chemical oxidant produces the relaxed radical cation. Additional studies will be required to see if this idea has merit.

Experimental Section

Preparations of the compounds studied here have been previously reported; **3–5**, **8**, and **10**,[13] **6**,[14] and **7** and **9**.[15] The techniques used for ESR and UV spectra were the same as those in our previous work.[2,15] Spectra were recorded on a Varian E-15 spectrometer, with temperature maintained with a V-4557 variable temperature Dewar and vacuum-jacketed carrier tube and a V-4540 variable temperature control. A copper constantan thermocouple and Leeds and Northrup temperature potentiometer (Model 8693-2) was used to measure the temperature (by using a dummy tube replacing the sample tube without changing the nitrogen flow rate). The field was calibrated at room temperature with 10^{-4} M Fremy's salt in saturated aqueous potassium carbonate, by using $a(N) = 13.09$ G, and the corrections were assumed to be temperature independent.

Acknowledgment. We thank the National Institutes of Health for support of this work under GM29549 and Dan Kapp for assistance in construction of the flow electrochemical cell.

Registry No. **3**, 26163-37-1; **3** (radical cation), 98705-11-4; **4**, 26171-64-2; **4** (radical cation), 35018-93-0; **5**, 38704-91-5; **5** (radical cation), 35018-94-1; **6**, 60387-16-8; **6** (radical cation), 98757-92-7; **7**, 60678-80-0; **7** (radical cation), 98719-94-9; **8**, 38704-92-6; **8** (radical cation), 98719-77-8; **9**, 60678-81-1; **9** (radical cation), 98757-93-8; **10**, 3661-15-2; **10** (radical cation), 98719-78-9; $NO^+PF_6^-$, 16921-91-8.

Supplementary Material Available: Expected and simulated ESR spectra for the spectra reported in Table I (8 pages). Ordering information is given on any current masthead page.

(13) Nelsen, S. F.; Hintz, P. J. *J. Am. Chem. Soc.* **1972**, *94*, 7108.
(14) Nelsen, S. F.; Weisman, G. R. *J. Am. Chem. Soc.* **1976**, *98*, 3281.
(15) Nelsen, S. F.; Peacock, V.; Weisman, G. R. *J. Am. Chem. Soc.* **1976**, *98*, 5269.
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Electrophilic Fluorination of Unsaturated Systems with the Recently Developed Acetyl Hypofluorite

Shlomo Rozen,* Ori Lerman, Moshe Kol, and David Hebel

School of Chemistry, Tel-Aviv University, Tel-Aviv 69978, Israel

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Acetyl hypofluorite (AcOF, **1**) is a relatively new reagent which is prepared in situ from F_2 and is an excellent source for electrophilic fluorine. Unlike the other known fluoroxy reagents, it reacts smoothly and quickly at −78 °C with many types of olefins to produce acetylated fluorohydrins. It is particularly important as a major tool for introducing the ^{18}F radio isotope into biologically interesting systems. AcOF has been added to arylethenes, isolated aliphatic double bonds, and steroidal olefins with absolute regiospecificity (Markovnikov mode) and good stereoselectivity (syn addition). The more deactivated enones react with **1** with full regio- and stereospecificity, providing they are located in rigid systems or conjugated to an aromatic ring. Other enones, as well as acetylenes, seem to be less reactive when treated with **1**. Raising the temperature usually results either in the destruction of the substrate due to thermal radical decomposition of **1** or in full recovery of the starting material. Electron-rich double bonds such as enol acetates react with **1** very rapidly, and after short treatment with base the corresponding α-fluoro ketones are obtained in good yields.

Acetyl hypofluorite was first synthesized from elemental fluorine in our laboratories about 4 years ago.[1] During this short period it has been found to be quite applicative for synthetical purposes[2] and a major reagent for efficient introduction of the radioisotope ^{18}F into biologically interesting compounds.[3] The latter is an essential component for many research or diagnostic studies connected with the highly important technique of Positron Emitting Transaxial Tomography (PETT).[4] Since AcOF has potentially great importance in this field, several variants of its synthesis have already been described[5] along with some of its physical and spectral features.[6]

However, because of the short period that has passed since its discovery and because of its promptly found applications in nuclear medicine, not much has yet been investigated concerning some of the basic chemical behavior of AcOF with various unsaturated centers. We wish to report here on the scope of the reactions of **1** with different types of π bonds, reactions which present further opportunities for the introduction of this important halogen to specific sites usually difficult to fluorinate, let alone efficiently introduce the ^{18}F radioisotope.

In general, acetyl hypofluorite reacts with olefins to produce the highly important fluorohydrin derivatives.

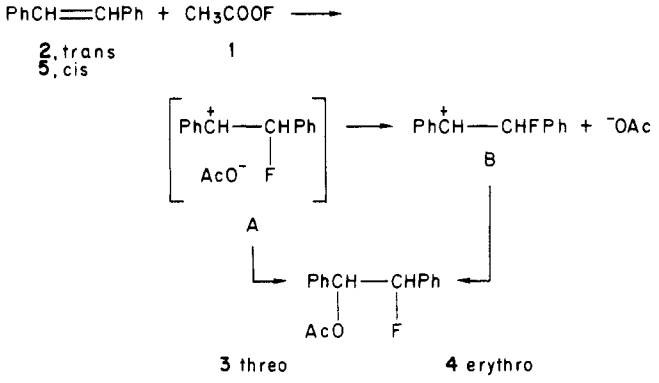
(1) Rozen, S.; Lerman, O.; Kol, M. *J. Chem. Soc., Chem. Commun.* **1981**, 443.
(2) (a) Lerman, O.; Rozen, S. *J. Org. Chem.* **1983**, *48*, 724. (b) Rozen, S.; Brand, M. *Synthesis*, **1985**, 665. (c) Lerman, O.; Tor, Y.; Hebel, D.; Rozen, S. *J. Org. Chem.* **1984**, *49*, 806. (d) Chirakal, R.; Firnau, G.; Cause, J.; Garnett, E. S. *Int. J. Appl. Radiat. Isot.* **1984**, *35*, 651. (e) See also ref 3a–g.
(3) (a) Shiue, C. Y.; Salvadori, P. A.; Wolf, A. P. *J. Nucl. Med.* **1982**, *23*, 108. (b) Adam, M. J. *J. Chem. Soc., Chem. Commun.* **1982**, 730. (c) Adam, M. J.; Pate, B. D.; Nesser, J. R.; Hall, L. D. *Carbohydr. Res.* **1983**, *124*, 215. (d) Fowler, J. S.; Shiue, C. Y.; Wolf, A. P.; Salvadori, P. A.; MacGregor, R. R. *J. Labeled Cmpds.* Radiopharm. **1982**, *19*, 1634. (e) Shiue, C. Y.; Salvadori, P. A.; Wolf, A. P.; Fowler, J. S.; MacGregor, R. R. *J. Nucl. Med.* **1982**, *23*, 899. (f) Adam, M. J.; Ruth, T. J.; Jivan, S.; Pate, B. D. *J. Fluorine Chem.* **1984**, *25*, 329. (g) Visser, G. W. M.; v. Halteren, B. W.; Herscheid, J. D. M.; Brinkman, G. A.; Hoekstra, A. *J. Chem. Soc., Chem. Commun.* **1984**, 655.
(4) Positron Emitting Transaxial Tomography (PETT) is one of the newest and most powerful diagnostic tools developed in the last few years. Apart from numerous professional reports two popular reviews can be found in *TIME* Magazine (September 4, 1981) and in *Chem. Eng. News* (November 9, 1981).
(5) (a) Jewett, D. M.; Potocki, J. F.; Ehrenkaufer, R. E. *Synth. Commun.* **1984**, *14*, 45. (b) Jewett, D. M.; Potocki, J. F.; Ehrenkaufer, R. E. *J. Fluorine Chem.* **1984**, *24*, 477. (c) See also ref 3d,e.
(6) Hebel, D.; Lerman, O.; Rozen, S. *J. Fluorine Chem.* **1985**, *30*, 141.

0022-3263/85/1950-4753$01.50/0

Despite the latter importance, only one practical method is at present known for its synthesis: the opening of an epoxide with the strong acids HF and BF_3·OEt_2 or with triethylammonium hydrofluoride.[7] In this respect AcOF may somewhat resemble its perfluorinated analogue—trifluoroacetyl hypofluorite.[8] This similarity, however, is somewhat limited since the very reactive CF_3COOF reacts cleanly only with stilbenes,[9] while the milder acetyl hypofluorite was found to react satisfactorily with many more types of olefins.

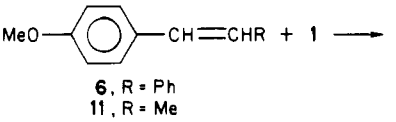
The reactions with alkenes can be performed either by adding a cold chloroform solution of the substrate to the AcOF solution or via the inverse addition of 1 to the cold substrate which usually is disolved in $CHCl_3$.[10] While the first method is easier to operate, it is often not the method of choice since in certain cases the excess of the reagent can overreact with the substrate to produce tars. Such side reactions are mainly of a radical nature as is also evident from the easy radical decomposition of 1 to methyl fluoride.[6] In the case of the inverse addition we found that in most cases 1 reacted very fast in an ionic mode which suppressed the radical decomposition pathways almost completely.

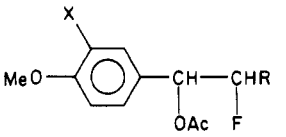
AcOF adds itself across the olefinic bond of *trans*-stilbene (2) mainly in a syn mode to produce *threo*-1-acetoxy-2-fluoro-1,2-diphenylethane (3) in 50% yield together with 7% yield of the corresponding erythro isomer, 4. The stereochemistry could easily be determined by examining the NMR spectra. Since the gauche conformation is predominant when two very electronegative atoms such as O and F are attached to vicinal carbons, the coupling constants of the benzylic protons are smaller in the erythro than in the threo isomer.[9,11] An additional indication concerning the stereochemistry was found in the corresponding ^{19}F NMR spectra where the fluorine atom in threo isomers resonates at a lower field than that in the erythro ones. The predominant syn addition is very characteristic of electrophilic fluorination reactions, since they proceed through the creation of a tight ion pair A, which includes the very unstable α-fluorocarbocation.



This tight ion pair collapses very rapidly resulting inevitably in a syn addition.[9,12,13] The anti addition, which in the case of 2 produces the erythro isomer, is a result of a diffusion of the acetoxy ion from the tight ion pair forming the intermediate B and consequent random recombination of the two ions.

It is worth pointing the difference between these results and the ones obtained from the corresponding reactions with CF_3COOF where no anti addition could be detected. This difference is in full agreement with the fact that the CH_3COO^- anion is a softer base than the CF_3COO^- one and therefore reacts somewhat more slowly with the hard α-fluorocarbocation.[9] Similar results were also obtained with *cis*-stilbene (5) where the syn addition produced the erythro isomer 4, in 51% yield along with 11% of the threo isomer 3 (anti addition). When 1 was reacted with an unsymmetrical olefins such as *trans*-4-methoxystilbene (6), four compounds were isolated, all of them having fluorine attached to the benzylic carbon next to the unsubstituted ring. This full regiospecificity is an additional indication



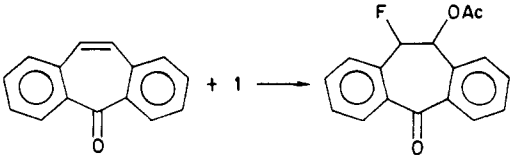


7, X = H; R = Ph; threo
8, X = H; R = Ph; erythro
12, X = H; R = Me; threo
13, X = H; R = Me; erythro
9, X = F; R = Ph; threo
10, X = F; R = Ph; erythro
14, X = F; R = Me; threo
15, X = F; R = Me; erythro

of the electrophilic character of the oxygen-bound fluorine in AcOF. Here, however, the stereocontrolled addition is less rigorous as is evident from the distribution of the two isomers *threo*-1-acetoxy-1-(4-methoxyphenyl)-2-fluoro-2-phenylethane (7) (42% yield, syn addition) and the corresponding erythro isomer 8 (15%, anti addition). This is a result of the greater stability of the corresponding α-fluorocarbonium ion in A, enhancing the chance of leakage to the open pair of ions B. Along with 7 and 8, an additional pair of isomers was isolated and identified as *threo*- and *erythro*-1-acetoxy-1-(3-fluoro-4-methoxyphenyl)-2-fluoro-2-phenylethane (9 and 10) in 14% and 5%, yield, respectively. The synthetic potential of this electrophilic aromatic fluorination for various activated aromatic systems has already been discussed.[2c]

Parallel results were obtained when *trans*-anethole (11) was reacted with 1. Again two pairs of compounds were obtained and separated. The major one consisted of *threo*- and *erythro*-1-acetoxy-1-(4-methoxyphenyl)-2-fluoropropane (12 and 13, respectively) (70% overall yield, 12:13 = 1:4.5), while the minor one was also fluorinated on the activated aromatic ring producing *threo*- and *erythro*-1-acetoxy-1-(3-fluoro-4-methoxyphenyl)-2-fluoropropane (14 and 15), in a 15% yield and a ratio of 1:4.5, respectively.

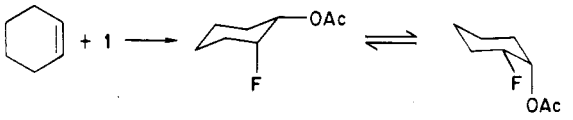
Suberenone 16, which can be considered a stilbene derivative, produces only tars with the reactive CF_3COOF but reacts reasonably well with CH_3COOF. Only the syn addition product was detected and identified as 10-acetoxy-11-fluoro-5*H*-dibenzo[*a*,*d*]cycloheptan-5-one (17) in 55% yield.



16 17

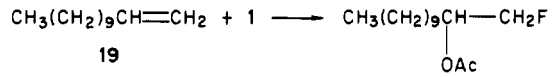
(7) Aranda, G.; Jullien, J.; Martin, J. A. *Bull. Soc. Chim. Fr.* **1966**, 2850. Olah, G. A.; Meidar, D. *Isr. J. Chem.* **1978**, *17*, 148.
(8) Rozen, S.; Lerman, O. *J. Am. Chem. Soc.* **1979**, *101*, 2782.
(9) Rozen, S.; Lerman, O. *J. Org. Chem.* **1980**, *45*, 672.
(10) When the substrate was insoluble in $CHCl_3$, other solvents such as AcOH, CH_3NO_2, or CH_3CN can be used. See also: Kosower, E. M.; Hebel, D.; Rozen, S.; Radkowski, A. E. *J. Org. Chem.*, in press.
(11) Phillips, L.; Wray, V. *J. Chem. Soc., Chem. Comm.* **1973**, *90*. Zefirov, N. S.; Samoshin, V. V.; Sabotin, O. A.; Baranenkov, V. I.; Wolf, S. *Tetrahedron* **1978**, *34*, 2953. Reference 9.
(12) Barton, D. H. R.; Hesse, R. H.; Jackman, G. P.; Ogunkoya, L.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 739.
(13) Lerman, O.; Rozen, S. *J. Org. Chem.* **1980**, *45*, 4122.

Double bonds, which do not benefit from such stabilizing factors as a vinylic aromatic ring, usually do not react cleanly with electrophilic fluorinating agents.[14] The main reason for this is their overreactivity, which is difficult to tame even at low temperatures. The milder acetyl hypofluorite, however, reacts with such olefins in more satisfactory way. Cyclohexene for example is converted to the fluorohydrin derivative *cis*-1-acetoxy-2-fluorocyclohexane (**18**) in 60% yield. Aliphatic alkenes also produce the



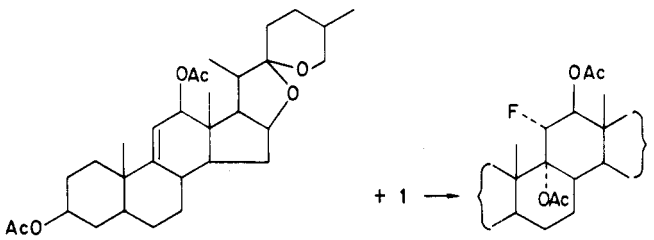
18

expected unrearranged products. In the case of the reaction of **1** with 1-dodecene (**19**) we were able to isolate after 1 min at −78 °C the Markovnikov adduct 1-fluoro-2-acetoxydodecane (**20**) in 30% yield, while attempts to react this alkene with other fluoroxy reagents produced only tars.



19 **20**

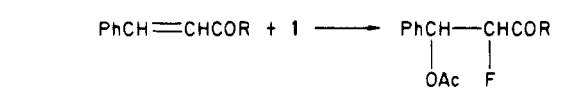
An ideal situation was found with rigid olefins, where the intermediate α-fluorocarbocation is a tertiary one, as in 9(11) (5α,20α,22α-25*D*-spirost-9(11)-ene-3β,12β-diol diacetate (**21**). This reacts cleanly with **1** to produce (5α,20α,22α)-11α-fluoro-25*D*-spirostan-3β,9α,12β-triol triacetate (**22**) in 90% yield. The high yield here reflects



21 **22**

also the fact that **1** can approach the π electrons only from the α side of the steroid skeleton, eliminating other potential stereoisomers. The formation of **22**, without affecting the ketal moiety on the steroid side chain, emphasizes the advantage of the neutral AcOF over other methods for fluorohydrin synthesis, which usually employ strong acids such as HF or BF_3·OEt_2.

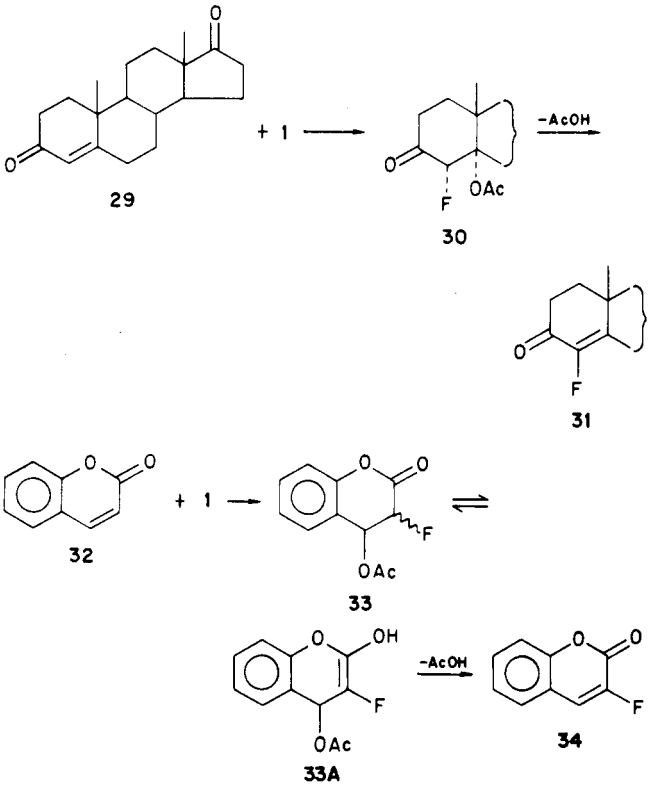
Electrophilic additions to deactivated α,β-unsaturated carbonyls are usually difficult and hence much less common than reactions with other systems. Acetyl hypofluorite, although mild in comparison to other fluoroxy reagents, is still reactive enough toward such compounds. We can distinguish between three categories of conjugated enones. The first consists of open aryl α,β-unsaturated carbonyls. The reactions proceeded smoothly and the expected β-acetoxy-α-fluoro derivatives were produced in good yields. Thus when *trans*-ethyl cinnamate (**23**) was allowed to react with **1** for 1 min, the only product obtained in 57% yield was *threo*-ethyl 2-fluoro-3-acetoxy-3-phenylpropionate (**24**). Similarly, only syn addition was



23, trans R = OEt **24**, threo
25, cis R = OMe **26**, erythro
27, trans R = Ph **28**, threo

observed with *cis*-methyl cinnamate (**25**), which resulted in the erythro isomer **26** (50% yield). This is true also with benzalacetophenone (**27**) which forms with practically absolute regio- and stereospecificity 1,3-diphenyl-1-acetoxy-2-fluoro-3-propanone (**28**) in 70% yield. The stereoselectivity of all these cases originates obviously in the carbonyl moiety, which destabilizes and hence shortens the life time of the α-fluorocarbocation, resulting in a faster collapse of the corresponding tight ion pairs.

A second category that we have examined is the rigid cyclic conjugated enones. As with the previous cases these compounds react initially as expected, but because of the anti configuration of the acetoxy group to a markedly acidic proton, adjacent to the fluorine atom and vicinal to the carbonyl moiety, ready elimination of AcOH takes place, forming the difficult to obtain α-fluoro enones. Androst-4-ene-3,17-dione (**29**) is a good example. There are clear spectral evidences that the crude reaction mixture consists mainly of the adduct 5α-acetoxy-4α-fluoroandrostane-3,17-dione (**30**), but any attempt to purify it by chromatography or crystallization produced 64% yield of 4-fluoroandrost-4-ene-3,17-dione (**31**). Coumarin (**32**)



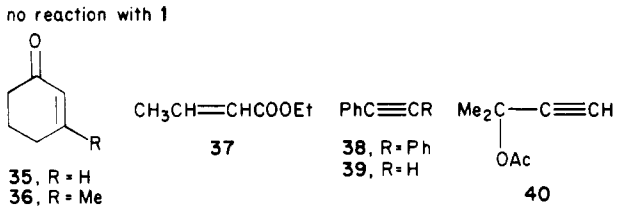
29 **30** **31** **32** **33** **33A** **34**

proved to be less reactive than **29**, and full conversion was achieved only after 24 h at −75 °C. The final results, however, were similar to those obtained with the steroidal enone **29**. The labile adduct 3-fluoro-4-acetoxydihydrocoumarin (**33**) eliminated the elements of AcOH at the first opportunity (chromatography or crystallization) thus producing the 3-fluorocoumarin (**34**) in almost quantitative yield. It is interesting to note that the ^{19}F NMR spectrum of **33** exhibits two fluorine atoms resonating at −198.1 and −204.7 ppm, which indicates that **33** is a mixture of cis and trans adducts in 1:1 ratio. This deviation from the usually found stereocontrolled addition can be explained by the

(14) Most of the examples with CF_3OF, CF_3CF_2OF, and CF_3COOF deal with double bonds which are stabilized in one way or another. See for example ref 9, 13, and 15. XeF_2 when reacting with olefins is lacking any stereospecificity, requires strong acidic catalyst as HF or BF_3, and is associated with various rearrangements, Shackelford, S. A. *J. Org. Chem.* **1979**, *44*, 3485. Zupan, M.; Sket, B. *J. Org. Chem.* **1978**, *43*, 696. Shackelford, S. A. *Tetrahedron Lett.* **1977**, 4265.

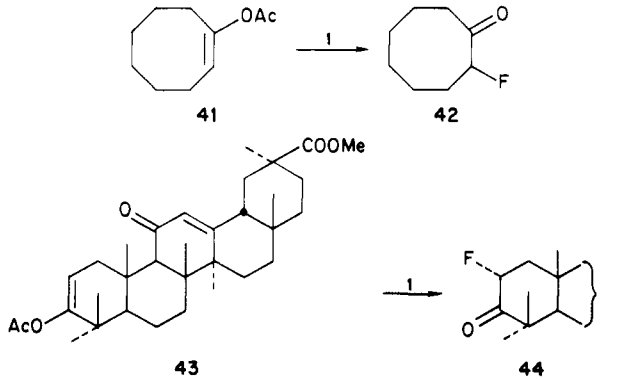
easily attained equilibrium between **33** and its enol form **33A**. In any case, both isomers were eventually transformed quantiatively to the fluoro enone **34**.

The third group of enones that was investigated consisted of flexible, aryl-free, α,β-unsaturated carbonyls. These substrates, represented by cyclohexenone (**35**), 3-methylcyclohexenone (**36**), ethyl crotonate (**37**), diethyl maleate, and diethyl fumarate, do not react with a large excess of **1** at −75 °C even after 48 h. When the reaction mixtures were allowed to warm up to room temperature, radical reactions took place, tars were produced, and no major single compound could be isolated. This lack of reactivity is also shared by acetylenic compounds, which usually are less reactive than olefinic ones. We have examined several types of acetylenes, **38–40**, and all of them were found to be totally unreactive, even when warmed to room temperature. This lack of reactivity is another



nice example emphasizing the difference between AcOF and all the known fluoroxy reagents, which immediately attack acetylenic bonds.[9,15,16] This fact increases the selectivity toward double bonds in molecules where, as is sometimes the case,[17] it is desirable to perform a reaction on them without affecting the acetylenic function.

No problems of reactivity exist when electron-rich double bonds, as exemplified by enol acetates, are treated with acetyl hypofluorite. After practically instantaneous reaction, the crude mixture consisted mainly of the adduct of **1** to the double bond,[18] and subsequent treatment with basic methanolic solution produced the desired α-fluoro ketone. The yields of these reactions are very good and similar to those obtained with the other electrophilic fluorinating agents.[15,19] 1-Acetoxycyclooctene (**41**), for example, was reacted with **1** and after short treatment with methanolic NaOH the α-fluorocyclooctanone (**42**) was obtained in 70% yield. Similarly, the enol acetate of the triterpenoidic methyl glycyrrhetate (**43**) was converted to the methyl 2-fluoro-3-ketoglycyrrhetate (**44**) in higher than 90% yield.



(15) Hesse, R. H. *Isr. J. Chem.* **1978** *17*, 60.
(16) An attempt to react **32**, **35**, and **36** with CF_3COOF resulted in immediate destruction of the substrates.
(17) (a) Camps, F.; Coll, J.; Fabrias, G.; Guerrero, A.; Riba, M. *Experientia* **1984**, *40*, 933. (b) Camps, F.; Coll, J.; Fabrias, G.; Guerrero, A. *Tetrahedron* **1984**, *40*, 2871.
(18) Barton, D. H. R.; Godinho, L. S.; Hesse, R. H.; Pechet, M. M. *Chem. Commun.* **1968**, 804.
(19) Rozen, S.; Menahem, Y. *J. Fluorine Chem.* **1980**, *16*, 19.

In conclusion, although known for a short period of time, acetyl hypofluorite has became a popular reagent in organic chemistry, especially when the question of introducing the fluorine atom into biologically important molecules is addressed. In particular it is used for labeling such compounds with ^{18}F for diagnostic and other studies connected with the PETT technique. Not much however was known about its basic reactions with various types of olefins which are one of AcOF's natural targets. This work has started to unveil the scope and limitations of this mild carrier of electrophilic fluorine which, after all, originates in the highly reactive elemental fluorine.

Experimental Section

^1H NMR spectra were recorded with a Bruker WH-90 and a Bruker WH-360 spectrometers at 90 and 360 MHz, respectively, with $CDCl_3$ as a solvent and Me_4Si as an internal standard. The ^{19}F spectra were measured at 84.67 and 338.8 MHz, respectively, and are reported in parts per million upfield from $CFCl_3$, which also served as internal standard. Mass spectra were measured with a Du Pont 21-491B spectrometer. IR spectra were recorded as neat films, in $CHCl_3$ solution or in KBr pellets, on a Perkin-Elmer 177 spectrometer.

General Fluorination Procedure. A description of the setup and the procedure for working with elemental fluorine has previously been described.[9,13] Although mentioned in previous works,[2c] it is worth stressing again that F_2 and AcOF should be treated with care since they are strong oxidizers. The work should be conducted in an efficient hood or in a well-ventilated area. The toxicity of AcOF is not yet known, but some of the fluoroxy reagents are suspected to be strong poisons. If elementary precautions are taken, work with fluorine and its derivatives is safe and relatively simple. In the past we have had no bad experience working with this element.

Preparation of AcOF and methods of reaction were described in our account of the reactions of **1** with aromatic compounds.[2c] Here again two methods of addition were used. Method A consists of the addition of a cold $CHCl_3$ solution of the olefin to the AcOF solution, while in method B the oxidizing solution of **1** was added dropwise with the aid of a pipet to the cold alkene solution so that the progress of the reaction could be monitored. In general the latter method resulted in cleaner products. The reactions were usually carried out on scales of 30–50 mmols using 2–3-fold excess of **1**, and, unless otherwise stated, the conversions were higher than 95%. The term "worked up as usual" means stopping the reaction by pouring it into 500 mL of water, washing the organic layer with $NaHCO_3$ solution followed by water until neutral, drying the organic layer over $MgSO_4$, and finally evaporating the solvent. The crude product was usually purified by vacuum flash chromatography using Silicagel 60-H (Merck) and if needed also by HPLC (Waters) on Merck's LiChrosorb Si-100. Unless a melting point is given, the products are liquids.

Fluorination of *trans*- and *cis*-Stilbenes (2 and 5). Fluorination of *trans*-stilbene may serve as a typical example for the reaction of **1** with olefins by method A. To the oxidizing solution containing 80 mmol of AcOF was added 5.4 g (30 mmol) of **2** dissolved in 50 mL of $CHCl_3$. The reaction was practically instantaneous, and after the usual workup, an oil was obtained and chromatographed with 2% EtOAc in petroleum ether as eluent. The major fraction (the more polar one) proved to be the threo adduct **3**: 50% yield; mp 60 °C (from cyclohexane); IR 1725 cm^{-1}; MS, *m/e* 199 $[(M - OAc)^+]$, 149 $[(PhCHCOOMe)^+]$, 109 $[(PhCHF)^+]$; ^1H NMR δ 7.08–7.34 (10 H, m), 6.04 (1 H, dd, J_1 = 14.4 Hz, J_2 = 17.4 Hz), 5.58 (1 H, dd, J_1 = 47 Hz, J_2 = 7.4 Hz), 2.11 (3 H, s); ^{19}F NMR −182.1 (dd, J_1 = 47 Hz, J_2 = 14.4 Hz). Anal. Calcd for $C_{16}H_{15}FO_2$: C, 74.42; H, 5.81; F, 7.36. Found: C, 74.34; H, 5.82; F, 7.66.

The less polar minor fraction was identified as the erythro isomer **4**: 0.54 g, 7% yield; mp 60 °C (from MeOH); IR and MS as above; ^1H NMR δ 7.12–7.29 (10 H, m), 6.08 (1 H, dd, J_1 = 17.9 Hz, J_2 = 4.7 Hz), 5.68 (1 H, dd, J_1 = 46 Hz, J_2 = 4.7 Hz), 1.99 (3 H, s); ^{19}F NMR −189.1 (dd, J_1 = 46 Hz, J_2 = 17.9 Hz). Anal. Calcd for $C_{16}H_{15}FO_2$: C, 74.42; H, 5.81. Found: C, 74.63; H, 5.67. With *cis*-stilbene (**5**) (9 g, 50 mmols) the same compounds (**3** and

4) were obtained, but in this case 6.6 g of the erythro isomer 4 was isolated (51% yield) while only 1.41 g (11% yield) of the threo isomer 3 was obtained.

Fluorination of *trans*-4-Methoxystilbene (6). Method A. After the instantaneous reaction and the usual workup, the yellow oil was flash chromatographed and then homogenized by HPLC using 12% EtOAc in cyclohexane as eluent. The major less-polar fraction proved to be a mixture of both threo isomers **7** and **9**, while the more polar one contained mainly the mixture of the erythro isomers **8** and **10**. Additional chromatography of both mixtures using the HPLC recycling capabilities resolved all four isomers, where the aromatic fluorine containing derivatives **9** and **10** were more polar then the major components **7** and **8**. **7**: 42% yield; mp 73 °C (from MeOH); IR 1730 cm^{-1}; MS, *m/e* 229 [(M − OAc)$^+$], 179 [($MeOC_6H_4CHOAc$)$^+$], 109 [(PhCHF)$^+$]; ^1H NMR δ 6.69–7.29 (9 H, m), 5.96 (1 H, dd, J_1 = 12.2 Hz, J_2 = 7.6 Hz), 5.55 (1 H, dd, J_1 = 47 Hz, J_2 = 7.6 Hz), 3.75 (3 H, s), 2.11 (3 H, s); ^{19}F NMR −181.4 (dd, J_1 = 47 Hz, J_2 = 12.2 Hz). Anal. Calcd for $C_{17}H_{17}FO_3$: C, 70.83; H, 5.90; F, 6.60. Found: C, 71.02; H, 5.97; F, 6.20. **9**: was 14% yield; mp 64 °C (from MeOH); IR 1730 cm^{-1}; MS, *m/e* 306 [M$^+$], 247 [(M − OAc)$^+$], 197 [($MeOC_6H_3FCHOAc$)$^+$], 109 [(PhCHF)$^+$]; ^1H NMR δ 6.79–7.35 (8 H, m), 6.00 (1 H, dd, J_1 = 14.3 Hz, J_2 = 7 Hz), 5.52 (1 H, dd, J_1 = 46.5 Hz, J_2 = 7 Hz), 3.82 (3 H, s), 2.11 (3 H, s); ^{19}F NMR −182.0 (1 F, dd, J_1 = 47 Hz, J_2 = 14 Hz), −134.8 (1 F, br s). Anal. Calcd for $C_{17}H_{16}F_2O_3$: C, 66.67; H, 5.29. Found: C, 66.45; H, 5.25. **8**: 15% yield; mp 57 °C (from MeOH); IR and MS as in **7**; ^1H NMR δ 6.69–7.29 (9 H, m), 6.00 (1 H, dd, J_1 = 18 Hz, J_2 = 6.8 Hz), 5.55 (1 H, dd, J_1 = 47 Hz, J_2 = 6.8 Hz), 3.71 (3 H, s), 2.08 (3 H, s); ^{19}F NMR −189.3 (dd, J_1 = 47 Hz, J_2 = 18 Hz). **10**: 5% yield; mp 47 °C (from MeOH); IR and MS as in **9**; ^1H NMR δ 6.88–7.35 (8 H, m), 5.97 (1 H, dd, J_1 = 18.3 Hz, J_2 = 4.4 Hz), 5.60 (1 H, dd, J_1 = 49 Hz, J_2 = 4.4 Hz), 3.86 (3 H, s), 2.07 (3 H, s); ^{19}F NMR −190.2 (1 F, dd, J_1 = 49 Hz, J_2 = 18 Hz), −135.5 (1 F, d, J = 12 Hz).

Fluorination of *trans*-Anethole (11). Method A. After the instantaneous reaction, the crude reaction mixture was worked up as usual, flash chromatographed with 30% EtOAc in petroleum ether, followed by further purification on the HPLC using 10% EtOAc in cyclohexane. In this case we were able to separate only two fractions, the first proved to be a mixture of the threo and erythro isomers **12** and **13** in 4.5:1 ratio, respectively: combined yield 70%; IR 1750 cm^{-1}; MS, *m/e* 226 [M$^+$], 206 [M − HF], 179 [(M − CH_3CHF)$^+$], 167 [(M − OAc)$^+$]; ^1H NMR δ 6.7–7.5 (4 H, AB spectrum), 5.70 (1 H, dm, J = 13.5 Hz), 4.75 (1 H, dm, J = 48 Hz), 3.68 (3 H, s), 1.90 (threo) and 1.98 (erythro) (3 H, s), 0.98 (threo) and 1.09 (erythro) (3 H, each signal dd, J_1 = 24 Hz, J_2 = 6 Hz); ^{19}F NMR −176.93 (threo) and −180.17 (erythro) (m). The second fraction was again a mixture of the threo **14** and erythro **15**, combined yield 15%, again in a ratio of 4.5:1, respectively: IR 1755 cm^{-1}; MS, *m/e* 244 [M$^+$], 224 [(M − HF)$^+$], 197 [(M − CH_3CHF)$^+$]; ^1H NMR δ 6.9–7.5 (3 H, m), 5.75 (1 H, dm, J = 16.5 Hz), 4.85 (1 H, dm, J = 48 Hz), 3.88 (3 H, s), 2.16 (threo) and 2.20 (erythro) (3 H, each signal s), 1.20 (threo) and 1.25 (erythro) (3 H, each signal dd, J_1 = 24 Hz, J_2 = 6 Hz); ^{19}F NMR [threo] −131.6 (1 F, br s), −177.76 (1 F, m), [erythro] −131.88 (1 F, br s), −180.68 (1 F, m). Anal. Calcd for $C_{12}H_{14}F_2O_3$: C, 59.1; H, 5.74. Found: C, 58.60; H, 5.82.

Fluorination of Suberenone 16. Method B. 16 (6.2 g, 30 mmol) was reacted with 60 mmol of AcOF. The reaction was completed after 5 min, worked up as usual, and chromatographed using 20% EtOAc in petroleum ether as eluent. The adduct **17** was thus obtained: 4.68 g, 55% yield; mp 92 °C (from Et_2O); IR 1740, 1650 cm^{-1}; MS, *m/e* 284 [M$^+$], 264 [(M − HF)$^+$], 225 [(M − OAc)$^+$]; ^1H NMR δ 7.1–8.0 (8 H, m), 6.27 (1 H, dd, J_1 = 17.8 Hz, J_2 = 0.7 Hz), 5.75 (1 H, dd, J_1 = 46.5 Hz, J_2 = 0.7 Hz), 1.90 (3 H, s); ^{19}F NMR −174.5 (dd, J_1 = 46.5 Hz, J_2 = 17.8 Hz). Anal. Calcd for $C_{17}H_{13}FO_3$: C, 71.83; H, 4.58. Found: C, 71.43; H, 4.66.

Fluorination of Cyclohexene. Method A. The reaction was completed after 1 min and worked up as usual, and the resulting crude oil was subjected to flash chromatography using 5% EtOAc in P.E. as eluent. The oily **18** was obtained in 60% yield. IR 1720 cm^{-1}; MS, *m/e* 160 (M$^+$), 117 (M-Ac)$^+$, 101 (M-OAc)$^+$; NMR δ 4.91 (1H,m), 4.73 (1H, dm, J = 47 Hz), 2.09 (3H, s) 1.35–2.05 (8 H, m); ^{19}F NMR −181.8 (bd, J = 47 Hz). Anal. Calcd for $C_8H_{13}FO_2$: C, 60.0; H, 8.12. Found: C, 60.12; H, 8.03.

Fluorination of 1-Dodecene (19). Method A. The reaction was stopped after 1 min, worked up as usual, chromatographed with 4% EtOAc in petroleum ether, and finally purified by HPLC with the same solvent. Pure **20** was obtained as a clear liquid: 30% yield; IR 1730 cm^{-1}; MS, *m/e* 187 [(M−OAc)$^+$], 165 [(CH(OAc)CH_2F)$^+$], 141 [($C_{10}H_{21}$)$^+$]; ^1H NMR δ 5.03 (1 H, dm, J = 21.4 Hz), 4.45 (2 H, dm, J = 47 Hz), 1.26–1.67 (18 H,m), 0.88 (3 H, t, J = 5 Hz); ^{19}F NMR −231.1 (dt, J_1 = 48 Hz, J_2 = 23 Hz). Anal. Calcd for $C_{14}H_{27}FO_2$: C, 68.29; H, 10.98; F, 7.72. Found: C, 69.06; H, 11.10; F, 7.48.

Fluorination of 21. Method B. A minute after the addition of **1** to **21**, the reaction was stopped and worked up as usual. The crude product was subjected to short column chromatography using 50% EtOAc in petroleum ether and then recrystallized from pentane: mp 110 °C; 90% yield; IR 1725 cm^{-1}; MS, *m/e* 592 [M$^+$], 533 [(M − OAc)$^+$]; ^1H NMR δ 5.50 (1 H, dd, J_1 = 47 Hz, J_2 = 8 Hz), 2.20, 2.07, 2.00 (3 OAc groups, s), 1.1 (Me-19, s), 0.79 (Me-18, s); ^{19}F NMR −195.03 (dd, J_1 = 47 Hz, J_2 = 8 Hz). Anal. Calcd for $C_{33}H_{49}FO_8$: C, 66.89; H, 8.28. Found: C, 66.90; H, 8.50.

Fluorination of *trans*-Ethyl Cinnamate (23). Method A. After the instantaneous reaction and the usual workup, the resulting oil was homogenized by HPLC using 12% EtOAc in cyclohexane to give the oily **24** in 57% yield: IR 1750 cm^{-1}; MS, *m/e* 195 [(M − OAc)$^+$], 149 [(PhCHOAc)$^+$], 105 [(CHFCOOEt)$^+$]; ^1H NMR δ 7.38 (5 H, br s), 6.19 (1 H, dd, J_1 = 24 Hz, J_2 = 3.5 Hz), 5.05 (1 H, dd, J_1 = 47 Hz, J_2 = 3.5 Hz), 4.22 (2 H, q, J = 7.3 Hz), 2.12 (3 H, s), 1.23 (3 H, t, J = 7.3 Hz); ^{19}F NMR −202.4 (dd, J_1 = 47 Hz, J_2 = 24 Hz). Anal. Calcd for $C_{13}H_{15}FO_4$: C, 61.42; H, 5.91; F, 7.48. Found: C, 61.29; H, 6.14; F, 7.67.

Fluorination of *cis*-Methyl Cinnamate (25). Method A. The same conditions were used as for **23**. The crude oil was flash chromatographed, followed by final purification by HPLC using 12% EtOAc in cyclohexane. Pure **26** melts at 68 °C (from MeOH): 50% yield; IR 1750 cm^{-1}; MS, *m/e* 181 [(M − OAc)$^+$], 149 [(PhCHOAc)$^+$], 91 [(CHFCOOMe)$^+$]; ^1H NMR δ 7.36 (5 H, br s), 6.17 (1 H, dd, J_1 = 22 Hz, J_2 = 3.5 Hz), 5.25 (1 H, dd J_1 = 49 Hz, J_2 = 3.5 Hz), 3.72 (3 H, s), 2.14 (3 H, s); ^{19}F NMR −202.7 (dd, J_1 = 49 Hz, J_2 = 22 Hz). Anal. Calcd for $C_{12}H_{13}FO_4$: C, 60.00; H, 5.42; F, 7.97. Found: C, 60.28; H, 5.47; F, 8.21.

Fluorination of Benzalacetophenone 27. Method A. The reaction of **27** with **1** was completed in less than 1 min and then worked up as usual. The crude oil was purified by flash chromatography, followed by HPLC using 10% EtOAc in cyclohexane as eluent. The pure oily **28** was thus isolated in 67% yield: IR 1740, 1685 cm^{-1}; MS, *m/e* 286 [M$^+$], 227 [(M − OAc)$^+$], 149 [(PhCHOAc)$^+$], 137 [(PhCOCHF)$^+$]; ^1H NMR δ 7.25–7.97 (10 H, m), 6.34 (1 H, dd, J_1 = 23 Hz, J_2 = 4 Hz), 5.62 (1 H, dd, J_1 = 48 Hz, J_2 = 4 Hz), 2.11 (3 H, s); ^{19}F NMR −199.8 (dd, J_1 = 48 Hz, J_2 = 23 Hz). Anal. Calcd for $C_{17}H_{15}FO_4$: C, 62.94; H, 5.24. Found: C, 62.82; H, 5.29.

Fluorination of Androst-4-ene-3,17-dione (29). Method B. About 5 min after the completion of the addition of **1**, the reaction was worked up as usual. The crude product was mainly the adduct **30** as evident from its NMR spectra: ^1H NMR δ 5.05 (d, J = 48 Hz), 2.0 (OAc, s), 1.3 (Me-19, s), 0.9 (Me-18, s); ^{19}F NMR −209.7 (d, J = 48 Hz). Leaving the crude adduct **30** absorbed on a Florisil column for 24 h and eluting it with EtOAc produced the elimination product **31**, which was further purified by HPLC with 20% EtOAc in cyclohexane: 64% yield; mp 172 °C (from MeOH); IR 1725, 1685, 1650 cm^{-1}; MS, *m/e* 304 [M$^+$], 289 [(M − Me)$^+$]; ^1H NMR δ 1.20 (Me-19, s), 0.87 (Me-18, s); ^{19}F NMR −139.0 (s). Anal. Calcd for $C_{19}H_{25}FO_2$: C, 75.00; H, 8.22. Found: C, 74.30; H, 8.14.

Fluorination of Coumarin (32). Method A. In this case the reaction mixture was left at −78 °C for 24 h and even then only 56% conversion was obtianed. The crude reaction mixture was worked up as usual and according to the NMR spectra it contained a mixture of the syn and anti adducts **33** in equal amounts: ^1H NMR δ 6.35 (dm, J = 18 Hz), 5.42 (dm, J = 48 Hz), 2.02 (OAc, s); ^{19}F NMR −204.7 (br d, J = 45 Hz), −198.1 (dd, J_1 = 48 Hz, J_2 = 18 Hz). The crude mixture was absorbed for 10 h on a basic alumina column and then eluted with 40% EtOAc in petroleum ether. The obtained solid **34**, was recyrstallized from MeOH: mp 150 °C; 95% yield (based on the reacted **32**); IR 1710 cm^{-1}; MS, *m/e* 164 [M$^+$]; ^1H NMR δ 7.2–7.7 (m); ^{19}F NMR −130.1 (d, J = 8 Hz). Anal. Calcd for $C_9H_5FO_2$: C, 65.85; H, 3.05. Found: C, 65.44; H, 2.95.

Fluorination of the Enol Acetates 41 and 43.[19] **Method A.** After the instantaneous reactions, in both cases the crude reaction mixtures were treated with methanolic NaOH solution for 2 h. The α-fluoroketones **42** and **44** were thus obtained in 70% and 90% yields, respectively. Their physical data are in full agreement with those published in the literature.

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Registry No. **1**, 78948-09-1; **2**, 103-30-0; **3**, 78948-08-0; **4**, 78948-07-9; **5**, 645-49-8; **6**, 1694-19-5; **7**, 98014-16-5; **8**, 98014-17-6; **9**, 98014-18-7; **10**, 98014-19-8; **11**, 4180-23-8; **12**, 98014-20-1; **13**, 98014-21-2; **14**, 98014-22-3; **15**, 98014-23-4; **16**, 35897-95-1; **17**, 98014-24-5; **18**, 98014-25-6; **19**, 112-41-4; **20**, 98014-26-7; **21**, 1063-81-6; **22**, 98014-27-8; **23**, 4192-77-2; **24**, 50778-20-6; **25**, 19713-73-6; **26**, 98014-28-9; **27**, 614-47-1; **28**, 98014-29-0; **29**, 63-05-8; **30**, 98014-30-3; **31**, 98102-30-8; **32**, 91-64-5; *cis*-**33**, 98014-31-4; *trans*-**33**, 98014-32-5; **34**, 704-60-9; **35**, 25512-62-3; **36**, 1193-18-6; **37**, 10544-63-5; **38**, 501-65-5; **39**, 536-74-3; **40**, 1604-29-1; **41**, 14478-13-8; **42**, 1755-14-2; **43**, 38736-92-4; **44**, 56114-30-8; diethyl maleate, 141-05-9; diethyl fumarate, 623-91-6; cyclohexene, 110-83-8.

MO Studies on S- to N-Nitrosation Rearrangement

Karl Anker Jørgensen

Department of Organic Chemistry, Chemical Institute, University of Aarhus, DK-8000 Aarhus C, Denmark

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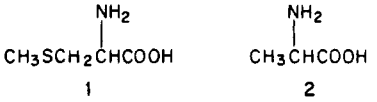
The nitrosation of sulfur–nitrogen ambident substrates has been studied by use of the frontier orbital approach. The increased diazotization rate of *S*-methyl-L-cysteine, **1**, compared with alanine, **2**, is well explained from the concept of charge and frontier controlled reactions. The nitrosyl cation prefers to attack sulfur in **1** rather than nitrogen in **1** and **2**, by an orbital controlled reaction followed by S to N rearrangement of the nitroso group. The structure of the different intermediates has been optimized by CNDO and/or INDO calculations and the electronic structure and total energy have been calculated by Gaussian 80 (4-31G). In a similar way has the nitrosation of thiourea been analyzed and the obtained results are analyzed in relation to the experimental results and a one electron-transfer mechanism.

In a recent paper[1] the diazotization of L-methionine and *S*-methyl-L-cysteine, **1**, was found to occur about 100 times faster than that of alanine, **2**.

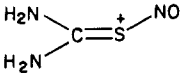


1 **2**

It was suggested that an initial S-nitrosation of L-methionine and *S*-methyl-L-cysteine was the first step, followed by an intra S to N rearrangement of the nitroso group (Scheme I).[1]

A part of the large difference in second-order rate constant for the reaction of **1** and **2** (0.109 and 0.0013 L mol^{-1} s^{-1}, respectively) can be accounted for by the difference in pK_a values of the reagents, but this effect accounts only for a factor of 7.6 relative to alanine.[1]

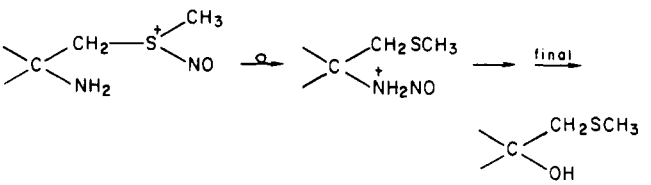
Thiourea is known to be a powerful catalyst for both nitrosation and diazotization.[2] Thiourea forms a somewhat unstable *S*-nitroso cation, **3**, which is directly observable as a yellow species.[3] Indirectly, it has also been shown that this cation can itself act as a nitrosation agent.



3

The nitrosation of thiourea can lead to different products depending on the acidity.[3] It was shown that reaction

Scheme I



1 was favored by high acidities, whereas reaction 2 was predominant at low acidities.[3]

$$2H^+ + 2HNO_2 + 2(H_2N)_2CS \rightarrow (NH_2)_2C^+SSC^+(NH_2)_2 + 2NO + 2H_2O \quad (1)$$

$$HNO_2 + (H_2N)_2CS \rightarrow H^+ + SCN^- + N_2 + 2H_2O \quad (2)$$

It has been suggested that N-nitrosation of thiourea which occurs at low acidity arises from an initial S attack followed by subsequent rearrangement,[3c] but ^{15}N NMR studies on the same system argue in favor of a direct attack on nitrogen.[4]

In an attempt to through light over these reactions, and as an extension of our MO studies concerning nitrosation mechanisms and ambident reactivity,[5] this paper presents a MO analysis of nitrosation *S*-methyl-L-cysteine and thiourea.

Methods, Results, and Discussion

The choice of CNDO[6] and INDO[6] as methods of calculation stems from the possibility of optimizing the geom-

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