1, CH), 3.23 (s, 3, OCH_3), 2.08–1.40 (complex, 6, CH_2).

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Registry No. CH_2=CHCH=CH_2, 106-99-0; CH_3CH=CHCH=C-HCH_2OCH_3, 16277-66-0; CH_2=$CHCH_2CH(OMe)CH$=CH_2, 82574-81-0; methyl vinyl ether cation radical, 59123-15-8; 4-methoxycyclohexene, 15766-93-5; 3-methoxycyclohexene, 2699-13-0.

Ab Initio Calculations of the Li^+ and Na^+ Affinities of Aziridine and Ethylene Oxide Rings

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Abstract: Li^+ and Na^+ affinities of the aziridine and ethylene oxide rings are calculated at the Hartree–Fock level with 6-31G* and 6-21G basis sets, respectively. The purpose of the calculations is to investigate the possible influence of the presence of the ions on the carcinogenicity of the ethylene oxide ring and on the antitumor activity of aziridine-containing drugs, such as mitomycin. The energy of activation of the opening of the ammoniated aziridine ion under nucleophilic attack by NH_3 is found to be slightly higher than that in the case of protonated aziridine, as calculated by Kikuchi et al.[15c]

The pH dependence of the activity of some carcinostatic drugs has formed the object of several studies.[1] The mitomycins, powerful antibiotics used as antitumor therapeutic agents against many forms of cancer,[1,2] are thought to act via the opening of the aziridine ring whose presence in the drug is responsible for its activity. Mitomycins interact with DNA either by alkylation, an easily repaired event, or by interstrand cross-linking, a lethal effect to the cell. As such, the interaction with the biological target DNA is considered to be the primary event in mitomycin's activity. Two different mechanisms have been proposed for the opening of the aziridine ring. The first one consists of the opening of the ring under nucleophilic attack by one of the DNA bases (most probably the O6 of guanine).[1] In the second one, proposed by Moore,[3] the ring opens by intramolecular rearrangements, a double bond is formed, and the nucleophilic attack by DNA occurs at one of the ends of the double bond.

The latter mechanism has been supported by the experiments of Tomasz and Lipman[4] and of Kohn and Zein.[5] A theoretical determination of the activation energy for the opening of the double bond under nucleophilic attack gives a value of 12 kcal/mol.[6] Both the above-mentioned reactions recognize the fact that mitomycins belong to the class of bioreductive alkylating agents. Also, both reactions show the activation to occur at low pH. A reason for this can be found in the increased ability of aziridines to undergo opening when a proton is attached to nitrogen.[7] Even though the basicity of the aziridine ring in mitomycin C is found to be small,[8] it is still to be presumed that a positive charge attached to the nitrogen will facilitate the opening of the ring.

Another class of compounds, this time carcinogens, the ethylene oxides, also are presumed to open under nucleophilic attack, made easier by the attachment of a proton to oxygen. As such, it seems clear that a positive charge attached to either the nitrogen of the aziridine ring or to the oxygen of the ethylene oxide will have influence on their biological activity. However, at physiological pH, an acidic activation is not to be expected. In this work, we examine the possibility of replacing the proton by a metal ion such as Li^+ or Na^+. Indeed, it has been shown by Del Bene et al.[9] that many nitrogen and oxygen bases exhibit substantial Li^+ affinity, related by an almost linear relationship to their proton affinity. To those, one of us and a co-worker[10] have added the calculation of the Li^+ affinity of guanidine, found to be around 70 kcal/mol. Accordingly, we calculate the Li^+ and Na^+ affinities of aziridine and ethylene oxide and compare them to their proton affinities. We also calculate the activation energy for the aziridine ring opening under nucleophilic attack by ammonia in the presence of an ammonium ion attached to the nitrogen of the ring.

Method and Results

For the Li^+ and Na^+ affinities to be obtained, ab initio Hartree–Fock calculations are performed with the GAUSSIAN-80 program.[11] The bases (aziridine and ethylene oxide), the acids, and the Li^+ compounds are subjected to geometry optimization using the 6-31G*[12a] basis set which adds polarization functions to all the atoms except hydrogen. Indeed using a fairly large basis set will decrease the superposition error. For the Na^+ compounds, the 6-21G[12b] basis set is used. For the error of using a smaller basis set to be tested, the 6-21G basis set is also used for calculations of the bases and of the Li^+ compounds. In each case, complete optimization is performed with the exception of Na^+ compounds where only the Na–O and Na–N distances are op-

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Table I. Optimized Bond Lengths (Å) and Angles (deg)

	C_2H_4NH		$C_2H_4NH_2^+$	$C_2H_4NHLi^+$		$C_2H_4NHNa^+$
	6-31G*	6-21G	6-31G*	6-31G*	6-21G	6-21G
N–C	1.444	1.494	1.484	1.493	1.526	1.526
C–C	1.469	1.494	1.460	1.476	1.475	1.475
C–H	1.076	1.071	1.073	1.072	1.070	1.070
N–H	0.999	1.007	1.005	1.001	1.010	1.010
HCN	117.7	116.5	113.7	115.1	115.0	115.0
HNC	111.9	112.2	118.6	110.3	110.9	110.9
CCN	61.2	60.0	58.9	59.3	57.8	57.8
N–Li				1.956	1.889	
N–Na						2.250
LiNC				125.1	125.6	
NaNC						125.6
	C_2H_4O		$C_2H_4OH^+$	$C_2H_4OLi^+$		$C_2H_4ONa^+$
	6-31G*	6-21G	6-31G*	6-31G*	6-21G	6-21G
O–C	1.402	1.474	1.493	1.437	1.499	1.510
C–C	1.453	1.473	1.477	1.448	1.465	1.464
C–H	1.077	1.071	1.073	1.073	1.070	1.070
O–H			0.961			
HCO	115.2	114.8	111.0	113.7	113.0	115.0
HOX[a]			120.3			
LiOX[a]				180.0	180.0	
NaOX[a]						169.3
O–Li				1.803	1.719	
O–Na						2.183

[a] X is the midpoint of CC.

Table II. Affinities of Aziridine and Ethylene Oxide (kcal/mol)

	H^+	Li^+		Na^+
	6-31G*	6-31G*	6-21G	6-21G
aziridine	232.18	47.28	60.51	42.57
ethylene oxide	193.87	43.45	60.13	40.99

timized, together with the NaNC angle or NaOX angle (X being the point set at halfway between the two carbons). The other parameters are taken from the 6-21G Li^+ compounds optimization. The optimization is performed with the Berny optimization technique.[13] Table I displays the results of the geometry optimization.

The affinities are calculated by subtracting the sum of the energies of the base and of the metal ion from that of the complex. Table II displays these results. Table III shows the net atomic charges and the Mulliken overlap populations. It is known that these values are not to be trusted too much when compounds with strong positive charges are studied. However, they might serve as an indication of the trends. The correlation energy contribution of the binding energy is expected to be small, as can be seen from the calculation of Del Bene et al.[9] for a number of bases. As a confirmation, we estimated the correlation energy of the aziridine Li^+ formation from aziridine and Li^+ with the Moller–Plesset perturbation method of third order (MP3)[14] used with the STO-6G minimal basis set. Taking the difference between the Hartree–Fock binding energy at STO-6G level and the binding energy calculated through the use of the MP3/STO-6G method, we estimate the change in correlation energy upon binding. The fact that the correlation energy changes are small for systems featuring a N–Li bond is also seen from the calculations of Raghavachari, Schlayer, and Sapse,[17] who find very small correlation energy changes for the tetramerization of NH_2Li.

Discussion of the Results

Aziridine and aziridine ion have been studied by a number of researchers.[15] For instance, D. T. Clark finds a proton affinity of 242 kcal/mol for aziridine, with minimal basis sets of Gaussians, without geometry optimization.[15a] Bonaccorsi et al.[15b] calculate the field around aziridine as well as that around ethylene oxide with a minimal set of Slater orbitals. Hopfinger et al.[15c] calculate the energy of activation of aziridine under nucleophilic attack, with the MINDO/3 semiempirical method. More recently, Aue et al.[15d] used 4-31G calculations to obtain the proton affinity of several rings, including aziridine and ethylene oxide, and compare them to the previous results of Basch et al.[15e] They find a proton affinity of 215.7 kcal/mol for aziridine and 189.6 kcal/mol for ethylene oxide. Experimental work by Staley and Beauchamp[15f] and by Uppal and Staley[15g] shows Li^+ affinity of ethylene oxide to be around 48 kcal/mol. As can be seen from Table II, our results are quite similar to the above-mentioned numbers.

The geometries found in this paper and displayed in Table I should be reliable, with the 6-21G predicting slightly longer bond lengths than 6-31G*. One interesting aspect is the fact that in the ethylene oxide ions, the H^+ is positioned in front of one of the lone pairs of oxygen, as expected, corresponding to the position most favorable for a positive charge in the field calculations of Bonaccorsi et al.[15b] Conversely, the Li^+ ion is positioned in the plane of the ring, and the Na^+ ion is positioned almost in the plane of the ring. This effect might be due to the increased size of the ions as well as to the increase of the positive charge as such. Indeed, Li and Na atoms in the complexes exhibit charges around 0.8 eu while the H atom added to the bases retains only around 0.5 eu of its original charge of 1+ eu. As such, the N–Li^+, N–Na^+, O–Li^+, and O–Na^+ will be more ionic—the metal ions will position themselves farther apart from the rings and see the O atom as a point negative charge. The hydrogen present on the nitrogen of aziridine prevents this effect. The difference in energy between the $EtOLi^+$ featuring the Li^+ in the same position as the H^+ in $EtOH^+$ and the optimum energy (with the Li^+ in the plane of the ring) is 6 kcal/mol. The affinities decrease in order H^+, Li^+, Na^+. As expected due to the superposition error,[16] the 6-21G predicts higher affinity than the 6-31G* but the difference is not too large. The H^+ vs. Li^+ affinity places these two bases on the

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Table III. Net Atomic Charges (eu) and Mulliken Populations (eu)

	C_2H_4NH		$C_2H_4NHLi^+$		$C_2H_4NHNa^+$	C_2H_4O		$C_2H_4OLi^+$		$C_2H_4ONa^+$
	6-31G*	6-21G	6-31G*	6-21G	6-21G	6-31G*	6-21G	6-31G*	6-21G	6-21G
C	−0.218	−0.292	−0.194	−0.269	−0.279	−0.090	−0.192	−0.085	−0.070	−0.185
H (on C)	0.185	0.238	0.235	0.283	0.290	0.180	0.231	0.249	0.302	0.280
			0.251		0.270					
H (on N)	0.349	0.303	0.417	0.381	0.362					
N	−0.625	−0.628	−0.845	−0.794	−0.768					
O						−0.538	−0.541	−0.711	−0.685	−0.645
Li			0.853	0.792				0.887	0.817	0.885
Na					0.852					
N–Li			0.136	0.170						
N–Na					0.105					
O–Li								0.102	0.144	
O–Na										0.092

Table IV. Distances (Å), Angles (deg), and Energy of Cis Aziridine–Ammonium Attack by NH_3

	total energy (kcal/mol) at angles =			
distance	30°	40°	50°	60°
4.00	167.6	168.0	168.7	170.3
2.20	192.3	194.5	196.6	211.1
1.95	202.9	205.8	208.0	211.12
1.80	209.8	212.7	214.3	199.4
1.70	214.6	216.7	197.3	191.0
1.50	196.2	188.1	185.0	179.7

Table V. Distances (Å), Angles (deg), and Energy of Trans Aziridine–Ammonium Attack by NH_3

	total energy (kcal/mol) angles =		
distance	−85°	−80°	−70°
4.00	167.3	167.3	167.3
2.20	186.9	186.6	187.5
1.95	195.5	194.6	194.9
1.80	201.1	199.3	198.1
1.70	198.3	193.9	189.5
1.50	191.7	186.4	180.4

line obtained by Del Bene et al.[9] Even though the Li^+ and Na^+ affinities are much smaller than the proton affinity, the possibility remains that counterions could be attached to the nitrogen of aziridine.

The change of correlation energy upon binding of aziridine–Li^+ at the STO-6G level is found to be only 0.51 kcal/mol.

The charge transfer from the ions to the base, as seen in Table III, is slightly higher in aziridine than in ethylene oxide and, as expected, higher in Li^+ than in Na^+ compounds.

Since Hopfinger et al.[15c] had previously studied the ring opening of protonated aziridine by ammonia using the MINDO/3 semiempirical method, this method appeared to be a rational approach toward studying the reactions with larger cation–aziridine complexes. The ammonium cation complex with aziridine was used in this study since no parameters for Li^+ or Na^+ are available in this program.

The reaction of opening of the aziridine ammonium complex proceeds via nucleophilic attack by NH_3 at one of the carbons. Aziridine itself normally opens via a trans (backside) approach of the incoming nucleophile,[7] but the mitomycins are found empirically to exhibit mostly a cis (frontal) opening of the aziridine ring. Inasmuch as we followed the procedure of Hopfinger, both approaches were examined. The approaching nucleophile (NH_3) was set at the distances and angles shown in Table IV (frontal opening) and Table V (backside opening), with the principal parameters of the reacting system optimized and the resulting energies calculated. These energies are also shown in Tables IV and V. As seen from Table IV, for the cis attack, the incoming nucleophile initially approaches at an angle of 30° from a line extended collinear to the C–C bond. As one approaches the transition state, this angle becomes steeper, placing the incoming ammonia relatively closer to the aziridine nitrogen. This is followed by the subsequent opening of the ring with an overall activation energy of 43.6 kcal/mol.

As seen from Table V, the trans opening proceeds in an identical fashion to that of the Hopfinger calculation, with an activation energy of 30.7 kcal/mol. These energies are slightly larger than those for protonated aziridine ring (36 and 23 kcal/mol, respectively). As such, one might conclude that the proton can be replaced by a light metal ion in order to facilitate the opening of the ring. Such a procedure would prove useful at physiological pH, where in absence of H^+ ions the mitomycins could be used in conjunction with salts.

The Mulliken population overlap, even though not completely reliable, shows electron density present in the N–Li^+ and O–Li^+ bonds.

Outlook. These calculations are gas-phase calculations and as such do not take into account solvent effects. As such, as a further step, the influence of the solvent on the affinities will be discussed in a future paper.

It is to be expected that setting the charged complex in a polar solvent cavity will increase the proton of the ring and light cation affinities. Indeed, such effects are embodied in the equation of Born and the corrected equation of Born.[18] When the proton affinities of amines were calculated with such effects taken into consideration, their values became somewhat larger and closer to experimental trends. As such, the solvent should facilitate the addition of positive charges to the ring. Whether the solvent will stabilize the transition state or not remains to be investigated, since one of the changes occurring in the reaction is related to the shape of the cavity of the solvent which is oblate for aziridine and prolate for the opened product. Such investigations are ongoing in our laboratory at the present time. Also, experiments which study the influence of counterions on the activity of mitiomycin would prove of great value.

Conclusion

As see from the above-described results, both aziridine and ethylene oxide exhibit a substantial Li^+ and Na^+ affinity. As such, using the mitomycin in conjunction with salts may facilitate the ring opening at neutral pH leading to an enhanced activity of the drug.

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Registry No. Li, 7439-93-2; Na, 7440-23-5; aziridine, 151-56-4; ethylene oxide, 75-21-8; ammonia, 7664-41-7.

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