expected difference between the C–C–C bond angles in the connections between the carboxylate and imidazole groups.

As can be seen in Figure 3, the changes in the ^{15}N shifts of *cis*-urocanic acid with pH are extraordinarily similar to those observed for the histidine of the catalytic triad of the serine protease α-lytic protease.[3] This parallelism provides confirmation of the conclusions drawn previously as to the nature of the species present at the Ser-His-Asp triad of the active site of α-lytic protease and especially the mode of interaction of the aspartic acid with the histidine. Nothing observed in the present research is contrary to the previous determination that His is a stronger base than the Asp carboxylate and that the "charge-relay" mechanism once postulated as the mode of action of serine proteases cannot be correct in its usual formulation.[3,20,21] This should hardly be taken to mean that the Asp carboxylate is unimportant—quite the contrary, it plays an important role in making K more favorable for attachment on the serine hydroxyl proton in the catalytic step. It will also stabilize the imidazolium cation when the Ser hydroxyl proton is transferred. In addition, the Asp carboxylate may help keep the imidazolium ring so oriented as to be effective in the protonation and cleavage steps necessary for breaking the peptide bond and formation of the serine ester from the "tetrahedral" intermediates.[3]
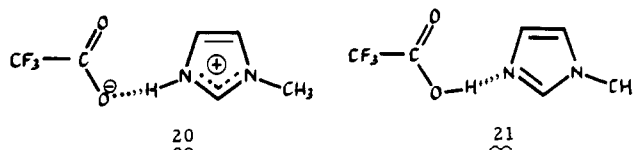
A special issue in the interpretation of the His ^{15}N shifts of α-lytic protease was the 12.6-ppm difference at pH 4.5 between the resonances of N1 and N3 with that of N3 being downfield (see Figure 3). This was interpreted as being a downfield perturbation of the N3 shift of the protonated histidine imidazole by the carboxylate anion of Asp (**19**). The assignment was made


19
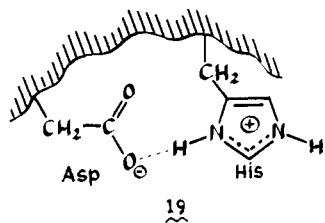
by analogy with an N1–N3 shift difference of 16 ppm observed for 2M each of *N*-methylimidazole and trifluoroethanoic acid in trichloromethane.[3,4] Infrared spectra and ^{15}N shifts indicated

20   **21**

proton transfer and formation of a carboxylate imidazolium cation **20** rather than the alternative complex **21**.[4] The extrapolation from trichloromethane solution to aqueous solution was a long one and it is gratifying that *cis*-urocanic acid exhibits the same pattern of shifts at pH 4.7 with an N1–N3 shift difference of 9.7 ppm, which can be confidently ascribed to **22**, an analogue of **19**.

22
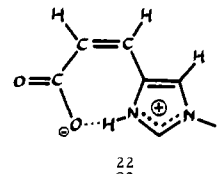
The similarity of ^{15}N shifts of **19** and **22** as well as of **9** and **13** suggests that it would be interesting to prepare substances such as **23** (with a guanidino or similar cationic group to enhance solubility) for testing as models for serine protease action. To

23
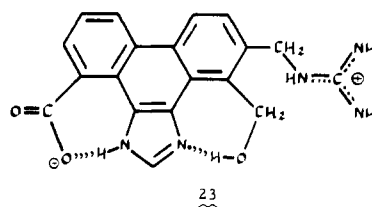
be sure, **23** lacks the "oxyanion hole" and other stabilizing groups for formation of the "tetrahedral intermediate" which characterize serine proteases, but it is possible that some modification of the cationic group shown as guanidinium in **23** could partly fulfill this purpose. An advantage of **23** over enzyme would be a substantially greater thermal stability.

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Effect of Isocyano Group Substitution in Simple Primary, Secondary, and Tertiary Carbanions

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Abstract: The stabilities, structures, and charge distributions of primary, secondary, and tertiary α-isocyano carbanions and their parent carbanions have been examined through ab initio (STO-3G) calculations. The data provide evidence that the isocyano group does not act as a delocalizing substituent but through an inductive effect, in agreement with the conclusions of Walborsky and Periasamy[4] obtained with a more complex isocyano carbanion.

The effect of substituents on carbanions is of interest for both synthetic and mechanistic reasons.[1] While a variety of substituent

groups have been employed to enhance the stability of carbanions, the isocyanide group is one of the more effective for such purposes.

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Moffat

Table I. Configurations of α-Isocyano Carbanions

molecule	bond lengths, Å				bond angles, deg	
	H–CNC	C^a–CNC	C–NC	N≡C	∠H–C–(NC)	∠C^a–C(NC)
CH_3NC	1.092		1.446	1.171	109.9	
CH_2NC^+	1.117		1.307	1.238	120.2	
CH_2NC^-	1.109		1.506	1.165	100.9	
CH_3^-	1.117					
C_2H_5NC	1.094	1.544	1.454	1.171	108.2	111.4
$C_2H_4NC^+$	1.117	1.516	1.322	1.226	116.8	123.0
$C_2H_4NC^-$	1.108	1.562	1.502	1.165	101.1	104.9
$C_2H_5^-$	1.112	1.576				
C_3H_7NC	1.096	1.550	1.450	1.172	107.6	110.1
$C_3H_6NC^+$		1.525	1.340	1.217		118.8
$C_3H_6NC^-$		1.560	1.501	1.165		104.6
$C_3H_7^-$	1.095	1.557				

^{a} C of CH_3.

The metalation of isocyanides has been employed in a variety of reactions of importance in synthetic chemistry[2] and in particular those involving nucleophilic aminoalkylation and heterocyclic synthesis. It has been suggested[3] that inductive stabilization by the dipole of the isocyanide group plays a significant role in these metalated isocyanides. Walborsky and Periasamy[4] have recently studied the configurational stability of the 1-isocyano-2,2-diphenylcyclopropyl carbanion, A, and have concluded that the

A
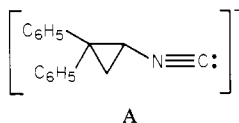
isocyano group acts through an inductive rather than a delocalizing effect.

1   2   3
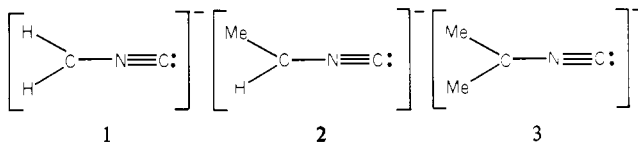
The present work examines the effect of substitution of an isocyano group on each of three simple carbanions CH_3^-, $C_2H_5^-$, and $C_3H_7^-$ to form representatives of a primary, (**1**), secondary (**2**), and tertiary (**3**), carbanion, respectively. These anions may be compared with their parent anions and corresponding neutral isocyanides to determine the effect of isocyano substitution on stabilities, structures, and electron densities. The effect of methyl substitution can also be ascertained by comparing structures **1**, **2**, and **3**.

Ab initio calculations[5] with an STO-3G basis and standard values of the exponents have been employed with geometry optimization continued until bond lengths and bond angles were constant to ±0.001 Å and ±0.1°, respectively. Calculations were done for CH_3^-, $C_2H_5^-$, and $C_3H_7^-$, their isocyano-substituted derivatives, and the related neutral species.

Results and Discussion

The C–NC bond lengths in the isocyano-substituted carbanions are approximately equal but considerably larger than those found in the corresponding cations and neutral parents (Table I). This suggests that a shift of electron density from the bonding region of the C–NC bond has occurred, at least relative to the neutral

Table II. Stabilization Energies (ΔE) of α-Isocyano Carbanions

α-isocyano carbanions	ΔE^a
CH_2NC^-	60.0
$C_2H_4NC^-$	53.9
$C_3H_6NC^-$	52.2

^{a} kcal/mol.

Table III. Atomic Charges on α-Isocyano Carbanions

molecule	C	N	C	C^a
H_2CNC^-	−0.278	−0.353	−0.172	
H_2CNC^+	+0.296	−0.273	+0.503	
H_3CNC	−0.062	−0.332	+0.098	
H_3C^-	−0.487			
CH_3HCNC^-	−0.195	−0.352	−0.157	−0.191
CH_3HCNC^+	+0.350	−0.296	+0.452	
CH_3HHCNC	+0.019	−0.338	+0.091	
$C_2H_5^-$	−0.398			−0.186
$(CH_3)_2CNC^-$	−0.116	−0.352	−0.144	−0.190
$(CH_3)_2CNC^+$	+0.405	−0.313	+0.408	
$(CH_3)_2HCNC$	+0.095	−0.341	+0.088	
$(CH_3)_2HC^-$	−0.333			−0.179

^{a} C of methyl group attached to C_1.

and positively charged species. The isocyanide bond itself is slightly shorter than that found in the corresponding neutral species but considerably shorter than that in the corresponding cationic species. The structures are all pyramidal about the anionic carbon atom.

The stabilization energies of the isocyano carbanions relative to the parent carbanionic species can be calculated by using the isodesmic reactions 1-3.

$$H_2CNC^- + CH_4 \rightarrow H_3CNC + CH_3^- \quad (1)$$

$$H_3CCHNC^- + C_2H_6 \rightarrow H_3CCH_2NC + C_2H_5^- \quad (2)$$

$$(H_3C)_2CNC^- + C_3H_8 \rightarrow (H_3C)_2CHNC + C_3H^- \quad (3)$$
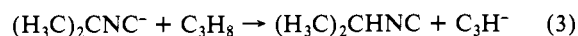
The stabilization energies of the three isocyano carbanions 1-3 are given by the values of ΔE found for reactions 1-3, respectively. Geometry-optimized energies for all molecules in these reactions were used in the calculations, the results from which are given in Table II. The large and positive stabilization energies are indicative of considerable stabilization produced by the substitution of an isocyano group.

With all the isocyano carbanions considered the negative charge on the anionic carbon atom is reduced by approximately 0.2 unit compared with that in the corresponding unsubstituted carbanionic species (Table III). The preponderance of this shift in electron density can be observed with the isocyano carbon atom which is found in the isocyano carbanions to be negatively charged in contrast with a positive charge in the neutral cyanides. In addition, a comparison of the charges on the three isocyano carbanions shows that substitution of a methyl group for a hydrogen atom

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reduces the negative charge on the carbanionic carbon atom by approximately 0.08 electron.

Although gas-phase acidities do not appear to be available for isocyanides, estimates of these can be made from the present work. The calculated gas-phase acidity ($\Delta H°$) for CH_4 (560.0 kcal/mol) reduced by the stabilization energies given in Table II will correspond to the gas-phase acidities of the neutral isocyanide molecules. The same information can be employed to assess the effects of methyl substitution. Addition of a first and a second methyl group reduces $\Delta H°$ (acid) by 6.1 and 1.7 kcal/mol, respectively.

Periasamy and Walborsky[4] have noted that when the carbanionic center is an asymmetric carbon, the configurational stability of the carbanion can then be measured. Hence the cyclopropyl anion system is appropriate for experimental study. Furthermore, the strain energy of approximately 26 kcal/mol which is associated with the cyclopropane ring[6] would be increased during the process of inversion, thus producing an intrinsic energy barrier to pyramidal inversion. Substituent effects can also be conveniently examined.

The geometries reported in the present work provide evidence for the relative unimportance of resonance delocalization in the isocyano carbanions studied. It has been pointed out by Periasamy and Walborsky (PW)[4] that resonance stabilization would be favored by a planar configuration in the substituted carbanion, while inductive effects should be favored by a pyramidal geometry. Further, PW[4] conclude that with (1-isocyano-2,2-diphenylcyclopropyl)lithium (IDCL), the α-isocyano carbanion favors a pyramidal configuration. Although the species examined in the present work are much less complex than that considered by PW, some comparisons appear to be valid. The present results appear to support those of PW in respect of the expectation of a pyramidal geometry for isocyanosubstituted carbanions. Further, the calculated distribution of charge from the present work lends support to their argument that the isocyano group does not act as a delocalizing substituent but as an electron-withdrawing group

operating largely through an inductive effect.[4]

Although minimal basis set data cannot be expected to produce absolute electronic energies, nevertheless it is anticipated that calculated nuclear configurations will be reasonably accurate. It has been noted[7,8] that the small amount of experimental structural data which is available for anions appears to be adequately reproduced by molecular orbital calculations at the minimal basis set STO-3G level. Further it is now well documented that such a basis set is capable of reproducing the known geometrical structures for a wide variety of neutral species.[9] In addition, the use of isodesmic reactions will provide at least a partial cancellation of errors due to neglect of electron correlation and limitations in the basis set.[10]

The present calculations are applicable to the free carbanion and do not include any consideration of the effects of interactions between the charged species or with a solvent. It has been pointed out[11] that the geometry of the carbanion depends on the nature of the ion pair in solution. However Periasamy and Walborsky[4] have demonstrated that, with IDCL, the anion is capable of retaining its configuration whether it exists as a contact ion pair, solvent separated ion pair, or a free ion pair. Consequently it may be expected that the introduction of perturbing species would not alter the semiquantitative conclusions from the present work.

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Stereochemistry of *trans*-1,4,5,8-Tetranitroso-1,4,5,8-tetraazadecalin: An Attractive Interaction between Peri Nitroso Groups

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Contribution from the Research Department—Code 3853, Naval Weapons Center, China Lake, California 93555, and Nicolet Magnetics, Inc., Mountain View, California 94041. Received December 3, 1981

Abstract: The preferred configuration of *trans*-1,4,5,8-tetranitroso-1,4,5,5-tetraazadecalin, **3**, is the anti,syn,anti,syn configuration, **3c**, with S_2 symmetry. It is more stable than the anti,anti,anti,syn configuration, **3d**, by approximately 1.5 kcal/mol, and the anti,anti,syn,syn and anti,anti,anti,anti configurations, **3b** and **3a**, by approximately 3.0 kcal/mol. These results were established on the basis of the ^1H and ^{15}N NMR spectra of **3**. The relative stability of **3a–d** and the ^{15}N NMR chemical shifts in **3a–d** have been rationalized on the basis of a bonding interaction between the oxygen of a syn nitroso group and the adjacent nitroso nitrogen in a 1,8- or 4,5-syn,anti configuration plus a strong destabilizing electrostatic interaction that occurs in the anti,anti,syn,syn configuration because two partial positive charges are placed in close proximity.

It is well-established that the nitrosamino group is planar and that there is restricted rotation about the N–N bond due to its partial double bond character.[1] In *N,N*-dimethylnitrosamine this barrier has been measured to be 23 kcal/mol.[2] Dinitrosamines

such as *N,N*-dinitrosopiperazine, **1**, exist as cis and trans isomers corresponding to the two possible relative arrangements of the nitroso groups.[3] The cis:trans ratio in this case has been de-

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