Conformational Preferences in Alkylnitrosoureas

John K. Snyder and Leon M. Stock*

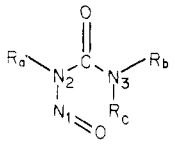
Department of Chemistry, The University of Chicago, Chicago, Illinois 60637

Received August 29, 1979

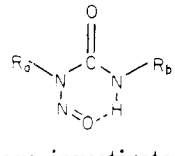
The spectroscopic properties of several *N*-alkyl-*N*-nitrosoureas, *N,N'*-dialkyl-*N*-nitrosoureas, and *N,N',N'*-trialkyl-*N*-nitrosoureas have been studied in carbon disulfide and chloroform solutions. The NH stretching frequencies in the IR spectra have been observed in both concentrated and dilute solution and in the presence of added dioxane. The results indicate that there is a strong intramolecular hydrogen bond in the mono- and dialkylnitrosoureas. The chemical shifts and line widths of the NMR spectra have also been studied in these solvents. The large chemical shift differences, about 1.3 ppm, for the NH protons in the monoalkylnitrosoureas and other spectroscopic features in the monoalkyl- and dialkylnitrosoureas also indicate that an intramolecular hydrogen bond contributes to a strong conformational preference. The temperature dependence of the NMR spectra of several *N,N',N'*-trialkyl-*N*-nitrosoureas establishes that the energy barrier for rotation about the carbon dialkylamide bond is about 13 kcal mol^{-1}. Dipolar resonance interactions are primarily responsible for this barrier. This interaction is augmented by a strong, 8–10 kcal mol^{-1}, hydrogen bond in the mono- and dialkylnitrosoureas.

Introduction

Interest in the mechanisms by which the alkylnitrosoureas decompose in aqueous and nonaqueous solution has prompted us to examine the conformational preferences of these compounds. Huisgen and his associates discussed the factors governing the rates of decomposition of many *N*-nitroso compounds.[1] They postulated that dipolar resonance contributions and various electrostatic interactions altered the energy content of the *N*-nitroso compounds and the reaction rate. For the alkylnitrosoureas, restricted rotations may occur about any of the three core bonds, N_1N_2, N_2C, and CN_3, in the trialkylnitrosoureas.



Eight conformational isomers can exist when R_b and R_c are different. Whereas restricted rotation about the carbon–nitrogen bond in amides and related compounds is very well established,[2] the corresponding barriers in ureas are much smaller. For example, line broadening has never been observed in the NMR spectra of tetramethylurea, which exhibits a single sharp methyl resonance at 150 K.[3] The rotational barrier has been estimated by the study of relaxation phenomena to be 6.1 kcal mol^{-1}.[4] It may be presumed, however, that dipolar resonance contributions are more important in the *N*-nitroso compounds than in the ureas and that hydrogen-bonding interactions may enhance the barrier in the mono- and dialkylnitrosoureas.



Consequently, we have investigated the IR and NMR spectra of several alkylnitrosoureas to establish their conformational preferences and to gauge the relative importance of double bond character and hydrogen-bonding interactions on the energy barriers.

Results

Preparations. The ureas were prepared by conventional methods. In most cases, the ureas were nitrosated by aqueous nitrous acid without difficulty. The *N*-methyl-*N'*-alkylureas can form two isomeric products. However, mixtures were obtained only when the *N'*-alkyl group had small steric requirements. These compounds were readily separated by chromatography. In each instance the desired *N*-methyl-*N*-nitroso compound was formed in preference (Table I).

Table I. Isomer Distribution for the Nitrosation of *N*-Methyl-*N'*-alkylureas

	product distribution, %	
N'-alkyl group	$CH_3N(NO)CONHR$	$CH_3NHCON(NO)R$
CH_3CH_2	78	22
$CH_3CH_2CH_2$	80	20
$(CH_3)_2CHCH_2$	83	17

Table II. Chemical Shifts for the Amido Protons of the Monoalkyl- and Dialkylnitrosoureas in Chloroform at 293 K

nitrosourea[a]	chemical shift, ppm	nitrosourea[b,c]	chemical shift, ppm
MNU	6.93, 5.60	DMNU	6.95
ENU	6.87, 5.42	EMNU	6.97
i-PNU	6.92, 5.64	*i*-PMNU	6.84
PhNU	6.81, 5.29	PhMNU	6.86

[a] MNU, ENU, *i*-PNU, and PhNU are *N*-methyl-, *N*-ethyl-, *N*-isopropyl-, and *N*-phenyl-*N*-nitrosourea. [b] DMNU, EMNU, *i*-PMNU, and PhMNU are *N,N'*-dimethyl-, *N*-methyl-*N'*-ethyl-, *N*-methyl-*N'*-isopropyl-, and *N*-methyl-*N'*-phenyl-*N*-nitrosourea. [c] Several other *N,N'*-dialkyl-*N*-nitrosoureas exhibited similar shifts.

When the steric requirements of the *N'*-alkyl group were large, e.g., isopropyl or cyclohexyl, or when there were two alkyl groups on the N' atom, the *N*-methyl-*N*-nitroso derivative was formed virtually exclusively.

NMR Spectra. The NMR spectra of *N*-methyl-*N'*-ethyl-, *N*-isopropyl-, and *N*-phenyl-*N*-nitrosourea had similar characteristics. In each case, the resonances of the hydrogen atoms of the alkyl and aryl groups were well resolved, with narrow line widths. On the other hand, the resonances of the NH protons were widely separated and broadened. The chemical shifts observed for these protons are summarized in Table II.

The observation that the widely separated signals for the NH protons in the monoalkyl compounds were readily observed at 293 K suggests that there is a substantial energy barrier for rotation about the CN_3 bond. The spectra of the related *N,N'*-dialkyl-*N*-nitrosoureas were examined to probe the factors governing the energy barrier. With one notable exception, the resonances of the alkyl

(1) Huisgen, R.; Reimlinger, H. *Justus Liebigs Ann. Chem.* **1956**, *599*, 183, and previous articles in this series.
(2) Stewart, W. E.; Siddall, T. H., III. *Chem. Rev.* **1970**, *70*, 517.
(3) Isaksson, G.; Sandström, J. *Acta Chem. Scand.* **1970**, *24*, 2565.
(4) Stilbs, P.; Moseley, M. E. *J. Magn. Reson.* **1978**, *31*, 55.

0022-3263/80/1945-0886$01.00/0

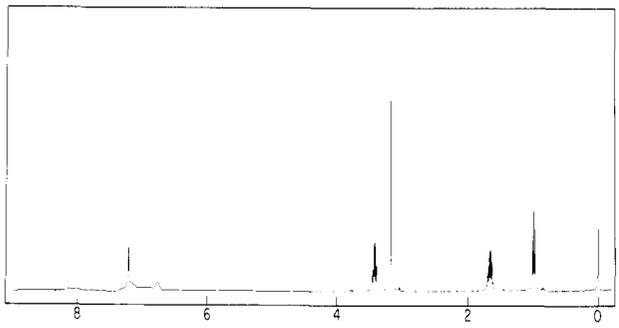


Figure 1. NMR spectrum of *N*-methyl-*N'*-propyl-*N*-nitrosourea in chloroform at 293 K. The compound was purified by preparative thin-layer chromatography to remove *N*-propyl-*N'*-methyl-*N*-nitrosourea. The resonances of the alkyl groups and the NH proton observed in this instance are typical of the results for the dialkylnitrosoureas.

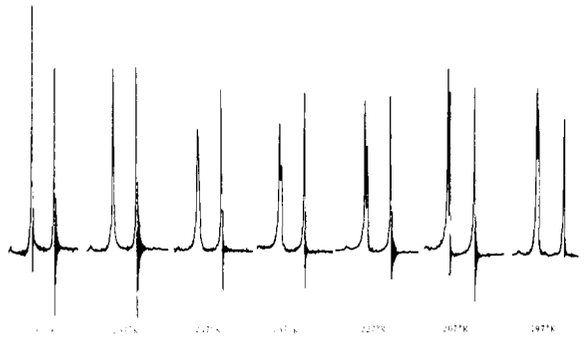


Figure 2. Temperature-dependent spectra of *N,N',N'*-trimethyl-*N*-nitrosourea from 267 to 197 K.

and aryl groups were very well resolved, with narrow line widths. In addition, a single resonance was observed for the NH proton in each molecule (Figure 1). The character of the resonance was not altered when the temperature of the solution was lowered to 233 K or increased to 343 K. These substances are known to decompose exothermically at higher temperatures, and the study could not be extended safely.

The exception mentioned in the preceding paragraph is *N*-methyl-*N'*-cyclohexyl-*N*-nitrosourea. The resonances of the hydrogen atoms of the cyclohexane ring in this molecule were broadened at ambient temperature.

We also examined the spectra of four *N,N',N'*-trialkylnitrosoureas to gain perspective on the nature of the conformational preference in the absence of hydrogen-bonding interactions. The resonances of all hydrogen atoms of *N,N',N'*-trimethyl- and *N*-methyl-*N',N'*-diethyl-*N*-nitrosourea were very well resolved and unbroadened in chloroform and carbon disulfide at 293 K. However, the resonances selectively broadened at lower temperature, and we studied the temperature dependence of the spectra in carbon disulfide solution.[5] The spectra of the trimethyl compound are presented in Figure 2.

At ambient temperature, there are only two methyl signals. However, as the temperature of the solution is decreased the *N',N'*-dimethyl resonance separates into two components. The separation of these signals is complete at 217 K. The results for the other trialkylnitrosoureas are very similar. The coalescence temperatures for the resonances of the *N',N'*-dialkyl groups, the chemical shift differences for these resonances, the estimated rates of rotation at the coalescence temperature, and the free-energy barrier for rotation about the CN_3 bond at the coalescence temperature are summarized in Table III.

(5) The solvent was selected on the basis of favorable solubility relationships and its modest solute–solvent interactions. Tichý, M. *Adv. Org. Chem.* **1965**, *5*, 115.

Table III. Spectroscopic Observations for the Trialkylnitrosoureas in Carbon Disulfide

nitrosourea[a]	coalescence temperature, T_c, K	rotation rate at T_c, s^{-1}	chemical shift, Hz	free energy barrier, kcal mol^{-1}
TMNU	247	6.7	3	13.4
DEMNU	257[b]	46.7	21	13.0
	247[b]	17.8	8	12.9
PiMNU	256	80.0	36	12.7
PyMNU	247	14.4	6.5	13.0

[a] TMNU and DEMNU are *N,N',N'*-trimethyl- and *N*-methyl-*N',N'*-diethyl-*N*-nitrosourea. PiMNU and PyMNU are *N*-(*N*-methyl-*N*-nitroso)carbamidopiperidine and -pyrrolidine. [b] Observation for the methylene fragment. [c] Observation for the methyl group.

There is a further broadening of the resonances of the methyl and ethyl groups of the trialkyl derivatives near 200 K. The results presented in Figure 2 indicate that the resonances of both the *N*- and *N'*-alkyl groups are broad. The resonance of tetramethylsilane remains narrow. Hence, another rate process is responsible for the line broadening at this temperature.

Infrared Spectra. The IR spectra of the nitrosoureas were recorded in dilute solutions of chloroform or carbon disulfide. The relevant absorptions are summarized in Table IV.

Dilute solutions, 5×10^{-3} M, were employed in this work. Further dilution of the solution did not alter the spectra. At higher concentrations, however, there were discernible differences in the spectra of certain molecules. For example, the symmetric and antisymmetric NH stretching frequencies of *N*-ethyl-*N*-nitrosourea appear at 3410 and 3530 cm^{-1} in dilute, 4×10^{-3} M, solution. When the concentration of this urea is increased by a factor of two, two broad absorptions appear at 3250 and 3310 cm^{-1}. These broad absorptions are attributed to intermolecular hydrogen bonding. In contrast, the NH stretching frequency of *N,N'*-dimethyl-*N*-nitrosourea appears at 3440 cm^{-1} in dilute, 4×10^{-3} M, solution. When the concentration of this urea is increased by a factor of four, there is no discernible change in the spectrum. Similar results were obtained with other *N*-methyl-*N'*-alkyl-*N*-nitrosoureas.

The IR spectra of *N*-ethyl- and *N,N'*-dimethyl-*N*-nitrosourea were examined in carbon disulfide containing 10, 20, and 50% dioxane by volume. Dioxane has a major influence on the spectrum of the ethyl derivative. The NH frequencies which appear in dilute carbon disulfide solution are significantly modified by 10% dioxane. Two broad bands appear at 3300 and 3500 cm^{-1} in the presence of the ether. These bands are dominant in 50% dioxane. In contrast, dioxane has only a modest influence on the spectrum of the dimethyl compound. The NH stretching frequency at 3440 cm^{-1} persists even in the presence of 50% dioxane.

Discussion

There are several notable features in the NMR and IR spectra of the mono- and dialkylnitrosoureas. First, the resonances of the hydrogen atoms of the amido groups in the *N*-alkyl-*N*-nitrosoureas are broad at 293 K. The line broadening is clearly the consequence of restricted rotation about the CN_3 bond. Second, the broad resonances of these hydrogen atoms are separated by more than 1.3 ppm. This chemical shift difference is much larger than the chemical shift differences observed for the related amides.

Table IV. Infrared Frequencies (cm^{-1}) for the Alkylnitrosoureas[a]

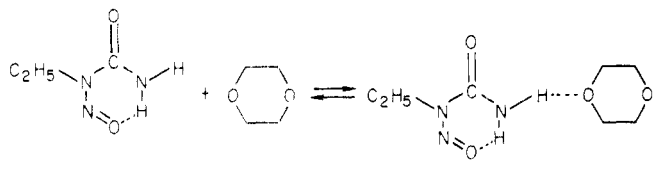
nitrosourea[b]	NH stretch in $CHCl_3$	NH stretch in CS_2	NH bend in CS_2	CO stretch in $CHCl_3$	CO stretch in CS_2
MNU	3540, 3420	3530, 3412		1740	1745
ENU	3540, 3420	3530, 3412		1741	1742
DMNU	3450	3440	774	1730	1730
EMNU	3440			1730	
i-PMNU	3430	3420	782	1730	1730
t-BMNU	3420	3415	795	1735	1735
TMNU				1696	1700
DEMNU				1690	

[a] Maximum concentration was 5×10^{-3} M. [b] Please see Tables I and II for compound identification.

Schaumann and his associates have discussed the chemical shifts of the amido protons in primary amides in various solvents.[6] The largest separation noted in their study was 0.7 ppm for benzamide in dimethylformamide-d_7 and the largest separation observed for a primary alkyl amide was 0.6 ppm for acetamide in the same solvent. The larger chemical shift observed for the nitrosoureas is indicative of a strong intramolecular hydrogen bond. Previous work strongly infers that the downfield resonances at about 7 ppm should be assigned to the hydrogen-bonded proton.[7,8] This assignment is confirmed by the observation that the single NH resonance in the dialkylnitrosoureas also occurs at about 7 ppm. Indeed, the finding that the one NH resonance of the dialkylnitrosoureas occurs at exactly the same frequency as in the low-field NH resonance in the monoalkylnitrosoureas implies that a single conformational isomer is present in solution. This contention is supported by the fact that the spectra of the dialkyl compounds are temperature independent from 257 to 343 K.

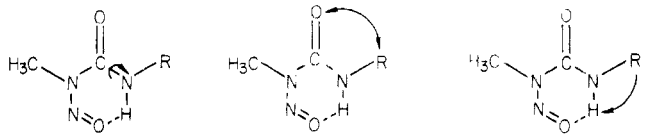
The infrared spectra of the mono- and dialkylnitrosoureas are also compatible with the predominance of one conformational isomer. In dilute solution, the frequencies exhibited by the monoalkyl derivatives are indicative of the symmetric and unsymmetric stretching frequencies of the NH_2 protons. An increase in the concentration of these molecules perturbs the spectrum. The appearance of two new broad bands at lower frequency is readily attributed to intermolecular hydrogen bonding. An equivalent change in the concentration of the dialkylnitrosourea did not produce an equivalent result. For *N*,*N*′-dimethyl-*N*-nitrosourea, the onset of intermolecular hydrogen bonding occurs at significantly higher concentration. The differences in the behavior of the mono- and dialkyl compounds are readily attributed to the differences in the accessibility of the amido protons. In the dialkyl compound the amido proton is confined in the intramolecular hydrogen bond. In the monoalkyl compound a second amido proton is available for intermolecular hydrogen bonding.

These conclusions are supported by the results of the experiments with added dioxane. Dioxane is an excellent

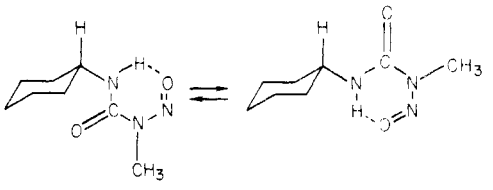


hydrogen-bond acceptor and bonds readily with proton donors.[5] The addition of dioxane to dilute solutions of the monoalkyl and dialkyl compounds alters the spectra. However, much higher concentrations of dioxane are necessary to eliminate the frequency assigned to the intramolecular hydrogen bond in the dimethylnitrosourea. Indeed, this frequency persists in 50% dioxane.

The stretching frequency depends upon the structure of the alkyl group. The results presented in Table IV indicate that this frequency decreases as the steric requirements of the alkyl group on N_3 increase. Inasmuch as the NMR spectra are essentially unaltered, we attribute the change in the IR frequency to a modest structural modification. A torsional distortion of the planar conformation about the CN_3 bond or a compressional distortion of the CNH fragment would relieve the steric interaction between the carbonyl group and the alkyl group. It is possible to distinguish between these interpretations because the torsional distortion is predicted to weaken the hydrogen bond whereas the compressional distortion is predicted to strengthen the bond. The experimental data (Table IV) indicate that the NH stretching frequencies decrease with an increase in the steric requirements of the alkyl group. Thus, we infer that compressional effects are dominant. This conclusion is supported by the variation in the NH bending frequencies.[9]



The NMR spectrum of *N*-methyl-*N*′-cyclohexyl-*N*-nitrosourea contrasts with the spectra for the other di-



alkylnitrosoureas. The resonance signals of the cyclohexyl group are broad at 293 K. In view of the results for other dialkylnitrosoureas, it is quite unlikely that these resonances are broad because of slow rotation about the CN_3 amide bond. There are several other possibilities, including slow ring inversion and slow rotation of the large substituent about the cyclohexyl–nitrogen bond. The barriers to ring inversion in cyclohexanes are only about 10 kcal mol^{-1}.[10] Consequently, we are reluctant to ascribe the observed line broadening to an interaction of this kind. On

(6) Walter, W.; Schaumann, E.; Rose, H. *Org. Magn. Reson.* **1973**, *5*, 191.
(7) Schneider, W. G. "Hydrogen Bonding"; Hadži, D., Ed.; Pergamon Press: New York, 1959; p 55.
(8) Pimentel, G. C.; McClellan, A. L. "The Hydrogen Bond"; W. H. Freeman: San Francisco, 1960; p 143.
(9) This point is discussed by McLachlan, R. D.; Nyquist, R. A. *Spectrochim. Acta* **1964**, *20*, 1397.
(10) (a) For cyclohexyl esters: Allan, E. A.; Premuzic, E.; Reeves, L. W. *Can. J. Chem.* **1963**, *41*, 204. (b) For cyclohexyl halides: Bovey, F. A.; Anderson, E. W.; Hood, F. D.; Kornegay, R. L. *J. Chem. Phys.* **1964**, *40*, 3099.

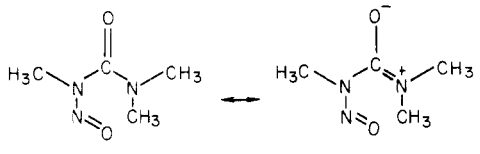
Table V. Preparation of Ureas

urea	method	solvent	mp, °C	yield, %
$C_6H_5NHCONH_2$	A	water[a]	142-143	71
$(CH_3)_2CHNHCONH_2$	A	methanol	153-154	52
$(CH_3)_3CNHCONH_2$	A	methanol	182-184	35
$(CH_2)_5NCONH_2$	A	water	91-92	85
$C_6H_5NHCONHCH_3$	A	water[a]	148-149	68
$CH_3NHCONHCH_2CH_3$	A	aqueous methanol	54-55	60
$CH_3NHCONHC(CH_3)_3$	B	ether	144-145	79
$CH_3NHCONHCH(CH_3)_2$	B	none	101-102	82
	B	ether	101-102	77
$CH_3NHCONH(c\text{-}C_6H_{11})$	B	ether	151-152	97
$CH_3NHCONHCH_2CH_2CH_3$	B	ether	61-62	100
$CH_3NHCONHCH(CH_3)CH_2CH_3$	B	ether	72-73	92
$CH_3NHCONHCH_2CH(CH_3)_2$	B	ether		99
$CH_3NHCON(CH_3)_2$	B	ether	73-74	84
$CH_3NHCON(CH_2CH_3)_2$	A	methanol		99
$CH_3NHCON(CH(CH_3)_2)_4$	B	none	99-101	96
	B	ether	99-101	99
$CH_3NHCON(CH_2)_5$	B	ether	73-74	59
$CH_3NHCON(CH_2)_4$	B	ether	123-124	97
$CH_3NHCON(CH_2CH_2CH_2CH_3)_2$	B	ether	46-47	100
$CH_3NHCON(CH_2CH_2CH_3)_2$	B	ether	61-62	99
$CH_3NHCON(CH_2CH(CH_3)_2)_2$	B	ether	oil	100

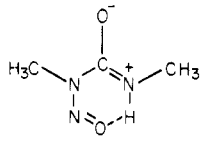
[a] The reaction mixture was heated on a steam bath.

the other hand, barriers resulting from significant steric interactions have been described by Siddall and his associates for amides and ureas.[2,11] They report that the resonances of the *N*-alkyl groups in *N,N*-diisopropylacetamide and *N,N*-diisopropylisobutylamide are broadened at 10 and 40 °C, respectively, and they attribute the line broadening to slow rotation about the alkyl carbon–nitrogen bond. A similar explanation seems appropriate for the cyclohexylnitrosourea.

In summary, the available information suggests that the energy barrier for rotation about the carbonyl carbon amide bond, CN_3, in the mono- and dialkylnitrosourea is substantial, perhaps in excess of 20 kcal mol^{-1}. Regrettably, the instability of the nitrosoureas prevented a direct assessment of the barrier by NMR spectroscopy. However, we were able to measure the barrier for rotation about this bond in the trialkylnitrosoureas. The results presented in Table III reveal that the energy barrier for this rotation is about 13 kcal mol^{-1} in four different compounds. The contribution of the dipolar resonance structure is presumably dominant.



Several other factors contribute to the much larger barrier in the mono- and dialkylnitrosoureas. First, hydrogen-bonding interactions are very important in noninteractive solvents. Second, the location of the nitroso group anti to the carbonyl group is apparently favorable.[12] Third, the location of the methyl group syn to the carbonyl group is also favorable.[13]



Another feature of the results deserves comment. Three processes, restricted rotation about the amide bond, ring inversion, and nitrogen inversion, may be responsible for the temperature dependence of the NMR spectra of piperidine and pyrrolidine derivatives. The fact that the energy barriers for these heterocyclic derivatives are the same as the barriers for the acyclic molecules strongly suggests that the restricted rotation about the amide bond is responsible for the temperature dependence in all four instances. While no definite evidence concerning this point was developed in this study, Hirsch and his students have estimated that the barrier to rotation about the amide bond is 14–15 kcal mol^{-1} for *N*-benzoylpiperidine and about 12 kcal mol^{-1} for the *N*-carboethoxy derivative.[14] The results obtained in the present study are in accord with these values.[15]

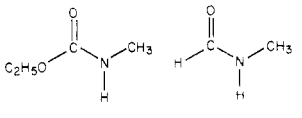
Conclusion

The spectroscopic information indicates that the monoalkyl- and dialkylnitrosoureas exist in one conformation in solution. Several factors, including the hydrogen bond, the contributions of dipolar resonance, and the favorable relationship between the fragments on the C_3N bond, apparently determine the large conformational preferences exhibited by these molecules. The spectroscopic data also indicate that the trialkylnitrosoureas are not restricted to any single conformation in solution at ambient temperature. Rather, the energy barrier for rotation about the CN_3 amide bond is only about 13 kcal mol^{-1}. The barriers for

(11) (a) Siddall, T. H., III. *J. Org. Chem.* **1966**, *31*, 3719. (b) Siddall, T. H., III; Stewart, W. E. *J. Chem. Phys.* **1968**, *48*, 2928. (c) Siddall, T. H., III; Stewart, W. E. *Chem. Commun.* **1968**, 617.

(12) Huisgen, R.; Reinertshofer, J. *Justus Liebigs Ann. Chem.* **1952**, *575*, 197.

(13) For example, the *N*-methylurethane exists 90% in the syn form [Russell, R. A.; Thompson, H. W. *Spectrochim. Acta* **1956**, *8*, 138] and the *N*-methylamide exists 92% in the syn form [Hallam, H. E.; Jones, C. M. *J. Mol. Struct.* **1970**, *5*, 1].



(14) Hirsch, J. A.; Augustine, R. L.; Koletar, G.; Wolf, H. G. *J. Org. Chem.* **1975**, *40*, 3547.

(15) It should be noted that the energy barriers for the ring inversion of piperidine derivatives are similar, but that the barriers for nitrogen inversion are much smaller than the observed values.

Table VI. Preparation of Nitrosoureas

nitrosourea	solvent	mp, °C	yield, %
$CH_3N(NO)CONH_2$	water	112-113	75
$CH_3CH_2N(NO)CONH_2$	water	94-95	37
$C_6H_5N(NO)CONH_2$	aqueous acetic acid	61	81
$CH_3N(NO)CONHCH_3$	water	95-96	58
$CH_3N(NO)CONHCH_2CH_3$	water	27-29	83[a]
$CH_3N(NO)CONHC(CH_3)_3$	aqueous methanol	20-22	78
$CH_3N(NO)CONHCH(CH_3)_2$	aqueous methanol	33-35	91
$CH_3N(NO)CONH(c\text{-}C_6H_{11})$	aqueous methanol	77-78	52
$CH_3N(NO)CONHCH_2CH_2CH_3$	aqueous methanol	oil	59[a]
$CH_3N(NO)CONHCH(CH_3)CH_2CH_3$	aqueous methanol	39-41	63
$CH_3N(NO)CONHCH_2CH(CH_3)_2$	aqueous methanol	oil	54[a]
$CH_3N(NO)CONHC_6H_5$	aqueous methanol	83-85	56
$CH_3N(NO)CON(CH_3)_2$	aqueous methanol	oil	66
$CH_3N(NO)CON(CH_2CH_3)_2$	water	oil	85
$CH_3N(NO)CON(CH(CH_3)_2)_2$	aqueous methanol	oil	81
$CH_3N(NO)CON(CH_2)_5$	aqueous methanol	30-31	26
$CH_3N(NO)CO(CH_2)_4$	aqueous methanol	50-51	38
$CH_3N(NO)CON(CH_2CH_2CH_2CH_3)_2$	aqueous methanol	38-40	63
$CH_3N(NO)CON(CH_2CH(CH_3)_2)_2$	aqueous methanol	oil	47
$CH_3N(NO)CON(CH_2CH_2CH_3)_2$	aqueous methanol	oil	38

[a] Total yield of both isomers.

Table VII. Proton NMR Spectra of Nitrosoureas[a,b]

nitrosourea	chemical shifts
$CH_3N(NO)CONH_2$	3.20 s, CH_3; 5.60 br; 6.93 br, NH_2
$CH_3CH_2N(NO)CONH_2$	1.00 t, CH_3; 3.86 q, CH_2; 5.42 br; 6.87 br, NH_2
$C_6H_5N(NO)CONH_2$	5.64 br; 6.92 br, NH_2; 6.99 m; 7.48 m, aryl
$CH_3N(NO)CONHCH_3$	3.08 d, CH_3; 3.21 s, CH_3; 6.95 br, NH
$CH_3N(NO)CONHCH_2CH_3$	1.29 t, CH_3; 3.20 s, CH_3; 3.53 m, CH_2; 6.96 br, NH
$CH_3NHCON(NO)CH_2CH_3$[c]	1.03 t, CH_3; 3.07 d, CH_3; 3.89 q, CH_2; 6.90 br, NH
$CH_3N(NO)CONHC(CH_3)_3$	1.47 s, 3 (CH_3); 3.16 s, CH_3; 6.92 br, NH
$CH_3N(NO)CONHCH(CH_3)_2$	1.27 d, 2 (CH_3); 3.16 s, CH_3; 4.16 m, CH; 6.84 br, NH
$CH_3N(NO)CONH(c\text{-}C_6H_{11})$	1.35 m; 1.65 m; 1.76 m; 2.06 m, 5 (CH_2); 3.20 s, CH_3; 6.93 br, NH
$CH_3N(NO)CONHCH_2CH_2CH_3$	1.00 t, CH_3; 1.67 m, CH_2; 3.21 s, CH_3; 3.45 q, CH_2; 6.99 br, NH
$CH_3NHCON(NO)CH_2CH_2CH_3$[c]	0.85 t, CH_3; 1.43 m, CH_2; 3.07 d, CH_3; 3.80 t, CH_2; 6.90 br, NH
$CH_3N(NO)CONHCH(CH_3)CH_2CH_3$	0.98 t, CH_3; 1.27 d, CH_3; 1.61 m, CH_2; 3.20 s, CH_3; 4.03 m, CH; 6.80 br, NH
$CH_3N(NO)CONHCH_2CH(CH_3)_2$	0.99 d, 2 (CH_3); 1.92 m, CH; 3.21 s, CH_3; 3.31 t, CH_2; 7.03 br, NH
$CH_3NHCON(NO)CH_2CH(CH_3)_2$[c,d]	0.82 d, 2 (CH_3); 3.07 d, CH_3; 3.68 d, CH_2; 6.90 NH
$CH_3N(NO)CONHC_6H_5$	3.29 s, CH_3; 7.20 t, 1 H; 7.40 t, 2 H; 7.59 d, 2 H; aryl; 8.86 br, NH
$CH_3N(NO)CON(CH_3)_2$	3.15 s, 2 (CH_3); 3.17 s, CH_3
$CH_3N(NO)CON(CH_3)_2$[e]	3.00 s, CH_3; 3.28 s, 2 (CH_3)
$CH_3N(NO)CON(CH_2CH_3)_2$	1.26 t, 2 (CH_3); 3.16 s, CH_3; 3.48 q, 2 (CH_2)
$CH_3N(NO)CON(CH(CH_3)_2)_2$	1.38 d, 2 (CH_3); 3.13 s, CH_3; 3.87 m, 2 (CH)
$CH_3N(NO)CON(CH_2)_5$	1.70 br, 3 (CH_2); 3.15 s, CH_3; 3.61 br, 2 (CH_2)
$CH_3N(NO)CON(CH_2)_4$	1.97 br, 2 (CH_2); 3.19 s, CH_3; 3.68 br, 2 (CH_2)
$CH_3N(NO)CON(CH_2CH_2CH_2CH_3)_2$	0.93 t, 2 (CH_3); 1.32 m, 2 (CH_2); 1.51 m, 2 (CH_2); 2.81 s, CH_3; 3.16 t, 2 (CH_2)
$CH_3N(NO)CON(CH_2CH(CH_3)_2)_2$	0.88 d, 4 (CH_3); 1.95 m, 2 (CH); 2.80 s, CH_3; 3.03 d, 2 (CH_2)
$CH_3N(NO)CON(CH_2CH_2CH_3)_2$	0.90 t, 2 (CH_3); 1.68 m, 2 (CH_2); 3.17 s, CH_3; 3.40 t, 2 (CH_2)
$(CH_3)_2CHN(NO)CONH_2$[f]	1.31 d, 2 (CH_3); 5.01 m, CH; 5.29 br, 6.81 b, NH_2

[a] The spectra were recorded in deuteriochloroform unless otherwise noted. Chemical shifts are reported in parts per million downfield from tetramethylsilane as internal standard. [b] The multiplicity of the signals is denoted by s singlet, d doublet, t triplet, q quartet, m multiplet, and br broad. [c] The chemical shifts were obtained from the spectra of a mixture of the isomers. [d] The multiplet for the CH resonance was obscured by other signals. [e] This spectrum was recorded in carbon disulfide with internal tetramethylsilane. [f] The crude product was studied because the compound was too unstable to purify by conventional methods.

rotation about the N_1N_2 and CN_2 bonds are much smaller.

Experimental Section

Caution: The alkylnitrosoureas are suspected to be carcinogenic substances. Suitable precautions must be observed in work with these compounds.

Preparation of Ureas. Method A. *N,N'*-Dimethyl-*N*-nitrosourea (20 mmol) was dissolved in an appropriate solvent. The appropriate amine (25 mmol) was added dropwise to the stirred solution. Stirring was continued until gas evolution ceased. The solvent was removed under reduced pressure without the application of heat. The solid residue was recrystallized from ether. The results are summarized in Table V.

Method B. Methyl isocyanate (5.3 mmol) was dissolved in anhydrous ether (5 mL) and chilled in an ice bath. The appropriate amine (5.3 mmol) was added dropwise to the stirred solution. For gaseous amines, the gas was passed into the solution slowly until precipitation of the product was complete. The precipitate was collected, washed with ether, and recrystallized from ether. The results are summarized in Table V.

***N*-Nitrosoalkylureas.** The appropriate urea and sodium nitrite in a 1:1.1 ratio were dissolved in water, aqueous methanol, or aqueous acetic acid and chilled in an ice bath. Aqueous sulfuric acid (1.0 equiv) was slowly added with stirring. When the product precipitated from solution it was collected. When the product was liquid, it was extracted from the mixture with ether. A solution of the product in ether or chloroform was washed with 5% aqueous sodium bicarbonate, water, and brine. The solution was dried over sodium sulfate. The solvent was removed in vacuo to yield a product which was sufficiently pure for most applications. In certain circumstances, the compounds were purified by

thin layer chromatography on silica gel. The results are summarized in Table VI. The compounds were characterized by their NMR spectra (Table VII).

Spectroscopic Data. The infrared spectra were recorded in dilute solutions employing cells of different path length on a Perkin-Elmer Model 283 instrument.

The NMR spectra were recorded on the Chicago 350-MHz and the Bruker 270-MHz instruments. The low-temperature spectra were recorded reproducibly over the broad temperature ranges. In all these experiments, tetramethylsilane was employed as an internal standard to ensure that the line broadening observations were not the consequence of field inhomogeneity or solvent viscosity effects.

The rotation rate, k_r, and the rotational free-energy barriers were calculated in the customary way at the coalescence temperature.

Acknowledgment. This investigation was supported by Grant No. 1-R01-CA-20049 awarded by the National Cancer Institute, DHEW, and by the Illinois Division of the American Chemical Society. The research was also supported by the NMR Special Facility Grant, CA 14599.

Registry No. $C_6H_5NHCONH_2$, 64-10-8; $(CH_3)_2CHNHCONH_2$, 691-60-1; $(CH_3)_3CNHCONH_2$, 1118-12-3; c-$C_5H_{10}NCONH_2$, 2158-03-4; $C_6H_5NHCONHCH_3$, 1007-36-9; $CH_3NHCONHCH_2CH_3$, 28145-10-0; $CH_3NHCONHC(CH_3)_3$, 25347-94-8; $CH_3NHCONHCH(CH_3)_2$, 38014-53-8; $CH_3NHCONH(c\text{-}C_6H_{11})$, 39804-96-1; $CH_3NHCONHCH_2CH_2CH_3$, 38014-52-7; $CH_3NHCONHCH(CH_3)CH_2CH_3$, 38014-55-0; $CH_3NHCONHCH_2CH(CH_3)_2$, 38014-54-9; $CH_3NHCON(CH_3)_2$, 632-14-4; $CH_3NHCON(CH_2CH_3)_2$, 39499-81-5; $CH_3NHCON(CH(CH_3)_2)_2$, 57883-81-5; $CH_3NHCONC_5H_{10}$-c, 36879-48-8; $CH_3NHCONC_4H_8$-c, 36879-46-6; $CH_3NHCON(CH_2CH_2CH_2CH_3)_2$, 21260-54-8; $CH_3NHCON(CH_2CH_2CH_3)_2$, 36614-21-8; $CH_3NHCON(CH_2CH(CH_3)_2)_2$, 72479-12-0; $CH_3N(NO)CONH_2$, 684-93-5; $CH_3CH_2N(NO)CONH_2$, 759-73-9; $C_6H_5N(NO)CONH_2$, 6268-32-2; $CH_3N(NO)CONHCH_3$, 13256-32-1; $CH_3N(NO)CONHCH_2CH_3$, 72479-13-1; $CH_3N(NO)CONHC(CH_3)_3$, 72479-14-2; $CH_3N(NO)CONHCH(CH_3)_2$, 72479-15-3; $CH_3N(NO)CONH(c\text{-}C_6H_{11})$, 16813-38-0; $CH_3N(NO)CONHCH_2CH_2CH_3$, 72479-16-4; $CH_3N(NO)CONHCH(CH_3)CH_2CH_3$, 72479-17-5; $CH_3N(NO)CONHCH_2CH(CH_3)_2$, 72479-18-6; $CH_3N(NO)CONHC_6H_5$, 21561-99-9; $CH_3N(NO)CON(CH_3)_2$, 3475-63-6; $CH_3N(NO)CON(CH_2CH_3)_2$, 50285-72-8; $CH_3N(NO)CON(CH(CH_3)_2)_2$, 72479-19-7; $CH_3N(NO)CONC_5H_{10}$-c, 72479-20-0; $CH_3N(NO)CONC_4H_8$-c, 67084-42-8; $CH_3N(NO)CON(CH_2CH_2CH_2CH_3)_2$, 72479-21-1; $CH_3N(NO)CON(CH_2CH(CH_3)_2)_2$, 72479-22-2; $CH_3N(NO)CON(CH_2CH_2CH_3)_2$, 72479-19-7; $CH_3NHCON(NO)CH_2CH_3$, 72479-23-3; $CH_3NHCON(NO)CH_2CH_2CH_3$, 72479-24-4; $CH_3NHCON(NO)CH_2CH(CH_3)_2$, 72479-25-5; $(CH_3)_2CHN(NO)CONH_2$, 16830-14-1; methyl isocyanate, 624-83-9.

Competitive [1,3]- and [3,3]-Sigmatropic Rearrangements

Richard T. Arnold* and Srdanka T. Kulenović

Department of Chemistry and Biochemistry, Southern Illinois University, Carbondale, Illinois 62901

Received August 14, 1979

Several cases of the oxy-Cope rearrangement, which typically prefers the [3,3]-sigmatropic route, are now known to occur in a [1,3]-sigmatropic fashion. By contrast, the symmetry-allowed thermal rearrangement of carbanions (or their enol derivatives; e.g., trialkylsilyl) derived from allylic esters occurs exclusively in a [3,3]-sigmatropic manner. However, the corresponding anions derived from benzyl esters, for which the [3,3]-sigmatropic path is energetically unfavorable, rearrange by a [1,3]-sigmatropic mechanism. We report the first two examples of this rearrangement.

The oxy-Cope isomerization, whose rate can be markedly affected by the experimental conditions employed,[1-3] proceeds, typically, via a [3,3]-sigmatropic rearrangement. However, in certain systems, and especially those involving medium-sized rings,[2] the reaction can occur, overwhelmingly, via a [1,3]-sigmatropic rearrangement.

In selected cases involving other reactions, substantial loss of π-electron delocalization, which is a requirement when cinnamyl systems undergo a [3,3]-sigmatropic rearrangement, can favor the [1,3] isomerization. For example, cinnamyl thiocyanate, when heated, is converted into cinnamyl isothiocyanate.[4]

By contrast, the large number of symmetry-allowed thermal rearrangements of allylic ester enolates which have been reported since the first examples were described over 30 years ago[5] occur exclusively in a [3,3]-sigmatropic manner. Even with the enolates derived from cinnamyl isobutyrate (**1a**), no [1,3]-sigmatropic shift is observed.[6] We have confirmed this result and, as expected, have demonstrated that the isomeric transformation **1b** → **2b** proceeds readily.

On the assumption that the transition state for the conversion **1** → **2** is more polar than **1**, we have explored a variety of experimental conditions designed to facilitate the process. During fixed intervals of time and temperature and by use of the lithium enolate, the silyloxy derivative,[7] or the corresponding enol diethyl phosphate, the amounts of **3a** and **3b** isolated fell within the range of 35–55%. However, under like conditions of time and temperature, the addition of moderate amounts of nitrobenzene (μ = 4.0) to the system resulted in yields of **3a** and **3b** of 75 and 71%, respectively.

It is, in fact, the dependable regiospecificity of the allylic ester enolate rearrangement that has made it such a valuable tool in the synthesis of complex natural products.[8,9]

(1) D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975).
(2) R. W. Thies and E. P. Seitz, *J. Org. Chem.*, **43**, 1050 (1978).
(3) Y. Fujita, T. Oniska, and N. Nishida, *J. Chem. Soc., Chem. Commun.*, 972 (1978).
(4) E. Bergmann, *J. Chem. Soc.*, 1361 (1935).
(5) R. T. Arnold and S. Searles, Jr., *J. Am. Chem. Soc.*, **71**, 1150 (1949). See G. Bennett, *Synthesis*, 589 (1977), for a review.
(6) R. Malzieu [*Bull. Soc. Chim. Fr.*, 879 (1976)] first reported the rearrangement of cinnamyl isobutyrate using sodium hydride in boiling toluene. Our sample was identical with one (mp 85–86 °C) graciously provided by R. R. Covington, Mead Johnson and Company, which he obtained by using lithium amide in dry toluene for the rearrangement.
(7) R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Org. Chem.*, **41**, 986 (1976).
(8) G. Fráter, *Helv. Chim. Acta*, **58**, 442 (1975).

0022-3263/80/1945-0891$01.00/0