Substituent Effects in *N*-Alkylacetamides

Stephen K. Knudson* and John P. Idoux

Department of Chemistry, Florida Technological University, Orlando, Florida 32816

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The variation in certain properties, especially NMR shifts, with substituent groups in N-monosubstituted alkylacetamides is analyzed in terms of charge distributions obtained from CNDO/2 self-consistent-field calculations. Experimental[11] ^{15}N substituent chemical shifts are found to be correlated to relative nitrogen π-charge density. The calculations are used to determine the relative importance of contributing resonance structures; for nonprimary substituents, the increased importance of the structure characterizing the partial double bond nature of the CN linkage provides a qualitative explanation of previous[1] experimental observations. An empirical relationship between the Taft polar substituent constant and the charge on the substituent is found and is used to estimate the extent of deviation from this relation by the class of molecules, consisting of the primary substituents, which display experimental anomalies. This relationship also provides a procedure to demonstrate the normal behavior of the acyl methyl ^1H SCS with respect to a (crudely) correlated polar substituent parameter. The chemical mechanism of the 7-position effect[1] is linked to the different types of π-electron systems in acetamides and in other carboxylic acid derivatives.

Experimental measurements[1] on N-monosubstituted alkylacetamides, CH_3CONHR', have shown anomalous results for several chemical and physical properties in certain of the homologues; for example, the acyl methyl hydrogen substituent chemical shifts in the isobutyl and neopentyl derivatives deviate from expectations based on steric and polar substituent constants. In the previous work,[1] the several anomalies have been correlated with the number of hydrogen atoms at the 7 position in the substituent R′ as counted from oxygen as position 1, a phenomenon termed the 7-position effect. As part of a program to investigate the general significance of this effect, we have carried out semiempirical self-consistent-field molecular orbital calculations with the long-range objective of identifying the chemical mechanism responsible for the observed anomalies. In this paper, we relate the experimental properties to various σ- and π-electron distributions in the amide bond portion of these molecules and suggest an interpretation of the anomalies and the 7-position effect.

Method

Approximate valence electron molecular orbitals for 13 members of the N-monosubstituted alkylacetamide series, including the parent compound *N*-methylacetamide, were calculated by the CNDO/2 method[2] using available codes[3] modified to attain charge-density convergence to $\pm 2 \times 10^{-4}$ electrons. Bond lengths and angles for the acetamide "backbone" of the molecules were taken from a compilation of peptide structural parameters[4] and are listed in Table I; geometrical parameters for the substituent atoms were taken as standard values.[2] The experimental conformation[4] for the acyl methyl group, eclipsed with respect to the oxygen, is adopted for all the molecules treated. Conformations[5] of the substituents were chosen to be as free from steric hindrance as possible; in cases where several conformations appeared possible, all were calculated and that giving the lowest energy was selected for use. The choice of a fixed geometry is predicated upon the assumption that trends in the properties are related to changes in electron distributions larger than the changes caused by geometry perturbations. A related assumption is that the changes in electron distributions calculated for a selected conformation are similar to those that would be found using the appropriate average of contributing conformations. The applicability of these assumptions is discussed in the next section.

Results and Discussion

The results of the calculations are presented in terms of relative σ- and π-charge densities Δq_A and relative σ- and π-bond densities ΔQ_{AB}, which are defined in eq 1 as the density in the substituted molecule referenced to that of the parent *N*-methylacetamide:

$$\Delta q_A(R') = q_A(R') - q_A\ (R' = Me) \tag{1a}$$

$$\Delta Q_{AB}(R') = Q_{AB}(R') - Q_{AB}\ (R' = Me) \tag{1b}$$

where $Q_{AB} = 2\Sigma_i^{occ} c_{Ai} c_{Bi}$. An appropriate selection of densities, in units of millielectrons, is given in Table II, with the compounds classified in a convenient, if not standard, fashion as normal (R′ = Me, Et, *n*-Pr, *n*-Bu, *n*-Pe), nonprimary (R′ = *i*-Pr, *s*-Br, *t*-Bu, Me_2EtC, *i*-PrMeCH), and primary (R′ = *i*-Bu, *t*-$BuCH_2$, *s*-$BuCH_2$) alkyl substituent groups.

Although calculation of NMR substituent chemical shifts (SCS) is not currently feasible[6] for the molecules of interest here, a number of studies[7] have shown that, within appropriately chosen systems of related molecules, correlations may be found between SCS and relative charge densities, at both semiempirical and ab initio levels of approximation. Most[8] but not all[9] such correlations have been for molecules with constrained geometries; an example for unconstrained molecules is that reported between ^{15}N SCS and CNDO/2 values for Δq_{N_π} and ΔQ_{CN_π} for a variety of dimethylamino derivatives.[10] Here the ten ^{15}N SCS values for *N*-alkylacetamides recently reported by Westerman and Roberts[11] (no. 1–9 and 11) are found to correlate with the calculated π-charge density on nitrogen (in millielectrons):

$$\delta^{15}N = \underset{(<0.001)}{-3.30}\ \Delta q_{N_\pi} - 7.5,\ r^2 = 89.7\%,\ s = 3.5 \tag{2}$$

where r^2 is the square of the correlation coefficient expressed as a percentage, s is the standard deviation, and the number in parentheses is the significance level of the regression coefficient as determined by a "Student's" t test.[12] The experimental data, listed in Table III, are plotted as a function of the calculated charge density in Figure 1, along with the regression line of eq 2. The successful replication of the major trends in the experimental data, as indicated by eq 2 and Figure 1, argues for the accuracy and reliability of the CNDO/2-fixed geometry method employed and is evidence for the accuracy of the computed changes in π-electron density at the nitrogen atom and, by extension, generally in the amide bond backbone of these molecules.

The variation in nitrogen π-charge considered above is best viewed along with the variation in charge for all three backbone atoms, N, C, and O, and with the variations in $\Delta q_{R'}$ discussed below; these are listed in Table II. Both σ- and π-charge densities on the carbonyl carbon are relatively insensitive to substituent changes; qualitative confirmation of this is provided by the nearly constant value of preliminary ^{13}C SCS

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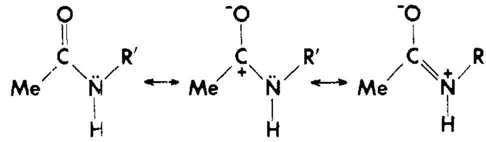
Table I. Geometry[a] of Amide Backbone $C^{\alpha}CONHC^{\alpha'}$

bond	length, Å	bond	angle, deg
$C^{\alpha}C$	1.53	$C^{\alpha}CN$	114
CO	1.24	OCN	125
CN	1.32	CNH	114
NH	1.01	$CNC^{\alpha'}$	123
$NC^{\alpha'}$	1.47		

[a] Reference 4.

data[13] for the carbonyl carbon for seven of these compounds. The large shift of electron density into the π-system for the nonprimary alkyl substituents suggested by the ^{15}N NMR data is shown most clearly by the sum of the π-charge densities on the three backbone atoms, $\Sigma(\mathrm{NCO})_{\pi}$. The primary alkyl substituents show a small shift of charge from the π-system, due mainly to the oxygen charge. No consistent pattern of shifts has been detected in the σ-system, however.

These charge density variations are most easily interpreted in terms of the resonance structures I–III for the acetamides.[14]



I II III

Since the resonance structures do not consider electron transfer from R′, the relative π-bond densities given in Table II are more readily related to the structures than are the charge densities themselves. The increase in the CN and simultaneous decrease in the CO π-bond densities for the nonprimary substituents indicates that for this class the relative contribution of resonance structure III increases compared to those of I and II. This conclusion is supported by the accompanying decrease in $\Delta\bar{q}_{\mathrm{HR}'}$, the average charge density on the hydrogen atoms in the substituent relative to the parent. The changes in N, C, and O charge densities then reflect these relative contributions plus the net charge transfer from the substituent.

The relative net charge on the substituent group, $\Delta q_{\mathrm{R}'}$, is defined as the net charge on the atoms in the substituent group compared to the net charge on the Me substituent in the parent. A positive value of $\Delta q_{\mathrm{R}'}$ then corresponds to a greater transfer of electron density from the substituent than in the parent. This measure can be used to establish a relationship to the substituent parameters of these acetamides. First, because the charge on the acyl methyl group is nearly constant, $\Delta q_{\mathrm{R}'}$ is approximately the charge on the three backbone atoms (plus the hydrogen bonded to nitrogen) and so reflects the large net transfer of charge for the nonprimary substituents. As might also be expected on an empirical

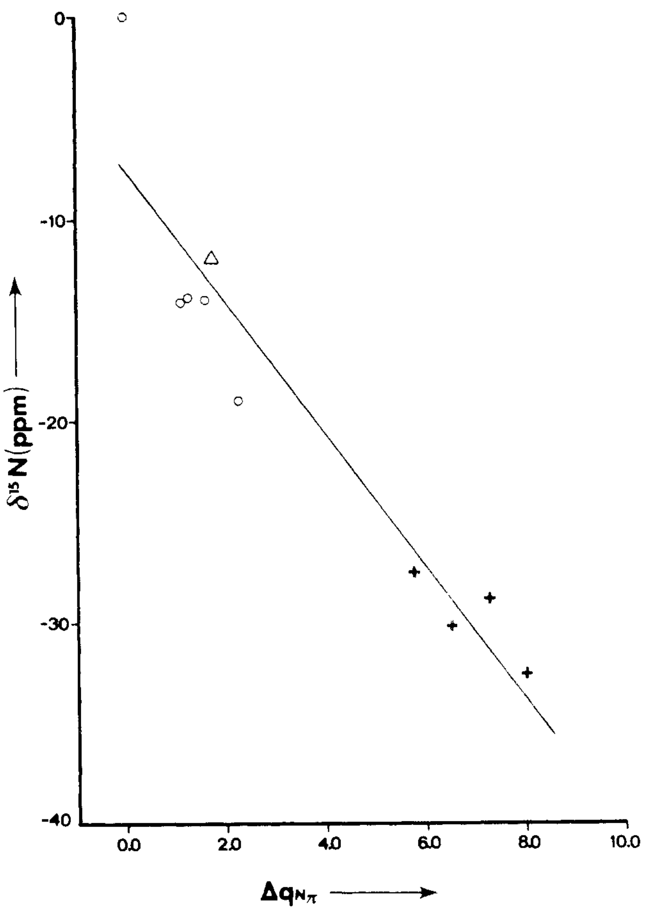


Figure 1. Correlation of ^{15}N SCS with relative nitrogen π-charge density $\Delta q_{\mathrm{N}_{\pi}}$ N-monosubstituted alkylacetamides: (○) normal alkyls; (+) nonprimary alkyls; (△) primary alkyls.

Table II. Relative Charge and Bond Densities (×10^3)

		Δq_{π}				Δq_{σ}							
no., R′	registry no.	N	C	O	$\Sigma(\mathrm{NCO})_{\pi}$	N	C	O	$\Sigma(\mathrm{NCO})_{\sigma}$	$\Delta\bar{q}_{\mathrm{HR}'}$	$\Delta q_{\mathrm{R}'}$	$\Delta Q_{\mathrm{CN}_{\pi}}$	$\Delta Q_{\mathrm{CO}_{\pi}}$
					Normal Alkyl								
1, Me[a]	79-16-3	1.7874	0.7864	1.4308		3.4031	2.8556	4.9378		0.9963	0.1026	0.4687	0.8224
2, Et	625-50-3	2.3	0.4	−3.0	−0.3	6.7	1.6	2.1	10.4	−1.1	14.7	−1.1	1.5
3, *n*-Pr	5331-48-6	1.6	0.0	−2.1	−0.5	10.6	2.2	2.2	15.0	2.5	20.0	−0.3	1.0
4, *n*-Bu	1119-49-9	1.3	−0.1	−1.8	−0.6	10.8	2.3	2.3	15.4	3.9	22.1	0.0	0.8
5, *n*-Pe	2524-60-9	1.1	0.1	−1.6	−0.4	11.1	2.4	2.2	15.7	4.9	22.7	0.2	0.7
					Nonprimary Alkyl								
6, *i*-Pr	1118-69-0	6.5	−0.7	6.5	12.3	12.0	2.0	−1.2	12.8	−4.6	30.2	8.0	−4.5
7, *s*-Bu	1189-05-5	5.8	−1.1	7.9	12.6	15.1	1.9	−1.0	16.0	−1.2	35.8	9.3	−5.4
8, *t*-Bu	762-84-5	8.0	−2.1	6.6	12.5	16.3	2.5	1.3	20.1	−5.2	44.1	7.9	−4.6
9, $(\mathrm{Me})_2$EtC	15501-38-9	7.3	−2.9	7.8	12.2	20.3	3.3	4.4	28.0	−2.5	50.4	9.0	−5.5
10, *i*-PrMeCH	40200-63-3	5.8	−1.4	7.8	12.2	15.4	2.2	−1.0	16.6	0.2	35.0	8.5	−5.2
					Primary Alkyl								
11, *i*-Bu	1540-94-9	1.7	0.3	−3.2	−1.2	8.6	2.1	2.3	13.0	5.0	16.1	−1.5	1.7
12, *t*-Bu$\mathrm{CH_2}$	15501-39-0	1.3	0.4	−2.2	−0.5	13.1	1.3	2.1	16.5	4.8	19.7	−0.1	0.9
13, *s*-Bu$\mathrm{CH_2}$	54824-90-7	1.4	0.2	−2.9	−1.3	9.2	2.2	2.4	13.8	4.9	17.9	−1.2	1.5

[a] Parent; entry is absolute charge or bond density in electron units.

Table III. Experimental Properties

no., R′	^{15}N SCS[a]	^{1}H SCS[b]	7-no.[c]	$E_s^{c\,b}$	$\sigma^{*\,b}$	$\sigma^{*\prime\,d}$
			Normal Alkyl			
1, Me	0	0	0	0	0	
2, Et	−19.0	−1.3	0	−0.38	−0.100	
3, *n*-Pr	−14.0	−1.5	3	−0.67	−0.115	
4, *n*-Bu	−13.9	−1.3	2	−0.70	−0.125	
5, *n*-Pe	−14.2	−1.3	2	−0.71	−0.130	
			Nonprimary Alkyl			
6, *i*-Pr	−30.3	−2.1	0	−1.08	−0.190	
7, *s*-Bu	−27.9	−1.6	3	−1.74	−0.210	
8, *t*-Bu	−32.6	−4.1	0	−2.46	−0.300	
9, $(Me)_2EtC$	−28.9					
10, *i*-PrMeCH		1.9	6		−0.230	
			Primary Alkyl			
11, *i*-Bu	−12.0	−0.2	6	−1.24	−0.130	−0.095
12, *t*-$BuCH_2$		1.7	9	−2.05	−0.165	−0.113
13, *s*-$BuCH_2$		0.2	5		−0.143	−0.105

[a] Reference 10. [b] Reference 1. [c] Number of hydrogens in 7-position of R′. [d] From eq 6.

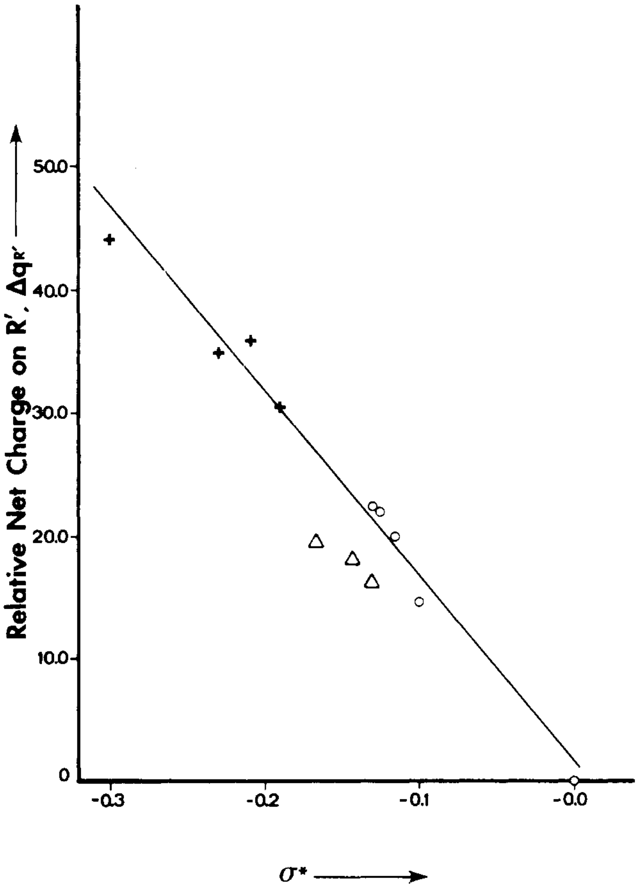


Figure 2. Correlation of substituent effects on net substituent charge density in N-monosubstituted alkylacetamides with polar substituent constant σ*. Symbols as in Figure 1.

basis,[15] it is related to the Taft polar substituent parameter σ*, as expressed in Figure 2 and eq 3:

$$\Delta q_{R'} = -1.5 \times 10^2\sigma^* + 2.0,\ r^2 = 97.8\%,\ s = 2.1 \qquad (3)$$

The correlation given in eq 3, and the corresponding line of Figure 2, excludes the data for all three primary substituents, which deviate systematically from the others in terms of the $\Delta q_{R'}$ data as well as most other charge and bond densities in Table II. The deviation in $\Delta q_{R'}$ indicates that charge transfer from these substituents is not as large as the polar substituent constant would seem to warrant. Because the effect is more pronounced in the π-system than the σ, we interpret it as due to the different type of π- and lone-pair electron system in the acetamides than in the carboxylic acid derivatives which formed the basis for the determination of the polar parameter σ*. The interaction of the π-electron system with the substituent occurs also for the nonprimary substituents; we ascribe the lack of a pronounced deviation for this class to the much stronger interaction which exists there, strong enough to be essentially maximal in both the acetamide and carboxylic acid systems.

An indirect relationship between acyl methyl hydrogen SCS, δ^1H, and calculated charge densities can now be obtained. Previous work[1] has shown that the correlation of δ^1H to E_s^c and σ* parameters is poor, and an improved correlation is obtained by replacing σ* with (H-7 no.). For the more limited set of ten compounds considered here (no. 1–8, 11, and 12 of Table III), the two correlations are essentially the same:

$$\delta^1\text{H} = \underset{(<.005)}{-2.84E_s^c} + \underset{(<.001)}{36.3\sigma^*} + 1.0,\ r^1 = 80.0\%,\ s = 0.8 \qquad (4)$$

$$\delta^1\text{H} = \underset{(<.01)}{+1.17E_s^c} + \underset{(<.001)}{0.480(\text{H-7 no.})} - 1.1,\ r^2 = 81.5\%,\ s = 0.7 \qquad (5)$$

By using the empirical correlation of σ* to $\Delta q_{R'}$ given in eq 3, we can obtain an estimate, σ*′, for the value of a polar parameter more appropriate to the amide problem for the substituents excluded from eq 3, the primary alkyls *i*-Bu, *t*-$BuCH_2$, and *s*-$BuCH_2$. These estimates for σ*′ are listed in Table III. Only two of these (*i*-Bu and *t*-$BuCH_2$) can be included in eq 4 and 5; replacing σ* by σ*′ for both, the correlation of these ten compounds becomes

$$\delta^1\text{H} = \underset{(<.005)}{-1.74E_s^c} + \underset{(<.001)}{27.0\sigma^{*\prime}} + 0.6,\ r^2 = 88.3\%,\ s = 0.6 \qquad (6)$$

The improvement compared to eq 4 shows that the anomalies, at least in δ^1H, can be treated within the normal framework of steric and polar effects.

In addition, while the calculations reported here show no evidence for a direct interaction between the carbonyl oxygen and hydrogens in the 7 position of R′, the main features of previous[1] qualitative assignments of the relative importance of the contributing resonance structures are essentially substantiated. Therefore, the seven number concept expressed in ref 1 is useful as a qualitative (or even semiquantitative) guide for determining the influence of structurally similar types of R′ groups.[16] Its practical utility rests on the basis that

(i) the anomalies are displayed by the primary alkyl substituents which have large numbers of hydrogens in the 7 position and (ii) the number of hydrogens in the 7 position has a direct, although small, effect on electron densities near the nitrogen.

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(5) All substituent groups R′ are where possible in a fully staggered conformation, with the exception of those with an odd number of α′-hydrogens (1, 6, 7, and 10), in which the oxygen is eclipsed. The *i*-Bu substituent conformation places the β′-H cis to the amide hydrogen. In *s*-Bu conformations, the γ′-C is nearly cis to the nonadjacent β′-C, being 15° above the β′, α′, β′-C plane. Finally, in *i*-PrMeCH, one γ′-C is trans to the nitrogen and the other trans to the α′-H.

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(13) The range of the ^{13}C chemical shift of the carbonyl carbon is only 2.1 ppm. We thank Dr. George Levy of Florida State University for making available this preliminary data (private communication).

(14) N-monosubstituted acetamides have been shown to exist predominantly in the trans or *Z* conformation.

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(16) Differences in second-order alkaline hydrolysis reactivities, N–H IR stretching frequencies, and C–N rotation angles have been explained in ref 1 in terms of the (H-7 no.) of R′.

Stereospecific Formation of 1,3,3-Trimethyl-2-*endo*-acetoxynorbornane in the Reaction of Acetylsulfoacetic Acid on Terpinolene

Robert Luft

Laboratoire de Chimie Organique,

Institut Polytechnique Méditerranéen, Université de Nice, F 06034 Nice Cedex, France

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The acetoxylation of terpinolene by acetylsulfoacetic acid in acetic anhydride seems to take place through the formation of an intimate ion pair which leads stereospecifically to the 1,3,3-trimethyl-2-*endo*-acetoxynorbornane.

Ethylenic ketones and alkylacetates are obtained[1,2,3] by addition of acetylsulfoacetic acid[4] to olefins. In this reaction both acetylation and acetoxylation seem to take place in a two-step pathway, as checked with open-chain and cyclic alkenes (unpublished work, to be submitted to this journal). In all cases the structure of the acetylation products fits with the hypothesis of electrophilic addition of an acetylium ion, followed by a proton elimination during a second stage. On the other hand the acetoxylation can be interpreted as a proton addition followed by that of an acetate ion.

Yet a problem arises in the acetoxylation of terpinolene which leads exclusively to the 1,3,3-trimethyl-2-*endo*-acetoxynorbornane, instead of the expected 1-acetoxy-4(8)-*p*-menthene or 8-acetoxy-1-*p*-menthene (Figure 1). At first sight, if the reaction takes place through a carbocation, terpinolene and limonene should give rise to a common acetoxylation product. As we can report, this is not the case. Next we must notice that, whereas in the acetoxylation of terpinolene the only product is a stereospecific bicyclic acetate, we obtained exclusively monocyclic acetates in the case of limonene. As previously observed,[5–8] limonene seems not to bicyclize under acid-catalysis conditions. In order to explain this behavior of limonene, Sorensen[9] assumes that the *p*-menth-1-en-8-yl cation, created in the first reaction step by addition of a proton to the C-9 atom, shows an equatorial disposition of the isopropylium substituent at the C-4 atom. Such a spatial arrangement disfavors overlapping between the empty 2p orbital at the C-8 atom and the π bond on C-1,C-2 atoms. The situation is quite different in the case of terpinolene, where the spatial disposition of the substituent on the C-4 atom is altered during the proton approach. By the rehybridization process the isopropylium is pushed in an axial disposition that facilitates the overlapping of the concerned orbitals and accordingly the bicyclization.

The last point to be considered is the nature of the reaction medium. As Whittacker et al.[10] showed, in anhydrous acetic acid solutions sulfuric acid adds in its undissociated form to ethylenic bonds, as does acetic acid itself. To our mind acetic anhydride is a bad ionizing solvent too, leading to the formation of an intimate ion pair during the primary attack of the alkene substrate, put forth by the un-ionized acid B–H.[11,12] Whatever the accurate structure of the counterion of the intimate ion pair would be, it seems to contribute so adequately to its stabilization that rearrangement[13] would take place before any capture by an external nucleophile.

Keeping these arguments in mind, the stereospecific formation of 1,3,3-trimethyl-2-*endo*-acetoxynorbornane can be anticipated as follows (Figure 2):

The approach of B–H initiates the formation of a bond between the C-4 atom of terpinolene and H which is paralleled by a movement of the C-4 substituent toward axial disposition, as indicated; the C-8 atom acquires a cationic character. Simultaneous overlapping of the C-8 2p$_z$ orbital with the π orbital resting on C-1,C-2 begins. The structure of an intimate ion pair is attained.

Because of unfavorable steric interactions between the substituents of C-1 and C-8, the orbital overlapping seems to strengthen the attraction between C-8 and C-2, the C-1 atom moving at the same time in the opposite direction. Overlapping of C-3 and C-1 orbitals begins by neighboring group

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