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An MO-Theoretical Study of Several Bimolecular Reactions of Nucleophilic Reagents

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The relative ease of the occurrence of S_N2 and E2 reactions and the mechanism of related bimolecular processes, such as the base-catalyzed hydrolysis of carboxylic esters and the acid-catalyzed halogenation of aliphatic ketones, are discussed in connection with the MO-theoretical reactivity indices. The results indicate that the valence-inactive populations in the lowest unoccupied (LU) MO are useful reactivity indices for these nucleophilic reactions.

The molecular orbital (MO) theory has been applied by the present authors to the discussion of the mechanism of S_N2 and E2 reactions.[1,2] These two processes are known to take place more or less concurrently, in the reaction of molecules bearing a nucleophilic group with a nucleophilic reagent. In the present paper the relative ease of the occurrence of these two processes is discussed in connection with the MO-theoretical reactivity indices, while a simultaneous discussion of related bimolecular processes, such as the base-catalyzed hydrolysis of carboxylic esters[3a] and the acid-catalyzed halogenation of aliphatic ketones,[3b] is given.

The method of calculation is based on the extended Hückel approach,[4] which has already proved to be useful in the elucidation of the mechanism of many other kinds of reactions.[5-10] As MO-theoretical reactivity indices, the populations of the frontier orbitals[11] are employed, which have been defined in the frame of the extended Hückel approach. For the nucleophilic reactions as treated in the present paper, the valence-inactive population[12] of each position (atom or atomic orbital (AO)) in the lowest unoccupied (LU) MO serves as the frontier electron density. It has been ascertained that this quantity becomes a useful

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[1] H. Kato, K. Morokuma, T. Yonezawa and K. Fukui, This Bulletin, **38**, 1749 (1965).

[2] K. Fukui and H. Fujimoto, *Tetrahedron Letters*, **1965**, 4303.

[3] *E. g.*, see E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, a) p. 314; b) 365; c) 374; d) 472 (1959).

[4] R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963); **40**, 2474, 2480, 2745 (1964).

[5] H. Kato, T. Yonezawa, K. Morokuma and K. Fukui, This Bulletin, **37**, 1710 (1964).

[6] H. Kato, K. Yamaguchi, T. Yonezawa and K. Fukui, *ibid.*, **38**, 2144 (1965).

[7] T. Yonezawa, O. Yamamoto, H. Kato and K. Fukui, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **87**, 26 (1966).

[8] H. Fujimoto and K. Fukui, *Tetrahedron Letters*, **1966**, 5551.

[9] T. Yonezawa, H. Konishi, H. Kato, K. Morokuma and K. Fukui, *Kogyo Kagaku Zasshi* (*J. Chem. Soc. Japan, Ind. Chem. Sect.*), **69**, 869 (1966).

[10] T. Yonezawa, K. Shimizu and H. Kato, This Bulletin, **40**, 456, 1302 (1967).

[11] K. Fukui and H. Fujimoto, *ibid.*, **40**, 2787 (1967).

[12] K. Ruedenberg, *Rev. Mod. Phys.*, **34**, 326 (1962).

reactivity index in various types of reactions.[13]

Calculations

For the sake of simplicity, chlorine is adopted as a representative of the nucleophilic group throughout the calculations.

The numerical values used in the extended Hückel calculation are given in Table 1. The overlap integrals are evaluated by the use of Mulliken's formula[14] with Slater-type AO's.

TABLE 1. THE EFFECTIVE NUCLEAR CHARGE ($\mathcal{Z}$) OF THE SLATER-TYPE ORBITALS AND THE COULOMB INTEGRALS (h_{rr})

	H	C	O	Cl	Ref.
$\mathcal{Z}$	1.0	3.25	4.55	6.10	
$h_{rr}(ns)$, eV	−13.60	−21.43	−35.30	−25.23	15
$h_{rr}(np)$, eV	——	−11.42	−13.61	−13.34	15

In order to interpret the experimental data, the following MO-theoretical quantities[16] are calculated and employed:

The partial valence-inactive[12] AO population of AO r in the jth MO:

$$p_r{}^j = 2(C_r{}^j)^2$$

The partial valence-inactive atom population of the atom A in the jth MO:

$$p_{\mathrm{A}}{}^j = \sum_r^{\mathrm{A}} p_r{}^j$$

The partial atom bond population between the atoms A and B in the jth MO:

$$M^j_{\mathrm{AB}} = 2\sum_r^{\mathrm{A}} \sum_s^{\mathrm{B}} C_r{}^j C_s{}^j S_{rs}$$

where $C_r{}^j$ stands for the coefficient of AO r in the jth MO and where $\sum^{\mathrm{A}}$ signifies the summation over all the AO's belonging to the atom A.

The geometry of molecules is determined by the following interatomic distances:

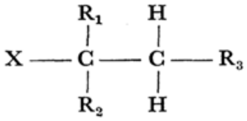
C—H 1.09 Å C—Cl 1.76 Å ${}^{\mathrm{acyl}}$C—O 1.36 Å
C—C 1.54 Å C=O 1.22 Å ${}^{\mathrm{alkyl}}$C—O 1.46 Å

with the valence angles of carbon and oxygen atoms given by Wheland's monograph,[17] except in chlorine-containing molecules, for which a uniform value, 109°28′, is adopted for carbon for the sake of simplicity.

Results and Discussion

As has been mentioned earlier, it should be noted that the comparison is made between the experimental results, in which the nucleophilic group X is not always a chlorine atom, and the theoretical values calculated with respect to the case where X is equal to chlorine.

1. S_N2 and E2 Reactions. A molecule bearing a nucleophilic group X:



$$\mathrm{X}-\overset{\mathrm{R_1}}{\underset{\mathrm{R_2}}{\mathrm{C}}}-\overset{\mathrm{H}}{\underset{\mathrm{H}}{\mathrm{C}}}-\mathrm{R_3}$$

is considered, in which R_1 and R_2 represent a hydrocarbon rest or a hydrogen atom, and in which R_3 is an arbitrary group. The reaction designated as E2[3d] is a double-linkage-forming process by way of the elimination of XH, in which the abstraction takes place dominantly at that hydrogen atom *trans* coplanar with respect to X. This process, which is known as the "*trans*" elimination, has already been treated by the present authors in the frame of the frontier electron method.[2] The experimental results have been interpreted satisfactorily by means of the population of LU MO at each hydrogen atom, $p^{\mathrm{LU}}_{\mathrm{H}}$; the population has completely paralleled the reactivity of many halogenated hydrocarbons, being largest at the β-hydrogen *trans* with respect to the halogen atom.

On the other hand, the S_N2 process is considered to occur by way of the attack of a nucleophile from the backside of the carbon to which the nucleophilic group is attached, leading in general to Walden's inversion. The present authors have already treated[1] this problem MO-theoretically with regard to methyl chloride. The LU MO has been found to localize strongly at the carbon 2p AO lying on the C–Cl axis, extending from the carbon mostly in the direction reverse to the C–Cl bond. This finding reflects the experimental result mentioned above.

It is well known that these two bimolecular processes can frequently take place in a competitive fashion in the same reactant molecule by way of the attack of the same nucleophilic reagent. In order to elucidate the factor determining the readiness of the two processes, the following reactivity indices are employed in interpreting the experimental results.

First, the partial valence-inactive population of the β-hydrogen 1s AO in LU MO, $p^{\mathrm{LU}}_{\beta\text{-H}}$, is used for the reactivity index of the β-hydrogen atom in the E2 reaction. As has been mentioned before, this value is expected to parallel the reactivity.

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[13] For instance, see K. Fukui, "Molecular Orbitals in Chemistry, Physics, and Biology," ed. by P.-O. Löwdin and B. Pullman, Academic Press, New York, N. Y. (1964), and K. Fukui, *Nippon Kagaku Sen-i Kenkyusho Koenshu*, **23**, 75 (1966), and the references cited therein.

[14] R. S. Mulliken, C. A. Rieke, D. Orloff and H. Orloff, *J. Chem. Phys.*, **17**, 1248 (1949).

[15] H. O. Pritchard and H. A. Skinner, *Chem. Revs.*, **55**, 745 (1955).

[16] R. S. Mulliken, *J. Chem. Phys.*, **23**, 1833, 1841, 2338, 2343 (1955).

[17] G. W. Wheland, "Resonance in Organic Chemistry," John Wiley & Sons, New York (1955), p. 695.

TABLE 2. THE COMPARISON OF $p^{\mathrm{LU}}_{x(\mathrm{C-Cl})}$ AND $p^{\mathrm{LU}}_{\beta-H}$ WITH $\mathrm{S_N2}$ AND E2 REACTIVITY

Reactions:

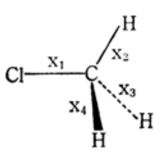
(1) $\mathrm{RBr} + \mathrm{C_2H_5O^-} \xrightarrow{k_1} \mathrm{ROC_2H_5} + \mathrm{Br^-}$ ($\mathrm{S_N2}$)[18b)]

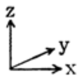
(2) $\mathrm{RBr} + \mathrm{Cl^-} \xrightarrow{k_2} \mathrm{RCl} + \mathrm{Br^-}$($\mathrm{S_N2}$)[18a)]

(3) $\mathrm{RCH_2CR'R''Br} + \mathrm{C_2H_5O^-} \xrightarrow{k_3} \mathrm{RCH{=}CR'R''} + \mathrm{C_2H_5OH} + \mathrm{Br^-}$ (E2)[18b)]

RCl	$\varepsilon^{\mathrm{LU}}$ (eV)	$\frac{1}{2}p^{\mathrm{LU}}_{x(\mathrm{C-Cl})}$	$\mathrm{S_N2}$ reactivity		$\frac{1}{2}p^{\mathrm{LU}}_{\beta-\mathrm{H}}$	E2 reactivity	$M^{\mathrm{LU}}_{\mathrm{CCl}}$
			$k_1 \times 10^5$ at 55°C ($l\,\mathrm{mol^{-1}\,sec^{-1}}$)	k_2 relative value		$k_3 \times 10^5$ at 55°C ($l\,\mathrm{mol^{-1}\,sec^{-1}}$)	
$\mathrm{CH_3Cl}$	1.8702	1.0914	——	100	——	——	−1.1392
$\mathrm{C_2H_5Cl}$	1.6242	0.9289	118.2	1.97	0.0793	1.2	−0.9321
$\mathrm{(CH_3)_2CHCl}$	1.4873	0.9137	2.1	0.040	0.0862	7.6	−0.9028
$\mathrm{(CH_3)_3CCl}$	1.2370	0.8466	small	0.009	0.0911	50	−0.8359

Secondly, the $\mathrm{S_N2}$ process is treated in the following way. The four hybrids belonging to the tetravalent carbon atom attached to the chlorine atom are designated as x_1, x_2, x_3, and x_4; of those, x_1 is taken to be associated with the C–Cl bond. The LU MO obtained by the extended Hückel calculation is transformed into the linear combination of x_1, x_2, x_3, and x_4. The partial valence-inactive AO population of $x_1(=x(\mathrm{C-Cl}))$ in LU MO, $p^{\mathrm{LU}}_{x(\mathrm{C-Cl})}$, is calculated as responsible for the data being comparable with those of the experimental data. This theoretical index corresponds to the frontier electron density for $\mathrm{S_N2}$ reactivity in the frame of the extended Hückel scheme.





An illustration of the calculations is the case of methyl chloride. The coordinates are taken as indicated. The hybrids are represented by:

$$x_1 = 0.5(2s) - 0.866025(2px)$$
$$x_2 = 0.5(2s) + 0.288675(2px) + 0.816497(2pz)$$
$$x_3 = 0.5(2s) + 0.288675(2px) + 0.707107(2py) - 0.408249(2pz)$$
$$x_4 = 0.5(2s) + 0.288675(2px) - 0.707107(2py) - 0.408249(2pz)$$

The extended Hückel MO of LU level is given by:

$$\phi^{\mathrm{LU}} = -\,0.193928\,x_{2s} + 1.094344\,x_{2px} + \cdots$$

which can easily be transformed into:

$$\phi'^{\mathrm{LU}} = -\,1.044694\,x_1 + 0.218946(x_2+x_3+x_4) + \cdots$$

Hence, the index $\frac{1}{2}p^{\mathrm{LU}}_{x(\mathrm{C-Cl})}$ is calculated to be 1.091386.

Such a computation was made with various alkyl chlorides; the results are indicated in Table 2, together with the experimental data. The partial atom bond population between α-carbon and chlorine in LU MO, $M^{\mathrm{LU}}_{\mathrm{CCl}}$, is also given in Table 2 in order to explain the reaction mechanism.

The experimental results are taken from the case of alkyl bromides, which can provide abundant data for a comparison with the theory. This substitution is possible as long as one is concerned only with the change in the relative rate resulting from the structural difference of alkyl groups.

From Table 2 it can be seen that, as the alkyl group varies from $\mathrm{CH_3}$ to $\mathrm{C_2H_5}$, i-$\mathrm{C_3H_9}$, and t-$\mathrm{C_4H_9}$, the index $p^{\mathrm{LU}}_{x(\mathrm{C-Cl})}$ clearly decreases, while $p^{\mathrm{LU}}_{\beta-\mathrm{H}}$ increases. This implies that the nucleophilic reactivity of α-carbon diminishes in this order and that the β-proton becomes more and more reactive toward abstraction by nucleophiles; this agrees with our experience that the $\mathrm{S_N2}$ reactivity is $\mathrm{CH_3} > \mathrm{C_2H_5} > i\text{-}\mathrm{C_3H_7} > t\text{-}\mathrm{C_4H_9}$, while the E2 reactivity is $\mathrm{C_2H_5} < i\text{-}\mathrm{C_3H_7} < t\text{-}\mathrm{C_4H_9}$.

The value of $M^{\mathrm{LU}}_{\mathrm{CCl}}$ is calculated to be always negative. This means that the C–Cl bond is weakened by the approach of an electron-donor reagent. In addition, the absolute value of $M^{\mathrm{LU}}_{\mathrm{CCl}}$ decreases in the order of alkyl groups mentioned above; this is consistent with, or, more strictly, not contradictory to, the experimental results in which the $\mathrm{S_N2}$ reactivity decreases in this order.

Table 2 also indicates the energy of LU MO, $\varepsilon^{\mathrm{LU}}$. This energy decreases in the order of alkyls stated above. It appears that this implies that the nucleophilic reactivity increases in this order. However, if one assumes the ionization potential of an

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18) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York (1953), a) p. 306; b) p. 419; c) M. L. Dhar, E. D. Hughes, C. K. Ingold and S. Masterman, *J. Chem. Soc.*, **1948**, 2055.

alkoxyl anion to be *ca.* 6—8 eV,[19] the ratio of $\Delta\varepsilon^{LU}$ to $(\varepsilon^{LU}-\varepsilon'^{HO})$, where ε'^{HO} is the energy of the highest occupied (HO) MO of the reagent, is small compared to $\Delta p_r^{LU}/p_r^{LU}$. According to the perturbation theory[20] for the interaction between reactant and reagent, the stabilization energy in an nucleophilic attack is approximately proportional to:

$$\frac{p_r^{LU}}{\varepsilon^{LU}-\varepsilon'^{HO}} \quad (r\text{: } x(\text{C–Cl}) \text{ or } \beta\text{-H})$$

Therefore, the result reported above implies that in the present case the reactivity can be discussed most conveniently in terms of p_r^{LU}.

The reason for the positive ε^{LU} value should be mentioned here. The basis functions usually adopted in extended Hückel MO's, and in the present case as well, are those AO's in the occupied valence shell only, so the unoccupied MO's are generally calculated to possess an unreasonably high energy. This point is improved by a suitable basis-set extension.[21]

Furthermore, $p_{\beta\text{-H}}^{LU}$ is calculated with respect to various alkyl chlorides and compared with their E2 reactivities in Table 3. Moreover, in this case, the E2 reactivity data are taken from the corresponding bromide reactions. The calculation is carried out with regard to the all-staggered conformation for each compound which is considered to possess the largest existence probability.

The parallel between the calculated results and the experimental results is satisfactory. However, primary alkyl halides like *n*-propyl chloride have no *trans*-hydrogen in the staggered conformation and its β-hydrogen has only a very small $p_{\beta\text{-H}}^{LU}$ value, as may be seen in Fig. 1. On the other hand, the *trans* β-hydrogen appearing in the gauche conformation has a very large $p_{\beta\text{-H}}^{LU}$ value. Although the staggered form is 2.0 kcal more stable than the gauche one, as is indicated in Fig. 1, it is of interest that the gauche form is *ca.* 2.4 kcal more stable than the staggered in the species in which CH_3O^- is placed near the β-hydrogen. This leads one to presume that, in the transition state, the gauche form is more stable instead. For primary alkyl halides, consequently, the values p_r^{LU} of the *trans* β-hydrogen in the gauche conformation have been calculated; they are listed in Table 3.

TABLE 3. PARALLEL OF $p_{\beta\text{-H}}^{LU}$ WITH E2 REACTIVITY[18b)]

(1) $R_1R_2CHCH_2Br + C_2H_5O^- \xrightarrow{k} R_1R_2C{=}CH_2 + C_2H_5OH + Br^-$

Compound	R_1	R_2	½ $p_{\beta\text{-H}}^{LU}$	$k\times10^5$ at 55°C ($l\,mol^{-1}\,sec^{-1}$)
i-BuCl	CH_3	CH_3	0.1289	8.6
n-PrCl	H	CH_3	0.1020	5.3
n-BuCl	H	C_2H_5	0.0663	4.3
n-AmCl	H	*n*-C_3H_7	0.0551	3.5

(2) $RCH_2CH(CH_3)Br + C_2H_5O^- \xrightarrow{k} RCH{=}CHCH_3 + C_2H_5OH + Br^-$

Compound	R	½ $p_{\beta\text{-H}}^{LU}$	$k\times10^5$ at 25°C ($l\,mol^{-1}\,sec^{-1}$)
2-BuCl	CH_3	0.0909	0.282
i-PrCl	H	0.0862	0.118

(3) $RCH_2C(CH_3)_2Br + C_2H_5O^- \xrightarrow{k} RCH{=}C(CH_3)_2 + C_2H_5OH + Br^-$

Compound	R	½ $p_{\beta\text{-H}}^{LU}$	$k\times10^5$ at 25°C ($l\,mol^{-1}\,sec^{-1}$)
t-AmCl	CH_3	0.0928	4.20
t-BuCl	H	0.0911	1.00

(4) $CH_3CR_1R_2Br + C_2H_5O^- \xrightarrow{k} CH_2{=}CR_1R_2 + C_2H_5OH + Br^-$

Compound	R_1	R_2	½ $p_{\beta\text{-H}}^{LU}$	$k\times10^5$ at 25°C ($l\,mol^{-1}\,sec^{-1}$)
t-BuCl	CH_3	CH_3	0.0911	1.00
t-AmCl	CH_3	C_2H_5	0.0909	0.85
i-PrCl	H	CH_3	0.0862	0.118
2-BuCl	H	C_2H_5	0.0842	0.065
EtCl	H	H	0.0793	0.025

(5) $CH_3CH_2CR_1R_2Br + C_2H_5O^- \xrightarrow{k} CH_3CH{=}CR_1R_2 + C_2H_5OH + Br^-$

Compound	R_1	R_2	½ $p_{\beta\text{-H}}^{LU}$	$k\times10^5$ at 25°C ($l\,mol^{-1}\,sec^{-1}$)
t-AmCl	CH_3	CH_3	0.0928	4.20
2-BuCl	H	CH_3	0.0909	0.282

The Saytzeff rule has already been given a theoretical foundation by the aid of the index $p_{\beta\text{-H}}^{LU}$ with regard to only one case 2-chlorobutane.[2)] Here the rule is similarly explained also in the

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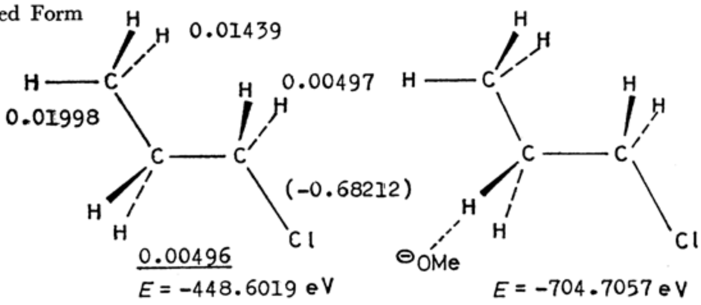
[19] The energy of the HO MO of OH^- is −1.26eV, and that of CH_3O^- is −2.28 eV, according to one calculation (T. Yonezawa, H. Kato and H. Konishi, This Bulletin, **40**, 1071 (1967)). The electron affinity of the OH radical has been reported to be 2.2 eV (H. O. Pritchard, *Chem. Revs.*, **52**, 529 (1953)) or 2.8 eV (F. M. Page, *Discussions Faraday Soc.*, **19**, 87 (1955). Consequently, the ionization potential of the free alkoxyl anion is assumed to be 2—3 eV. The value in the solvated state can be presumed to be 4—5 eV larger.

[20] For instance, see K. Fukui, "Ryoshi-Kagaku (Quantum Chemistry)," Asakura-Shoten (1968), p. 407; K. Fukui and H. Fujimoto, This Bulletin, **41**, 1989 (1968).

[21] K. Fukui and H. Fujimoto, unpublished paper; K. Fukui and T. Yamabe, unpublished paper.

1. Staggered Form



2. Gauche Form

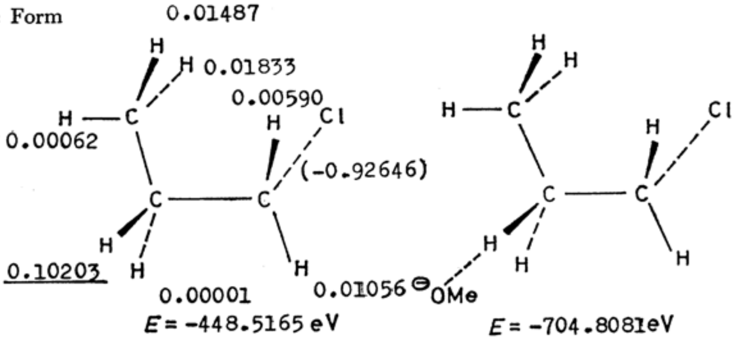
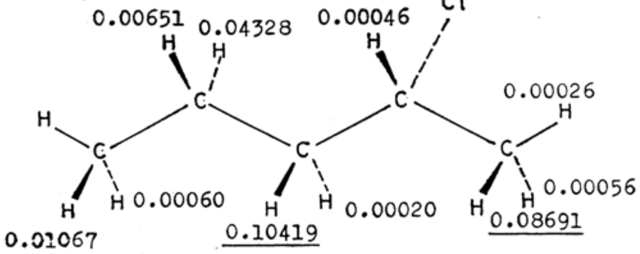


Fig. 1. The transition state E2 reactivity in *n*-PrCl. (The figures without parentheses indicate $\frac{1}{2}p_{H}^{LU}$; the figures with parentheses stand for M_{CCl}^{LU}; E is the total energy.)

1. 2-Amyl Chloride



2. *t*-Amyl Chloride

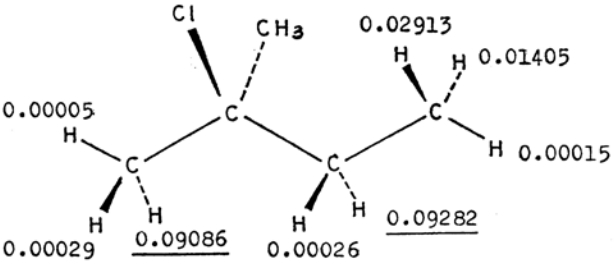


Fig. 2. The $\frac{1}{2}p_{H}^{LU}$ values of secondary and tertiary alkyl chlorides.

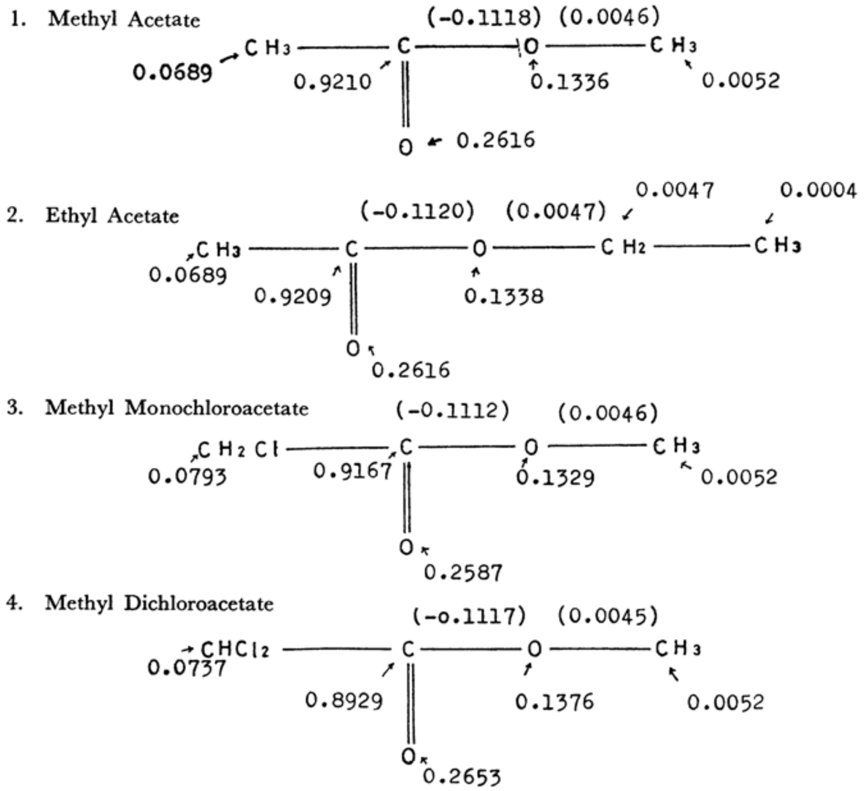


Fig. 3. The values of $\frac{1}{2}p_A^{LU}$ and M_{AB}^{LU} of carboxylic esters. (M_{AB}^{LU} values are in parentheses; $\frac{1}{2}p_A^{LU}$ for CH_2, CH_3, CH_2Cl and $CHCl_2$ are the total sum of the group.)

TABLE 4. RELATION BETWEEN M_{CCl}^{LU} AND TOTAL RATE OF BIMOLECULAR NUCLEOPHILIC REACTIONS[18c)]

Reaction: $RBr + C_2H_5O^- \xrightarrow{k}$ Olefin and ROC_2H_5

RCl	M_{CCl}^{LU}	$k\times10^5$ at 55°C (l mol^{-1} sec^{-1})
C_2H_5Cl	−0.9321	174
$CH_3CH_2CH_2Cl$	−0.9149	60.0
$CH_3CH_2CH_2CH_2Cl$	−0.6028	43.9
$CH_3CH_2CH_2CH_2CH_2Cl$	−0.3164	39.2

cases of 2-amyl chloride and *t*-amyl chloride, so as to demonstrate a more general applicability of the theory. The results are indicated in Fig. 2, exhibiting the predominance of secondary β-hydrogens over primary ones.

The partial atom bond population of α-carbon and the chlorine atom in LU MO, M_{CCl}^{LU}, is compared to the total rate of S_N2 and E2 reactions in Table 4. As has been pointed out earlier, the LU MO localizes in the C–Cl bond and is antibonding with respect to C–Cl, contributing to the weakening of the bond in the interaction with an electron donor. It should be noted that a parallel can be seen in the table between the absolute value of M_{CCl}^{LU} and the total rate.

2. Base-catalyzed Hydrolysis of Carboxylic Esters. The base-catalyzed bimolecular hydrolysis of carboxylic esters with acyl-oxygen fission (B_{AC} 2), the mechanism of which was established by the early experiment of Polanyi and Szabo[22)] using $H_2{}^{18}O$, is considered to take place through the attack of a nucleophile on the acyl carbon.

The partial valence-inactive atom populations in LU MO, p_A^{LU}, calculated for methyl acetate, ethyl acetate, methyl monochloroacetate, and methyl dichloroacetate are indicated in Fig. 3. The results indicate a distinct population localization at the acyl carbon; this is in accordance with our expectation of the selective attack of a nucleophile at that position.

The values of the partial atom bond population in LU MO, M_{AB}^{LU}, are also shown in the same figure; they indicate the strong antibonding character of this MO at the bond between acyl carbon

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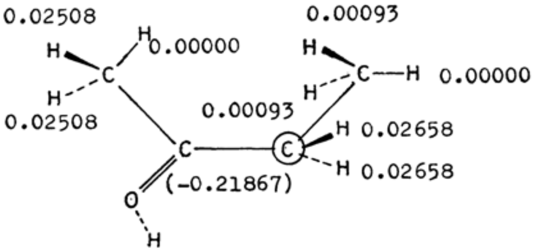
[22)] M. Polanyi and A. L. Szabo, *Trans. Faraday Soc.*, **30**, 508 (1934).

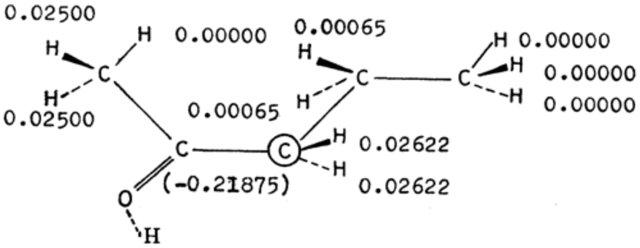
and ester oxygen, whereas this MO is bonding at the alkyl-oxygen bond, in agreement with the experimental results.

3. Acid-catalyzed Halogenation of Ketones. The accelerating effect of acids in the halogenation (and also in the deuteration and racemization) of enolizable ketones is thought to take place by way of an enol intermediate.[3c] Cardwell and Kilner[23] have reported that the Saytzeff rule applies in this process. Recently, Rappe[24] attributed the predominance of the position 3 over the position 1 in the acid-catalyzed halogenation or deuteration of 2-butanone to the difference in stability between the corresponding enol intermediates.

1. Methyl Ethyl Ketone

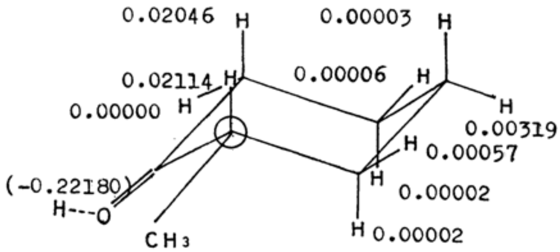


2. Methyl *n*-Propyl Ketone

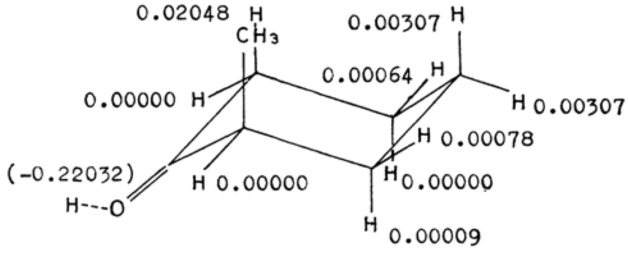


3. 2-Methylcyclohexanone

(a) Equatorial-methyl



(b) Axial-methyl



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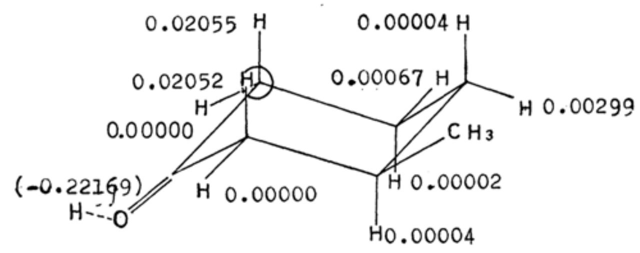
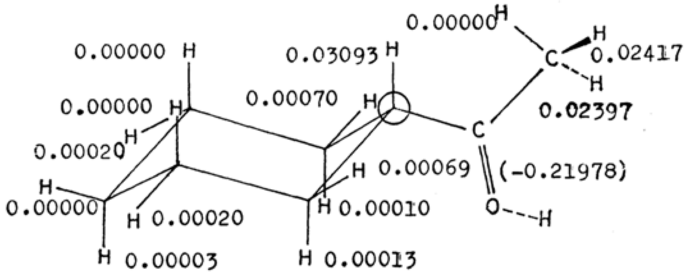
[23] H. M. E. Cardwell and A. E. H. Kilner, *J. Chem. Soc.*, **1951**, 2430.

[24] C. Rappe, *Arkiv Kemi*, **24**, 321 (1965); *Acta Chem. Scand.*, **20**, 2236 (1966); C. Rappe and W. Sachs, *J. Org. Chem.*, **32**, 3700 (1967); see also A. A. Bothner-By and C. Sun, *ibid.*, **32**, 492 (1967).

4. 3-Methyl Cyclohexanone



5. Methyl Cyclohexylketone



6. 2,5-Dimethyl Clohexanone

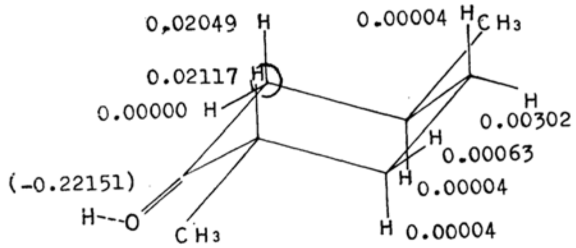


Fig. 4. The $\frac{1}{2}p_H^{LU}$ values of protonated ketones. (The position of proton is 1.1 Å from oxygen in the carbonyl plane, the angle H–O–C being 105°. The figurues in parentheses are M_{AB}^{LU}.)

In connection with this information, the p_H^{LU} values are calculated with respect to the various aliphatic or alicyclic ketones in which a proton is attached to their carbonyl oxygen. Since the location of the proton does not seriously affect the result, it is tentatively taken to be as is indicated in Fig. 4. The methylene hydrogen has a larger p_H^{LU} than the methyl hydrogen in aliphatic ketones, while in alicyclic ketones the p_H^{LU} of the methyne hydrogen is larger than that of the methylene hydrogen.

The site of attack known from experimentation is shown by a circle;[23] this site is easily verified to be consistent with the theoretical result, except in the case of 2,5-dimethylcyclohexanone. As the reagent nucleophile (the acid anion or the base part of a solvent molecule) approaches a hydrogen atom, the carbonyl C–O double bond is weakened and shifts toward a single bond, since LU MO is strongly antibonding in this region. (The M_{AB}^{LU} values are indicated in parentheses in Fig. 4). These circumstances display the orienting effect of the carbonyl group, resembling that of the nucleophilic group in E2 reactions.

It is also of interest to note the reactivity of α-hydrogens in cyclohexanones. As the diagrams for 2-methylcyclohexanone and 3-methylcyclohexanone indicate, axial hydrogens are expected to be more reactive than equatorial ones; this is in accord with Corey's observation of the enolization of 3-β-acetoxycholestan-7-one in hydrobromic acid.[25]

The calculations were carried out on the HITAC 5020 computer at the computation center of the University of Tokyo.

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[25] E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1959). The present authors are grateful to Professor Katsuhiko Ichikawa for pointing out this article.