AM1 STUDIES ON THE INTRAMOLECULAR CYCLIZATION OF ω-HALOENOLATE ANIONS*

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The intramolecular cyclizations of ω-haloenolate anions, $^-C_\alpha H_2-C(=O)-(CH_2)_{n-3}-C_\omega H_2-X$ with X = F, Cl and Br and $n = 3-7$, were investigated by the AM1 method. In most cases, cycloketone formation proceeds more favourably than cycloether formation, as predicted by the HSAB principle. The reactivity increases in the order X = F < Br < Cl for both processes, and for cycloether formation it is in the order $n = 3 < 4 < 7 < 6 < 5$ for all X but the relative order for $n = 5$ and 6 reverses in favour of $n = 6$ for cycloketone formation with X = Cl and Br. The softness of the acid centre, C_ω, decreases for a harder X($= F$) whereas it increases for a softer X($= Br$). Thus the reactivity order with respect to X suggests that the softness of the base centres O and C_α belongs to the borderline class. The transition state (TS) structures indicate that the BEP principle is obeyed in all cases, and a less reactive process has a more product-like TS.

INTRODUCTION

Reactivities of intramolecular ring-closure reactions are influenced by both activation enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$). The two, however, have compensatory effects; the enthalpy effect reflects an unfavourable strain energy[2] that hinders formation of small rings, whereas the entropy effect arises from frozen internal rotations around C—C single bonds on cyclization[3] and also from the probability of ends meeting (Ruzicka hypothesis[4]) that favour the small ring formation. Further, the reactivity order with respect to the ring size (n) varies with the leaving ability of the leaving group, the nucleophilicity of a functional group and the reaction medium.[5]

In order to unravel the mechanism of the intramolecular ring-closure reactions by clarifying the intrinsic factors controlling the reactivity, we have initiated a series of MO theoretical studies using the AM1 method.[6] In continuation to our previous work on the intramolecular cyclization of alkyl halide anions,[7] we have carried out AM1 calculations on the intramole-

cular cyclization reactions of ω-haloenolate anions, I, with $n = 3-7$ and X = F, Cl and Br, equations (1) and (2). The enolates are well known ambident substrates and reactions can take place at two different positions, C and O in equations (1) and (2), depending on the nature of the electrophilic centre, C_ω.[8]

$$(1)$$

$$(2)$$
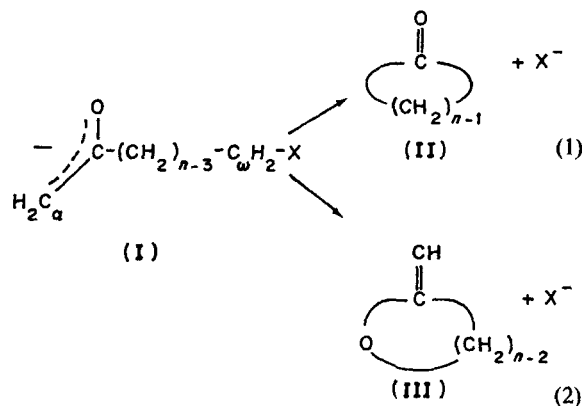
In this work, the effects of chain length, n, and the leaving group, X, on the reactivities of the ambident reaction centres were investigated, making special refer-

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ence to the Pearson's hard and soft acid and base (HSAB) principle.[9]

COMPUTATIONAL METHOD

The RHF–AM1 procedure[10] was used throughout. The AM1 method includes some electron correlation effect[11] through its parameterization[12] and it requires 2–3 orders of magnitude less computing time than even those using the relatively low-level ab initio (3–21G) method.[6,12] It has been shown that AM1 gives good results for reactions of anionic species,[13] and several studies have indicated that the AM1 method is the best mimic of the ab initio method in the computations of transition-state (TS) geometries.[14]

Ground-state geometries and energies of enolate anions were obtained for a model in which heavy atoms form a zig-zag pattern within the molecular plane, by fully optimizing all geometric parameters and confirming that all eigenvalues of the Hessian matrix are positive.[15] In the determination of the TS structures, end-to-end cyclization TSs were initially approximated, refined them by gradient norm minimization,[16,17] and characterized by confirming only one negative eigenvalue in the Hessian matrix.[15] The entropy of activation was obtained at 298 K by subtracting the entropy of the ground state from that of the TS calculated using a program implemented in AMPAC.[10]

RESULTS AND DISCUSSION

Formation of cycloketones, II [equation (1)]

The C_α atom of ω-haloenolate anions, I, can attack C_ω displacing X in an intramolecular nucleophilic substitution reaction (Intramolecular S_N2)[18] and produces cycloketones. For X = F with $n = 3$, however, we were unable to obtain the three-membered cycloketone as a product, and a proton abstraction from C_ω by C_α was found to take place instead. This is because the two hydrogen atoms on C_ω become considerably acidic owing to the two adjacent electron-withdrawing groups, F and carbonyl oxygen. Moreover, the carbonyl double bond intensifies ring strain of the cyclopropyl ring, making the three-membered cycloketone extremely unstable. When n increases further ($n \geqslant 4$), the intervening CH_2 group (or groups) reduces the electron-withdrawing power of the carbonyl group in addition to the ring strain due to the carbonyl double bond and the cycloketone formation becomes possible. [The carbon atom of a carbonyl group has a strong sp^2 hybridization character with bond angles ca 120°. This angle is reduced to 62·5° in cyclopropanone so that ring strain should be excessive, whereas in cyclobutanone this angle is relieved to ca 92° resulting in much less ring strain for the four- (or higher) membered ring ketone.] Calculated thermodynamic data are summarized in Table 1 for the ground (GS) and transition states (TS) involved in the cycloketone formation from ω-fluoroenolate anions.

The reactivity order based on the enthalpy of activation in Table 1 is $n = 6 \geqslant 5 > 7 > 4$, but when the entropy factor is taken into consideration, i.e. based on $\Delta G^{\ddagger}$, it changes to $n = 5 \geqslant 6 > 7 > 4$, slightly in favour of the small ring, $n = 5$, as expected from a general trend that smaller ring formation is favoured entropically.[3,4] The $\Delta H^{\ddagger}$ values for $n = 5$ and 6 are similar ($\delta \Delta H^{\ddagger} = 0 \cdot 1$ kcal mol^{-1}); the ring strain effect[2] in the TS (Figure 1) will be favourable for $n = 6$ since in general a six-membered ring has less strain than a five-membered ring, but the electrostatic effect[19] between the two electronegative heteroatoms, F and O, in the TS is unfavourable for $n = 6$ owing to greater repulsion at a shorter interatomic distance (d_{OF}) between them [$d_{OF} = 5 \cdot 406$ Å ($n = 5$) and $5 \cdot 271$ Å ($n = 6$)] as shown in Table 2.

The TS for the seven-membered ring system ($n = 7$) is less stable in both respects and hence has a higher $\Delta H^{\ddagger}$ than that for $n = 6$; the ring strain is greater, which will be similar to that for $n = 5$, and the electrostatic repulsion will also be greater owing to the shorter d_{OF} compared to those for $n = 6$. Further, the TS for the $n = 7$ system has an unfavourable entropy factor, $\Delta S^{\ddagger}$, so

Table 1. AM1 thermodynamic data for the cycloketone formation processes of ω-fluoroenolate anions

	GS		TS		Activation parameter[d]		
n^a	ΔH_f^b	S^c	ΔH_f^b	S^c	$\Delta H^{\ddagger b}$	$\Delta S^{\ddagger c}$	$\Delta G^{\ddagger}$
4	− 104·6	83·6	− 13·0	79·2	91·6	− 4·4	92·9
5	− 109·8	91·7	− 32·5	83·5	77·3	− 8·2	79·8
6	− 116·2	98·2	− 39·0	88·2	77·2	− 10·0	80·2
7	− 122·4	107·5	− 42·9	92·0	79·4	− 15·5	84·1

[a] Ring size of the ring to be formed.
[b] Values in kcal mol^{-1}.
[c] Values in cal K^{-1} mol^{-1} at 298 K.
[d] Activation parameter = TS − GS.
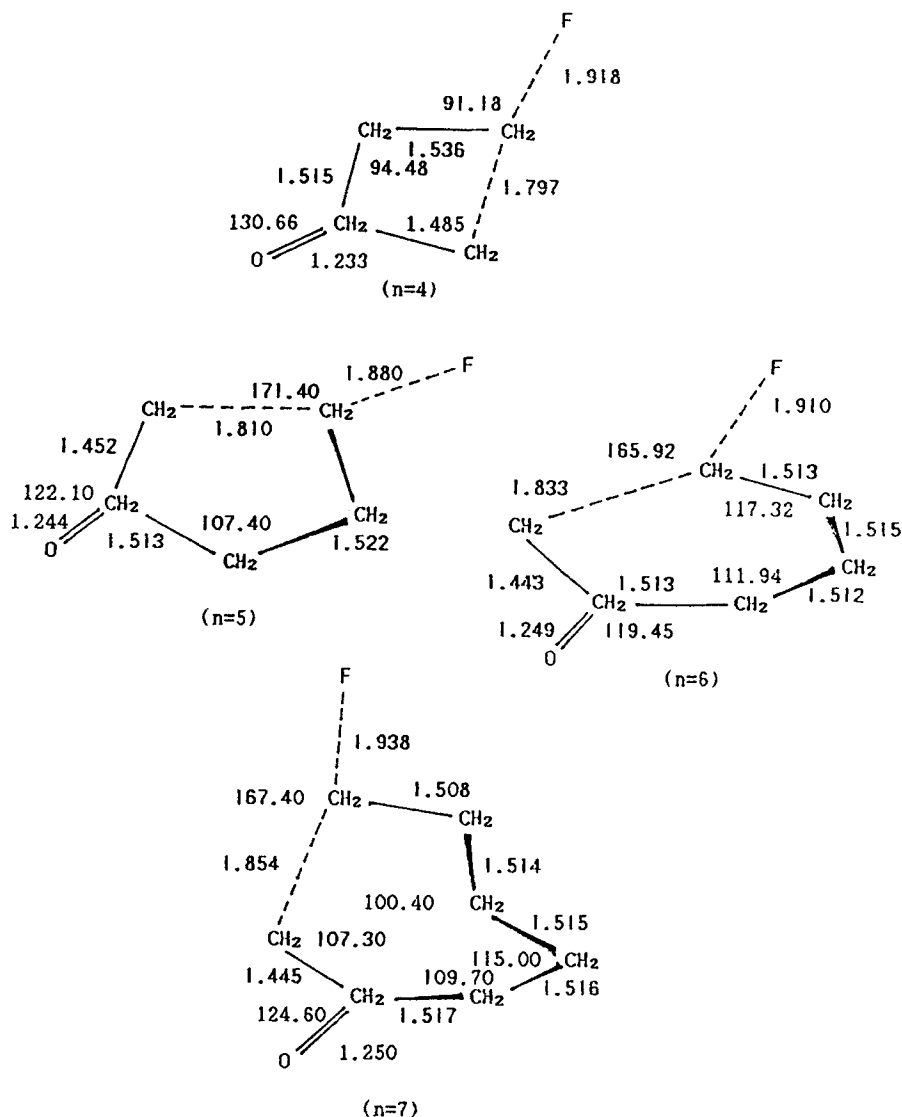
Figure 1. TS structures for cycloketone formation from ω-fluoroenolate anions

that both $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ are higher than those for $n = 5$ and 6.

The TS for the $n = 4$ system is the least favoured energetically since it has the highest ring strain and the strongest repulsion between O and F (the shortest distance between them). The favourable small ring entropy effect for $n = 4$ is, however, insufficient to enhance the overall reactivity $(\Delta G^{\ddagger})$ over that of the other larger ring systems ($n \geqslant 5$).

For ω-chloroenolate anions (X = Cl), the Cω hydrogens are less acidic than those for the fluoro analogue

(X = F) owing to the weaker electronegativity of Cl, and cyclopropanone formation can proceed through an $S_{N}i$ process for $n = 3$. The thermodynamic data for cycloketone formation from ω-chloroenolate anions calculated by AM1 are given in Table 3. The data reveal that the $\Delta H^{\ddagger}$ values are similar for $n = 5$ and 7, but the overall reactivity order $(\Delta G^{\ddagger})$ decreases in the order $n = 6 > 5 > 7 > 4 > 3$, again the entropy factor favouring small ring formation of the $n = 5$ system. This order of reactivity for X = Cl is different from that for X = F.

Table 2. Interatomic distances (d_{OF}, Å) between carbonyl oxygen and leaving group X in the TSs for equation (1)

n^a	X		
	F	Cl	Br
3	—	3·529	3·573
4	4·950	5·210	5·362
5	5·406	5·553	5·703
6	5·271	5·530	5·675
7	5·169	5·325	5·457

^{a} Ring size of the ring to be formed.

We note that the TS structures for X = Cl in Figure 2 are more reactant-like and the degree of bond formation between C_α and C_ω in the TS is much less compared to that for X = F (Figure 1). This can be attributed to a greater leaving ability of X = Cl compared with X = F leading to a relatively lower activation energy ($\Delta H^{\ddagger}$) barrier. The lower energy process (with X = Cl) thus has an earlier TS in agreement with the Bell—Evans—Polanyi (BEP) principle.[20] As a result, the interatomic distance (d_{OX}) between the two electronegative atoms, O and X, is longer for X = Cl by ca 0·3 Å than that for X = F and, accordingly, the electrostatic effect on $\Delta H^{\ddagger}$ will be reduced substantially. This means that the major contributing factor to $\Delta H^{\ddagger}$ for
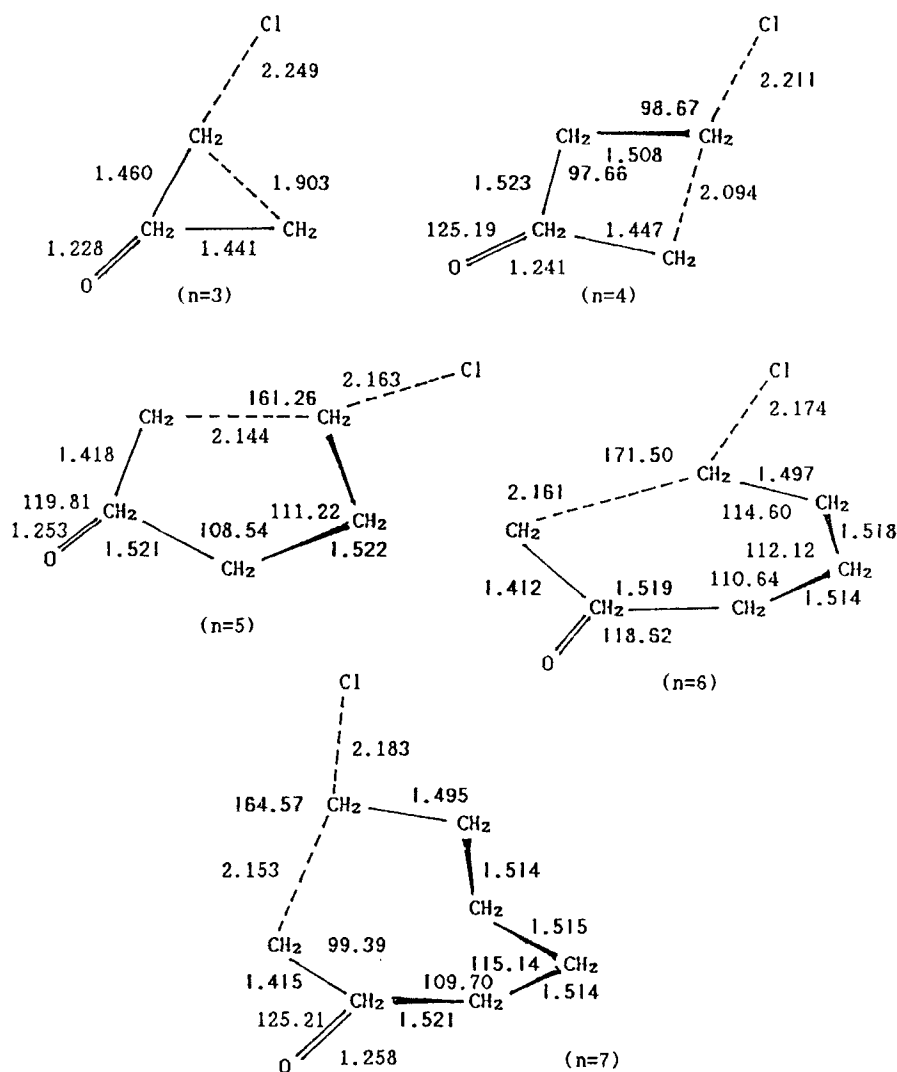

Figure 2. TS structures for cycloketone formation from ω-chloroenolate anions

X = Cl is the ring strain energy, which is known to be similar for the $n = 5$ and 7 systems as we find in Table 3. The $n = 3$ system has the highest $\Delta H^{\neq}$ value owing to the strong ring strain involved in the TS, and results in the least reactivity despite the favourable entropy factor of small ring formation.

The cycloketone formation process of ω-bromoenolate anions (X = Br) exhibits (Table 4) a similar reactivity trend to that for the corresponding reaction of the chloro analogue (X = Cl). Here again, the $\Delta H^{\neq}$ values differ very little between $n = 5$ and 7, but $n = 5$ has a greater overall reactivity ($\Delta G^{\neq}$). The greatest reactivity obtained for the six-membered cycloketone formation (Table 4) is consistent with the most facile reaction found for the cycloketone formation of ω-bromoenolate anions in the ether medium.[21]

The TS structures for X = Br are similar to those for X = Cl in Figure 2 and are not shown here.

Formation of exo-methylene cycloethers, III [equation (2)]

An alternative route for the intramolecular nucleophilic attack at the C_ω atom is by the carbonyl oxygen forming exo-methylene cycloethers, equation (2). In this type of cyclization, three-membered ring formation ($n = 3$) is forbidden with the ω-fluoroenolate (X = F), for the same reason as in the three-membered cycloketone formation with X = F; the C_ω hydrogens are too acidic owing to the two adjacent electronegative atoms, F and O, and proton abstraction by oxygen takes place instead.

Table 3. AM1 thermodynamic data for the cycloketone formation processes of ω-chloroenolate anions

n^a	GS		TS		Activation parameter[d]		
	ΔH_f^b	S^c	ΔH_f^b	S^c	$\Delta H^{\neq b}$	$\Delta S^{\neq c}$	$\Delta G^{\neq}$
3	−58·1	76·7	−14·5	76·1	43·6	−0·6	43·8
4	−65·7	83·3	−35·6	79·9	30·1	−3·4	31·1
5	−70·0	91·7	−52·8	85·4	17·2	−6·2	19·1
6	−76·2	99·8	−60·5	91·1	15·7	−8·7	18·3
7	−82·2	107·8	−65·1	94·5	17·1	−13·3	21·1

[a-d] See footnotes to Table 1.

Table 4. AM1 thermodynamic data for the cycloketone formation processes of ω-bromoenolate anions

n^a	GS		TS		Activation parameter[d]		
	ΔH_f^b	S^c	ΔH_f^b	S^c	$\Delta H^{\neq b}$	$\Delta S^{\neq c}$	$\Delta G^{\neq}$
3	−46·2	78·8	−0·9	79·3	45·3	0·9	45·1
4	−53·1	88·1	−21·1	82·6	32·0	−5·6	33·6
5	−57·2	95·9	−38·3	87·7	18·9	−6·4	21·4
6	−63·4	104·4	−45·7	93·7	17·7	−10·6	20·8
7	−69·3	112·5	−50·8	97·0	18·5	−15·5	23·1

[a-d] See footnotes to Table 1.

Table 5. AM1 thermodynamic data for the cycloketone formation processes of ω-haloenolate anions

n^a	X = F			X = Cl			X = Br		
	$\Delta H^{\neq b}$	$\Delta S^{\neq c}$	$\Delta G^{\neq}$	$\Delta H^{\neq b}$	$\Delta S^{\neq c}$	$\Delta G^{\neq}$	$\Delta H^{\neq b}$	$\Delta S^{\neq c}$	$\Delta G^{\neq}$
3	—	—	—	43·7	−0·3	43·8	48·4	0·4	48·3
4	101·3	−5·9	103·1	33·4	−3·4	34·4	37·2	−5·5	38·9
5	79·3	−7·6	81·6	16·1	−5·0	17·6	18·8	−6·3	20·7
6	83·2	−9·8	86·1	19·8	−9·0	22·5	22·7	−11·1	25·9
7	86·5	−15·0	91·0	21·81	−12·7	25·6	24·9	−14·9	29·4

[a-c] See footnotes to Table 1.

The activation parameters calculated by AM1 for the cycloether formation processes from the ω-haloenolate anions with X = F, Cl and Br and n = 3–7 are summarized in Table 5.

The reactivity order, based on both $\Delta H^{\neq}$ and $\Delta G^{\neq}$, n = 5 > 6 > 7 > 4 > 3, is the same in all cases with X = F, Cl and Br; all the reactions are therefore enthalpy controlled. In the exo-methylene cycloether formation process, the n = 5 system is more reactive compared with the n = 6 system in all cases. This is attributed to the more favourable stereoelectronic orientation of a lone pair on the oxygen atom for a rear-side attack, IV, and is in good agreement with the experimental results reported for the reactions with ω-bromoenolate anion in ether solvent.[21] The same reactivity order was also obtained by Mandolini and co-workers[22] for the lactonization reaction of ω-bromoalkanoate anions in 99% dimethyl sulphoxide. They reported lower $\Delta H^{\neq}$ values than our AM1 values, but a direct comparison may not be justified since our theoretical values are for gas-phase reactions and the substrates used are not exactly the same. Even though the entropy of activation ($\Delta S^{\neq}$) has no major

θ = $\angle$ LOC$_\omega$ (in plain)
ϕ = $\angle$ LOC$_\omega$ (out of plain)
(L is a lone pair)

$(\theta; \phi)$
30·7°; 0·0° for n = 5
31·9°; 12·6° for n = 6

(IV)

effect on the reactivity, it is interesting that the $\Delta S^{\neq}$ values are similar and tend to decrease as n increases in the two cases. Representative TS structures are given for X = Br in Figure 3.

Relative reactivity and the HSAB principle

Enolates are well known ambident substrates, in which reactions can take place at two different positions depending on the reagent. Alkylation occurs predominantly at the (softer) carbon atom whereas acylation takes place mostly at the (harder) alkoxide oxygen atom, equation (3).[23]

Comparison of activation enthalpies ($\Delta G^{\neq}$) and free energies ($\Delta H^{\neq}$) in Tables 1–5 indicates that in general the cycloketone pathway [equation (1)] is favoured, as expected from the predominant alkylation [equation (3a)] at the softer carbon centre, C_α. However, there are two exceptions: for the n = 5 system with X = Cl and Br, we find that the cycloether pathway [equation

(2)] is both energetically ($\Delta H^{\neq}$) and entropically ($\Delta S^{\neq}$) more favourable, albeit the differences in $\Delta S^{\neq}$ between the two processes are small. These results can be rationalized by the HSAB concept as follows.

Energetically, the cycloether formation process is unfavourable in all cases since it has a later TS than the cycloketone formation process, leading to higher $\Delta H^{\neq}$ as required by the BEP principle. The degree of bond formation is always greater for the former, i.e. the distance between the two closing ends is shorter, $d(O—C_\omega) < d(C_\alpha—C\omega)$, as shown in Table 6. However, the comparison of frontier molecular orbitals (FMO)[24] involved in the two processes (Table 7) indicates that the HOMO for the cycloketone path reacting at C_α is higher (and hence C_α is a softer base centre) than that for the cycloether path reacting at O (and hence O is a less soft base centre), and the interfrontier energy gap, $\Delta\mathscr{E}_{FMO}$, is narrower for the former process. In terms of the perturbation MO(PMO) theory,[25] the intermolecular interaction energy, ΔE_i, in the early stages of a series of related reactions between a nucleophile (base) and an electrophile (acid) can be approximated by a sum of electrostatic (E_{es}) and charge transfer (E_{ct}) interaction energy terms, equation (4):[26]

$$\Delta E_i = -\frac{q_n q_e}{4\pi\varepsilon d} + \frac{H_{HO,LU}{}^2}{\Delta\varepsilon_{FMO}}$$ (4)

$\qquad\qquad\uparrow\qquad\quad\uparrow$
$\qquad\qquad(E_{es})\quad\ (E_{ct})$

in which q_n and q_e are charges on the nucleophile and electrophile, respectively, d is the distance between them, and $H_{HO,LU}$ is the interaction matrix element between FMOs which is proportionality related to the overlap integral $H_{HO,LU} = kS_{HO,LU}$.[27] The attractive force between hard acids and bases is mainly due to the electrostatic term, whereas that between soft acids and bases is mainly due to the HOMO–LUMO overlap term. In the HSAB concept, for a relatively soft acid centre (C_ω), a softer base centre with a higher HOMO (C_α) will be more reactive compared with a less soft base centre with a lower HOMO (O). This reactivity trend expected from the HSAB principle is indeed borne out in our AM1 results.
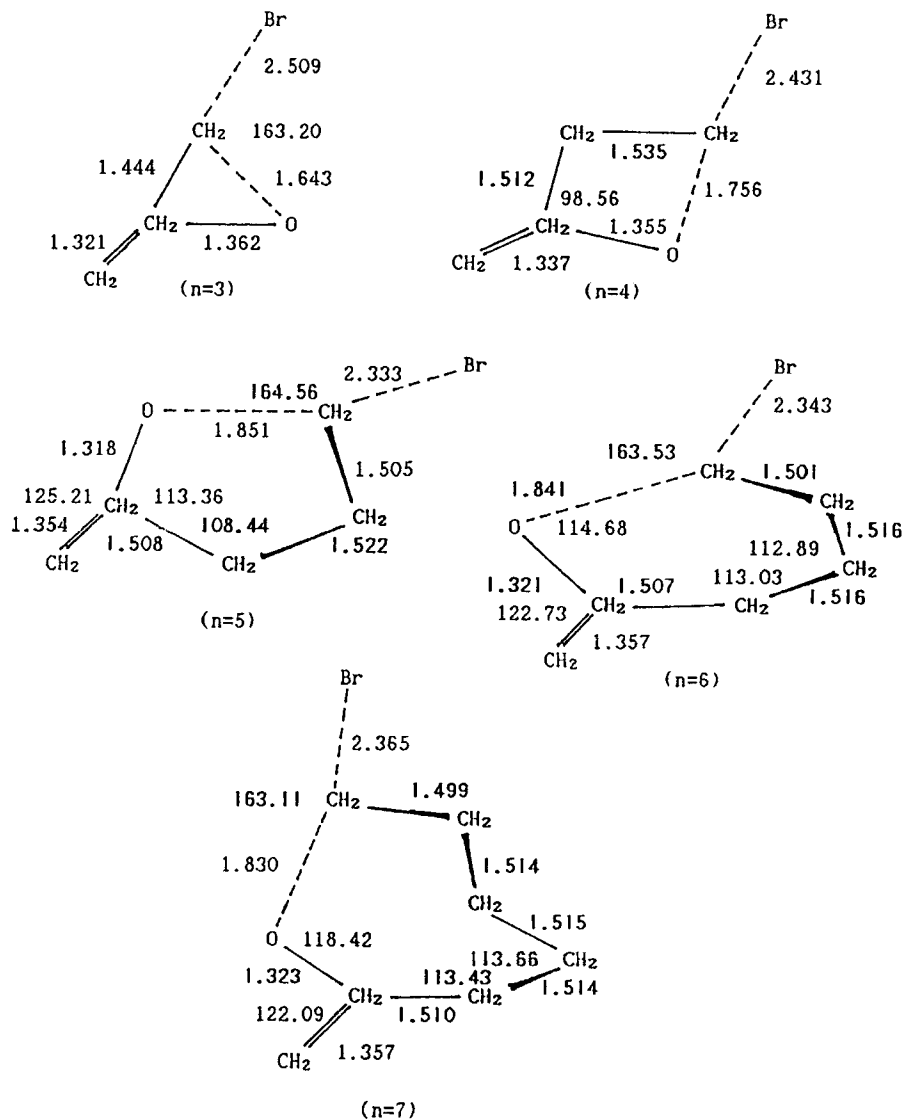
Figure 3. Representative TS structures for cycloether formation from ω-bromoenolate anions

However, this is based on only one factor, $\Delta\mathscr{E}_{FMO}$, which determines the charge-transfer stabilization energy, E_{ct}. We noted above that for the $n = 5$ system the stereoelectronic orientation of a lone pair on the oxygen atom is the most favourable for the attack by the acidic centre, C_ω, in the TS for the cycloether formation process. This means that the overlap and hence H_{ij} in equation (4) between basic (lone pair on O) and acidic (C_ω) centres will be large, resulting in a greater relative reactivity. The efficient overlap between the lone pair on O and C_ω due to an optimum relative orientation for bond formation is apparent in the longest $d(O-C_\omega)$ for $n = 5$ with X = Cl and Br; there is no such extremum in $d(C_\alpha-C_\omega)$ for the cycloketone path (Table 6). Hence the anomalously high reactivity of the $n = 5$ system for X = Cl and Br is due to the greater matrix element [equation (4)] in the cycloether pathway despite the (unfavourable) greater energy gap, $\Delta\mathscr{E}_{FMO}$. In the case of X = F, however, the TS is relatively more product-like since the leaving ability of F is much poorer than that of Cl or Br. A greater degree of product likeness (cyclicether) in the TS will introduce a greater ring strain so that the stereoelectronic effect is overridden by the strain energy. The overriding effect of

the ring strain energy is also a general trend within a homologous series, since the interaction energy, ΔE_i, is favoured by the decreasing energy gap $\Delta\mathscr{E}_{FMO}$ (and hence E_{ct}) and E_{es} as the chain length (n) grows (Tables 7 and 8).

The reactivities of the two processes, equations (1) and (2), are also dependent on the leaving group. Reference to Tables 1–5 reveals that the reactivity order, F < Br < Cl, is the same for both processes. However, the energy difference between the two processes for each substrate decreases as the reactivity increases, e.g. $\delta\Delta G^{\neq}$ is lower for X = Cl than for X = F. This is consistent with the reactivity–selectivity principle (RSP).[28]

Strikingly, the reactivity of X = Br is intermediate between X = Cl and F. The tendency to accumulate ligands of the same (soft or hard) type is known as symbiosis, which accounts for the difference in leaving ability of various leaving groups (X) in S_N2 reactions, since the TS of those reactions can be viewed as an acid–base complex of nucleophile Nu and CR_3X. Olmstead and Brauman[29] showed in gas-phase studies that when the nucleophile is a hard base:

$$\text{Nu} + \text{CR}_3\text{X} \longrightarrow \text{Nu} \overset{R}{\underset{\underset{R}{|}}{\overset{\diagdown}{\text{C}}}} \overset{R}{\overset{\diagup}{}} \text{X} \qquad (5)$$
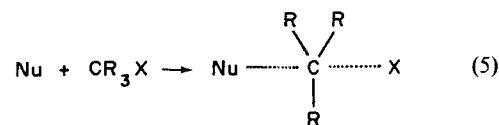
Table 6. Interatomic distances ($\mathring{A}$) between two atoms of bond-forming [$d(C_\alpha\text{—}C_\omega)$ and $d(O\text{—}C_\omega)$] and -breaking [$\Delta d_1(C_\omega\text{—}X)$ and $\Delta d_2(C_\omega\text{—}X)$] bonds in the cyclizations of ω-haloenolate anions

	$d(C_\alpha\text{—}C_\omega)$			$d(O\text{—}C_\omega)$			$\Delta d_1(C_\omega\text{—}X)^b$			$\Delta d_2(C_\omega\text{—}X)^b$		
n^a	X = F	Cl	Br	X = F	Cl	Br	X = F	Cl	Br	X = F	Cl	Br
3	—	1·903	1·856	—	1·706	1·643	—	0·469	0·355	—	0·593	0·560
4	1·797	2·094	2·034	1·661	1·823	1·756	0·529	0·422	0·360	0·743	0·498	0·472
5	1·810	2·144	2·078	1·690	1·920	1·851	0·495	0·391	0·356	0·631	0·422	0·391
6	1·833	2·161	2·086	1·692	1·911	1·841	0·525	0·405	0·379	0·621	0·439	0·404
7	1·854	2·153	2·077	1·691	1·898	1·830	0·554	0·418	0·390	0·641	0·469	0·430

[a] Ring size of the ring to be formed.
[b] Δd_1 and Δd_2 denote bond length changes in the activation process for equations (1) and (2).

Table 7. HOMO–LUMO energy levels (eV) involved in the cyclization processes of ω-haloenolate anions by AM1

X	n^a	π Orbital^b (C_α)	n Orbital^c $(\text{—}O^-)$	σ^* Orbital^d $(C_\omega\text{—}X)$	$\Delta\mathscr{E}_{FMO}(1)^e$	$\Delta\mathscr{E}_{FMO(2)}{}^f$
F	4	−2·32	−4·09	8·41	10·73	12·50
	5	−2·25	−4·01	6·96	9·21	10·97
	6	−2·23	−3·97	6·45	8·68	10·42
	7	−2·20	−3·94	5·99	8·19	9·93
Cl	3	−2·41	−4·20	5·79	8·20	9·99
	4	−2·46	−4·21	5·04	7·50	9·25
	5	−2·29	−4·06	4·38	6·67	8·44
	6	−2·26	−4·01	3·91	6·17	7·92
	7	−2·21	−3·96	3·55	5·76	7·51
Br	3	−2·45	−4·27	5·11	7·56	9·38
	4	−2·50	−4·22	4·36	6·86	8·58
	5	−2·32	−4·07	3·69	6·01	7·76
	6	−2·27	−4·01	3·22	5·49	7·23
	7	−2·22	−3·96	2·86	5·08	6·82

[a] Ring size of the ring to be formed.
[b] HOMOs of cycloketone formation processes.
[c] HOMOs of cycloether formation processes.
[d] LUMOs of two cyclization processes.
[e] HOMO–LUMO energy gaps of cycloketone formation processes, equation (1).
[f] HOMO–LUMO energy gaps of cycloether formation processes, equation (2).

Table 8. Electrostatic interaction energies (kcal mol^{-1}) for the two cyclization processes

n^a	Cycloketone formation process (interaction at $C\alpha$)			Cycloether formation processes (interaction at O)		
	X = F	X = Cl	X = Br	X = F	X = Cl	X = Br
3	—	34·2	43·8	—	6·3	13·6
4	1·3	7·3	17·3	1·0	−4·0	4·3
5	−2·3	5·0	14·9	−5·3	−6·3	1·7
6	−1·3	4·0	13·6	−7·6	−8·6	0·3
7	0·0	3·3	12·9	−7·3	−8·6	0·0

^{a} Ring size of the ring to be formed.

e.g. Nu = F^-, the leaving ability is X = Cl > Br, but the leaving ability reverses to X = Br > Cl when the nucleophile is a soft base, e.g. Nu = Cl^-, and for the nucleophile of an intermediate softness (or hardness), e.g. Nu = OH^-, the leaving ability becomes approximately equal for the two, X = Cl = Br. This suggests that as a result of symbiosis the acid centre C_ω in equations (1) and (2) will attract a softer base when X = Cl and Br, whereas it will favour a harder base with X = F. This is clear in Table 7; the HOMO levels of the basic centres, C_α and O, change very little but the LUMO levels of the acidic centre, C_ω, are lowered considerably, i.e. made softer when the hard leaving group X = F is replaced with a softer X = Cl or Br. Thus the softness of the basic centres remains almost constant whereas the acidic centre, C_ω, becomes harder with X = F and softer with X = Cl or Br. The increase in the softness, i.e. lowering of the LUMO of C_ω—X, led to a greater reactivity for X = Cl but a further increase in the softness with X = Br decreased the reactivity of the cyclization processes, equations (1) and (2), instead. This suggest that the basic centres, C_α and O, have a softness of a borderline nature, i.e. an intermediate softness, so that the E_{es} term is also contributing to the reactivity. In both processes, the electrostatic term favours X = Cl rather than X = Br, and moreover it is far more important in the cycloether formation process, as expected from an interaction at a harder base centre, O (Table 8). This is in contrast to the more favourable charge-transfer interaction term, E_{ct} [as evidenced by the narrower gap, $\Delta\mathscr{E}_{FMO}$ (Table 7)] for the cycloketone formation, as expected from an interaction at a softer base, than for the cycloether formation. We also note that in both processes, equations (1) and (2), the TS is the earliest [d(O—C_ω) and d(C_α—C_ω) are the longest] for X = Cl with the greatest reactivity, and is the latest [d(O—C_ω) and d(C_α—Cω) are the shortest] for X = F with the least reactivity, which are again consistent with the BEP principle.

REFERENCES

1. C. K. Kim, I. Lee and B.-S. Lee, J. Phys. Org. Chem. 4, 315–329 (1991).
2. J. F. Liebman and A. Greenberg, Chem. Rev. 76, 311 (1976); J. F. Liebman and A. Greenberg, Strained Organic Molecules. Academic Press, New York (1978); J. M. Brown, A. D. Conn, G. Pilcher, M. P. L. Leitao and Y. M. Yan, J. Chem. Soc., Chem, Commun. 1817 (1989); A. Streitwieser, Jr, and C. H. Heathcock, Introduction to Organic Chemistry, 3rd ed., p. 82. Macmillan, New York (1985).
3. N. S. Isaacs, Physical Organic Chemistry, pp. 608–613. Wiley, New York (1987).
4. L. Ruzicka, W. Brugger, M. Pfeiffer, H. Schinz and M. Stoll, Helv. Chim. Acta 9, 499 (1926); L. Ruzicka, Chem. Ind. (London) 54, 2 (1935).
5. C. J. M. Stirling, J. Chem. Educ. 50, 844 (1973); C. J. M. Stirling, Tetrahedron 41, 1613 (1986).
6. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, J. Am. Chem. Soc. 107, 3902 (1985).
7. I. Lee and C. K. Kim, J. Comput. Chem. 11, 1119 (1990).
8. G. W. Klump, Reactivity in Organic Chemistry, p. 145. Wiley, New York (1982).
9. R. G. Pearson, J. Am. Chem. Soc. 85, 3533 (1963); T. ho, Hard and Soft Acids and Bases Principle in Organic Chemistry. Academic Press, New York (1977).
10. M. J. S. Dewar, AMPAC: Austin Model 1 Package, QCPE No. 506.
11. T. A. Albright, J. K. Burdett and M. H. Whangbo, Orbital Interactions in Chemistry, p. 125. Wiley, New York (1985); F. L. Pilar, Elementary Quantum Chemistry. McGraw-Hill, New York (1968).
12. M. J. S. Dewar, A. J. Holder, E. F. Healy and S. Olivella, J. Chem. Soc., Chem. Commun. (1989) 1452.
13. M. J. S. Dewar and Y.-C. Yuan, J. Am. Chem. Soc. 112, 2088 (1990); S. Hoz, K. Yang and S. Wolfe, J. Am. Chem. Soc. 112, 1319 (1990).
14. D. C. Spellmeyer and K. N. Houk, J. Am. Chem. Soc. 110, 3412 (1988); M. J. S. Dewar and E. F. Healy, Chem. Phys. Lett 141, 521 (1987); M. J. S. Dewar and B. M. O'Connor, Chem. Phys. Lett 138, 141 (1987); M. Müller and G. Hohlneicher, J. Am. Chem. Soc. 112, 1273 (1990).

15. I. G. Csizmadia, *Theory and Practice of MO Calculations on Organic Molecules*, p. 239. Elsevier, Amsterdam (1976).

16. A. Komornicki, K. Ishida and K. Morokuma, *Chem. Phys. Lett.* **45**, 595 (1979).

17. J. W. McIver, Jr, and A. Komornicki, *J. Am. Chem. Soc.* **94**, 2025 (1972).

18. A. Streitwieser, Jr, and C. H. Heathcock, *Introduction to Organic Chemistry*, 2nd ed., p. 179. Macmillan, New York (1981).

19. R. A. Y. Jones, *Physical and Mechanistic Organic Chemistry*, 2nd ed., p. 134. Cambridge University Press, Cambridge (1984).

20. M. G. Evans and M. Polanyi, *Trans. Faraday Soc.* **32**, 1340 (1936); M. J. S. Dewar, *The Molecular Orbital Theory of Organic Chemistry*, pp. 284–288. McGraw-Hill, New York (1969).

21. J. E. Baldwin and L. I. Kruse, *J. Chem. Soc., Chem. Commun.* 233 (1977).

22. L. Mandolini, *J. Am. Chem. Soc.* **100**, 550 (1978); C. Galli, G. Illuminati, L. Mandolini and D. Tauborra, *J. Am. Chem. Soc.* **99**, 2591 (1977).

23. F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry, Part B*, 2nd ed., p. 21 Plenum Press, New York (1983).

24. I. Fleming, *Frontier Orbitals and Organic Chemical Reaction*. Wiley–Interscience, New York (1976); K. Fukui, *Angew. Chem. Int. Ed. Engl.* **21**, 801 (1982); K. Fukui, *Theory of Orientation and Stereoselection*. Springer, Berlin (1975).

25. M. J. S. Dewar and R. C. Dougherty, *The PMO Theory of Organic Chemistry*. Plenum, New York (1975).

26. L. Salem, *J. Am. Chem. Soc.* **90**, 543 (1968); N. S. Isaacs, *Physical Organic Chemistry*, p. 241. Wiley, New York (1987).

27. R. Hoffmann and W. N. Lipscomb, *J. Chem. Phys.* **36**, 2179, 3489 (1962); R. Hoffmann, *J. Chem. Phys.* **40**, 2745 (1966).

28. J. E. Leffler and E. Grunwald, *Rates and Equilibria of Organic Reactions*. Wiley, New York (1963); W. Good, D. B. Ingham and J. Stone, *Tetrahedron* **31**, 257 (1975); J. Hine, *Adv. Phys. Org. Chem.* **15**, 1 (1977).

29. W. N. Olmstead and J. I. Brauman, *J. Am. Chem. Soc.* **99**, 4219 (1977).