S_A = S_B$. They also assumed that the interaction is more favored when the two grand potential values are equal, leading to equal fukui functions of atoms k and l. Combining the two conditions, they arrived at a condition of equal condensed local softnesses on atoms k and l. In one of our previous papers[15] we regained this conclusion by minimizing directly the grand potential versus condensed local softnesses without the requirement of equal global softnesses and/or equal fukui functions.

**2.3. Evaluation of the Quantities in Equation 1.** The usual finite difference approach[9] has been followed in order to evaluate $\mu$, $f(\underline{r})$, $S$, and $s(\underline{r})$. The working equations can be summarized as follows

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(\underline{r})} \approx -\left(\frac{I+A}{2}\right) \qquad \text{(for A and B)} \quad (2)$$

$$S = \frac{1}{2\eta} \quad \text{with} \quad \eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\underline{r})} \approx \left(\frac{I-A}{2}\right) \qquad \text{(for A and B)} \quad (3)$$

$$f(\underline{r}) = \left(\frac{\partial \rho(\underline{r})}{\partial N}\right)_v \quad \text{with} \quad f^-(\underline{r}) \approx \rho_N(\underline{r}) - \rho_{N-1}(\underline{r}) \qquad \text{(for A)} \quad (4)$$

$$s^-(\underline{r}) = Sf^-(\underline{r}) \quad (5)$$

where $I$ and $A$ are the vertical ionization energy and the electron affinity, respectively. When the electron density $\rho(\underline{r})$ is integrated over all orbitals centered on an atom k, one obtains the atomic charge, which, according to Yang and Mortier, can be used to obtain the condensed forms of the above mentioned properties[29]

$$f_k = f_k^- = q_k(N) - q_k(N-1) \quad (6a)$$

and

$$s_k^- = Sf_k^- \quad (6b)$$

These condensed quantities can easily be calculated from the atomic charges $q_k(N)$ and $q_k(N-1)$ on the atom k in $N$ and $N-1$ systems, obtained via various techniques for population analysis methods. Easily interpreted, the condensed fukui function and condensed local softness have been proven by Yang and Mortier to be very useful local reactivity descriptors.[29]

Note that the $f^-(\underline{r})$ and $s^-(\underline{r})$ expressions and their corresponding condensed forms have been used in view of the nucleophilic nature of A.

All calculations were performed at the Hartree–Fock level using a 3-21+G* basis set which can be expected to be adequate in view of our previous studies on regioselectivity.[15-17] Indeed, the 3-21+G* basis set was found to give an optimal quality cost/ratio for a calculation of the fukui function[30] and to be suitable for double anionic systems as considered in the calculation of the electron affinity of ethyl acetoacetate in which, with an extended basis set, an extra electron in the valence orbital no longer guarantees the confinement of the electron to the molecular region. Moreover, the use of a large basis set will prevent us from using experimental data available for the precious series containing methyl iodide. (No larger Pople-type basis set than 3-21+G* is available for iodine.)

For each compound a geometry optimization has been carried out for A. Figure 1, giving the optimized structure, shows a H-bonded sixring conformation involving the carbonyl oxygen of the ester group and a methyl hydrogen atom. The $N-1$ and $N-2$ system calculations were carried out at the same geometry to fulfill a constant external potential requirement in the evaluation of the Fukui function (eq 4).

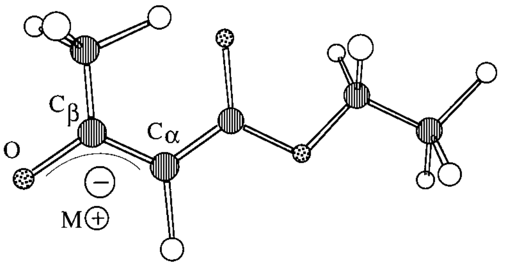


**Figure 1.** The optimized structure of the ethyl acetoacetate ion showing the sixring conformation involving the carbonyl oxygen of the ester group and a methyl hydrogen atom as well as the two competing reactive sites, the oxygen atom O and the carbon atom C$_\alpha$.

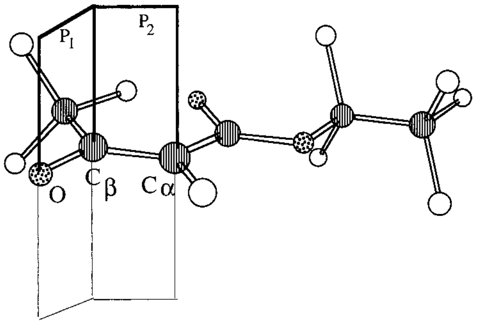


**Figure 2.** The planes $P_1$ and $P_2$ perpendicular to the C$_\alpha$C$_\beta$O plane and containing the C$_\beta$O ($P_1$) and C$_\alpha$C$_\beta$ ($P_2$) bonds, respectively.

The influence of the solvent, to be discussed at the end of this paper, is studied using the self-consistent isodensity polarized continuum model (SCI-PM),[31] which proved to be successful in studying the influence of solvent on group electronegativities and softnesses in a context of solvent effect on acidities of alkyl alcohols and basicities of alkylamines.[20,21] In this reaction field method, the solute molecular cavity is an isodensity surface of the molecule, determined by an iterative process, thereby taking into account the effect of the solvent in a self-consistent way and offering a complete coupling of the cavity and the electron density.

All calculations were performed with the Gaussian 94 program.[32] on the Cray J-916/8-1024 computer of the Free Universities of Brussels Computer Centre combined with the UniChem software package on a Silicon Graphics ONYX Extreme workstation.[33]

## 3. Results and Discussion

**3.1. Local and Condensed Local Softness in the Enolate Ion.** As eq 1 has to be examined for both C- and O-alkylations, the local softness values $s$ are needed both for the C- and the O-atoms (k = C, O). In Figure 3, we depict the local softness plot of the above mentioned enolate ion A, concentrating on the two planes containing the C$_\alpha$C$_\beta$ and C$_\beta$O bonds, respectively, and perpendicular to the C$_\alpha$C$_\beta$O plane, as can be seen in Figure 2.

The nonintegrated $s^-(\underline{r})$ function clearly indicates the larger extent of high contour values in the neighborhood of the α-carbon atom as compared to the carbonyl oxygen. This sequence is preserved upon integration, yielding a condensed local softness of 1.99 for carbon and 1.77 for oxygen, in line with the harder character of the oxygen atom already put forward by Reutov[3] and Klopman,[5] and it agrees with previous work by us on the simplest enolate $CH_2CHO^-$, where high level calculations (CISD using a 6-31 ++ G** basis) were performed.[34]

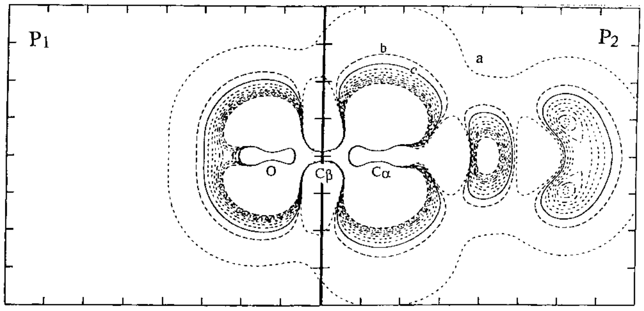


**Figure 3.** Local softness s(r) of the $CH_3COCHCHCOOC_2H_5$ enolate ion A in the planes $P_1$ and $P_2$ as shown in Figure 2, the two figures being juxtaposed sharing an axis through the $C_\beta$ atom. Contour values in au: $a = 0.00005$, $b = 0.00050$, and $c = 0.00095$.

**TABLE 2: Calculated Softness Values of the Alkylating Agent ($S_B$), Electronic Chemical Potential Differences ($(\mu_A - \mu_B)^2$) and Interaction Energies ($\lambda = 0.5$) for Both C- and O-alkylation[a]**

| | alkylating agent B | reaction number[a] | $S_B$ | $(\mu_A - \mu_B)^2$ | $\Delta E_O$ | $\Delta E_C$ |
|---|---|---|---|---|---|---|
| I | $CH_3F$ | 1 | 1.426 | 0.0186 | −0.0865 | −0.0808 |
| | $CH_3OTs$ | 2 | 1.907 | 0.0247 | −0.0799 | −0.0761 |
| | $CH_3Br$ | 3 | 2.106 | 0.0266 | −0.0778 | −0.0746 |
| | $CH_3I$ | 4 | 2.466 | 0.0294 | −0.0745 | −0.0723 |
| II | $CH_3OCH_2Cl$ | 5 | 2.148 | 0.0291 | −0.0784 | −0.0754 |
| | $CH_3SCH_2Cl$ | 6 | 2.437 | 0.0253 | −0.0728 | −0.0703 |
| III | $CH_3CH_2CH_2Cl$ | 7 | 2.025 | 0.0214 | −0.0803 | −0.0770 |
| | $CH_2{=}CHCH_2Cl$ | 8 | 2.311 | 0.0191 | −0.0769 | −0.0744 |

[a] Reaction numbers refer to the SB classification.

**3.2. Site Selectivity in Vacuo.** In Table 2 we depict the calculated total softness values for the alkylating agents, $S_B$, the square of the difference between the chemical potentials and the interaction energy both in the case of C- and O-alkylation, $\Delta E_C$ and $\Delta E_O$, in the case of a $\lambda = 0.5$ choice, as suggested by Méndez and Gázquez.[14] This $\lambda$ value will be taken in the rest of this paper. It will be seen that only its order of magnitude will be important, the one chosen being avocated in ref 18 and in agreement with the detailed discussion in ref 27.

The interaction energy turns out to be always more important (i.e., more negative) in the case of O-alkylation, as might be expected for the harder alkylating agents (cf. ref 3). However experiment (Table 1) indicates that upon increasing the softness of the alkylating agent, C-alkylation becomes more and more favored. In Figure 4 we therefore plotted both $\Delta E_C$ and $\Delta E_O$ as functions of the softness of the alkylating agent. It is clear that upon increasing softness $S_B$ the difference $\Delta E_C$ and $\Delta E_O$ becomes smaller without however reaching the cases chosen for a crossing point. Figure 5 illustrates that this difference between $\Delta E_C$ and $\Delta E_O$ decreases almost linearly (an extrapolation procedure might yield a $S_B = 3.2$ value at the crossing point). It is pleasing that all three sets, containing independent measurements, point into the same direction and confirm Reutov's arguments: as tosylate is a harder base and oxygen the hard center of an enolate ion, the O/C-alkylation ratio with alkyl tosylates must be greater than that with softer bases, such as bromides and iodides.[8b]

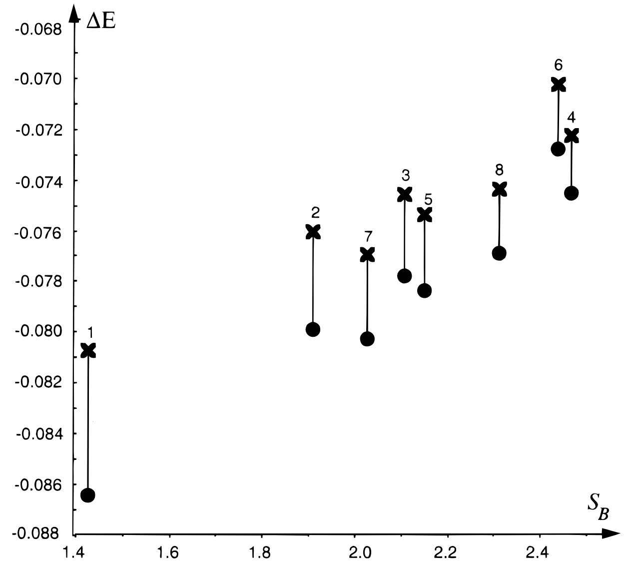


**Figure 4.** Variation of the interation energy for *C* (× = $\Delta E_C$) and O (● = $\Delta E_O$) alkylations as a function of the softness of the alkylating agent B (all values in au). Reaction numbers refer to Table 1.

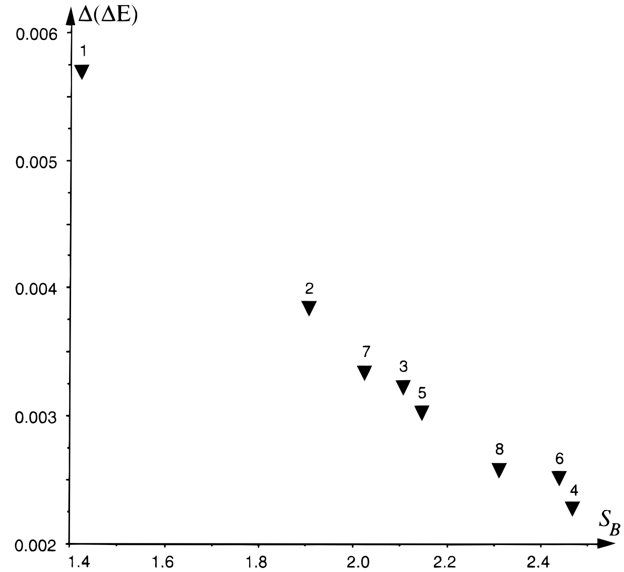


**Figure 5.** Variation of the difference between $\Delta E_C$ and $\Delta E_O$, $\Delta(\Delta E)$ ($=\Delta E_O - \Delta E_C$) as a function of the softness of the alkylating agent B (all values in au). Reaction numbers refer to Table 1.

In order to get some detailed idea on the relative importance of the two terms in eq 1 and the reasons for the noncrossing, we evaluated analytically the difference between $\Delta E_C$ and $\Delta E_O$, introducing the notations $s_{A,C}$ and $s_{A,O}$ for the local softness values at the carbon and oxygen atoms of the enolate and supposing an equal $\lambda$ value for both reactions. After some simple algebra one arrives at the expression

$$\Delta(\Delta E)_{C,O} = \Delta E_C - \Delta E_O = \frac{s_{A,C} - s_{A,O}}{(s_{A,C} + S_B)(s_{A,O} + S_B)}[-(\mu_A - \mu_B)^2 S_B{}^2 + \lambda] \quad (7)$$

where the first term in square brackets completely originates from the first term in eq 1, the second one being the difference of the two $\lambda$-type terms in eq 1. It is clear from eq 7 that the $\mu$ term, originating from difference in $\Delta E_v$ in eq 1, always favors alkylation at the C atom in view of the negative sign in front, combined with the higher softness of carbon. Otherwise stated, this term will favor interaction at the softest center, whatever the softness of the akylating agent ($S_B$).

The second term ($\lambda$ term originating from the difference in $\Delta E_\mu$ in eq 1) on the other hand invariably favors reaction at the oxygen in view of the $s_{A,C}$, $s_{A,O}$ sequence. The two terms are thus competing due to the opposite sign for a given $s_{A,C}$, $s_{A,O}$ combination. Looking now at the order of magnitude of both

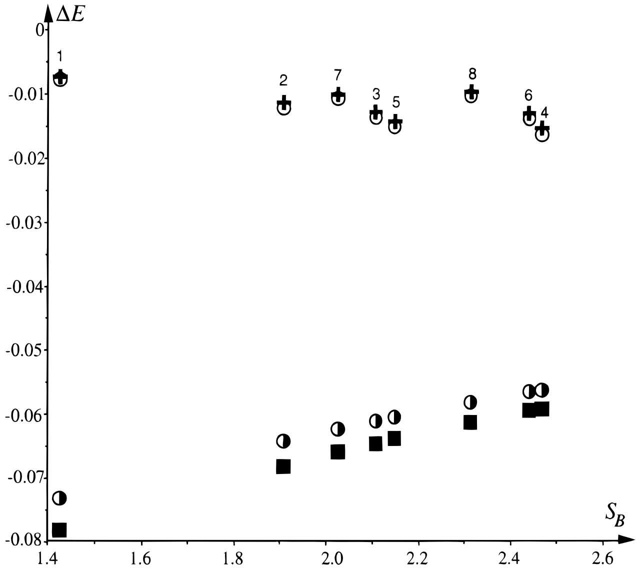


**Figure 6.** Variation of the two components of $\Delta(\Delta E)$ (cf. Figure 5) with $S_B$; the indices $\mu$ and $v$ referring to the terms in eq 1 and reaction numbers refer to Table 1 (■ = $\Delta E_{\mu,O}$, ◑ = $\Delta E_{\mu,C}$, + = $\Delta E_{v,O}$ ($\lambda = 0.5$), ○ = $\Delta E_{v,C}$ ($\lambda = 0.5$)).

terms, essentially due to the smallness of the electronic chemical potential difference, the $\lambda$ term is more important, thereby leading to oxygen alkylation. However it is clear that upon increasing the softness of B, the C-alkylation gets less disfavored and that after crossing at $S_B = 3.2$ the highly soft alkylating agent will attack the softest of both nucleophilic centers in the enolate. It is interesting to see that this crossing occurs for an alkylating reagent softness $s_B$ equal to

$$s_B = \frac{\sqrt{\lambda}}{|\mu_A - \mu_B|} \tag{8}$$

which decreases with increasing $|\mu_A - \mu_B|$.

The positive quantity $s_{A,C} - s_{A,O} = s_A(f_{A,C} - f_{A,O})$ has been shown to be only slightly sensitive to the computational method in view of the relatively small dependence of the fukui function differences within a single molecule on basis sets[30] and computational methods[35] used. The $\lambda$ value is constant and positive, the $|\mu_A - \mu_B|$ term on the other hand turns out to be more sensitive and remains the only term in eq 7 responsible for a possible crossing. This effect can be expected to be of special importance here, as one of the reactants is an anion necessitating the study of a double anion when evaluating $\mu$.

In Figure 6 we visualize the reason for the noncrossing of the curves in Figure 4. The $|\mu_A - \mu_B|$ value, to be squared later on, is too low to be compensated already by the total softness of B, so the differences in the $\Delta E_\mu$ term (favoring O attack) remain dominant definitely at the origin.

As these quantities are however computationally demanding (cf. the passage from an $N$ to an $(N + 1)$ and $(N - 1)$ systems) much higher level calculations, including correlation effects to be combined with the recently proposed use of smaller steps in the finite difference approximation might be considered[36] in order to bring more clarity about the noncrossing. We, however, think that the present study highlights trends and effects present in these well-documented experimental studies. Computationally more elaborate studies will indoubtedly finetune this results.

**3.3. Inclusion of the Solvent Effect.** As all experiments mentioned in Table 1 were performed in HMPT, we finally decided to recalculate the data of Table 2 with inclusion of the solvent effect. The SCI-PM calculations were performed as described in section 2.3, the $\epsilon$ value taken being 29.6.[37]

**TABLE 3: Solvent (HMPT) Corrected Calculated Softness Values of the Alkylating Agents ($S_B$), Electronic Chemical Potential Differences and Interaction Energies ($\lambda = 0.5$) for Both C- and O-Alkylations**[a]

| | alkylating agent B | reaction number | $S_B$ | $(\mu_A - \mu_B)^2 \times 10^{-3}$ | $\Delta E_O$ | $\Delta E_C$ |
|---|---|---|---|---|---|---|
| I | $CH_3F$ | 1 | 2.048 | 0.40 | −0.0585 | −0.0512 |
| | $CH_3Cl$ | *b* | 2.935 | 2.21 | −0.0497 | −0.0448 |
| | $CH_3Br$ | 3 | 3.401 | 2.39 | −0.0455 | −0.0413 |
| | $CH_3I$ | 4 | 4.523 | 2.89 | −0.0391 | −0.0364 |
| II | $CH_3OCH_2Cl$ | 5 | 3.295 | 1.07 | −0.0458 | −0.0414 |
| | $CH_3SCH_2Cl$ | 6 | 3.978 | 0.47 | −0.0405 | −0.0370 |
| III | $CH_2CHCH_2Cl$ | 8 | 3.697 | 0.82 | −0.0426 | −0.0388 |

[a] $CH_3CH_2CH_2Cl$ and $CH_3OTs$ cases were not calculated due to computational difficulties. [b] $CH_3Cl$ is introduced for comparative purposes.

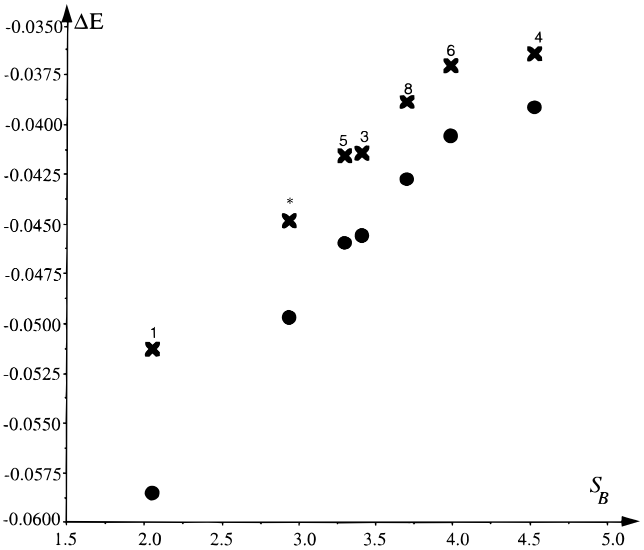


**Figure 7.** Variation of the interaction energy for C (× = $\Delta E_C$) and O (● = $\Delta E_O$) ($\lambda = 0.5$) alkylations as a function of the softness of the alkylating agent B, including solvent effect (all values in au). Reaction numbers refer to Table 3, (* = $CH_3Cl$).

In Table 3 we gather the most important results starting from calculated $s_{A,C}$ and $s_{A,O}$ values of 2.85 and 2.24, respectively. Both softness values are thus increasing in solution, as is also the case for the total B softness. This joins our results in refs 20 and 21, indicating a steady increase in (group) softness when passing from gas phase to solution, the effect being more pronounced with increasing $\epsilon$. As $\epsilon$ is relatively small [cf. acetone (20.7) and water (78.39)[37]] the effect can be expected not to be too large.

The $\Delta E$ results (for $\lambda = 0.5$) are qualitatively identical to the gas phase, as can also be seen in Figure 7, where the differences between the C- and the O-alkylation energies are given. A decomposition of the $\Delta E$ values in the $\Delta E_v$ and $\Delta E_\mu$ (Table 4) shows that the contribution of the first term, corresponding to a first step of the overall interaction and favoring the interaction of A throughout its softer reactive center, remains weak as compared to the contribution of the second term, which favors the interaction on the harder oxygen atom of A as it increases with a decreasing value of $s_{A,k}$.

The nature of HMPT, which is a dipolar aprotic solvent, may account for the unchanged global pattern, only leading to a global softening of the electrophile alkylating agents.

**TABLE 4: Calculated Interaction Energies, in Solvent (HMPT), at Constant External Potential, $\Delta E_v$, and at Constant Chemical Potential, $\Delta E_\mu(\lambda = 0.5)$, on the Oxygen and on the Carbon Atoms, Respectively**

| alkylating agent B | reaction number | $\Delta E_{v,\mathrm{O}}$ | $\Delta E_{v,\mathrm{C}}$ | $\Delta E_{\mu,\mathrm{O}}$ | $\Delta E_{\mu,\mathrm{C}}$ |
|---|---|---|---|---|---|
| $CH_3F$ | 1 | −0.00021 | −0.00023 | −0.05829 | −0.05103 |
| $CH_3Cl$ |  | −0.00140 | −0.00160 | −0.04830 | −0.04321 |
| $CH_3Br$ | 3 | −0.00122 | −0.00140 | −0.04431 | −0.03999 |
| $CH_3I$ | 4 | −0.00216 | −0.00253 | −0.03696 | −0.03390 |
| $CH_3OCH_2Cl$ | 5 | −0.00071 | −0.00082 | −0.04516 | −0.04070 |
| $CH_3SCH_2Cl$ | 6 | −0.00034 | −0.00040 | −0.04020 | −0.03661 |
| $CH_2CHCH_2Cl$ | 8 | −0.00057 | −0.00066 | −0.04210 | −0.03818 |

## IV. Conclusions

The local HSAB principle has been investigated quantitatively in a series of well-documented cases of C- vs O-alkylation problems in enolate alkylation. The influence of the nature (softness) of the alkylating reagent has been quantified, indicating that upon increasing softness, C-alkylation becomes less and less disfavored.

The reason for noncrossing of the C- and O-alkylation curves might reside in the low $(\mu_A - \mu_B)^2$ value, the only quantity highly dependent on the level of computation and which can, as was explained in detailed analysis of eq 7, give a crossing. Higher levels of calculation might shed further light upon this problem in the future.

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