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Cyclisation of Tryptophans. III. The Crystal Structure of a Product Derived from Trifluoroacetylation of N_b-Methoxycarbonyl-L-Tryptophan Methyl Ester in Pyridine

Uffe Anthoni, Carsten Christophersen,* Andreas Obel and Per Halfdan Nielsen

Chemical Institute, The H. C. Ørsted Institute University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

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The reaction between N_b-methoxycarbonyl-L-tryptophan methyl ester and trifluoroacetic acid anhydride in pyridine furnished, as the main product, (2*S*,3a*R*,8a*S*)-dimethyl 3a-(*N*-trifluoroacetyl-1,4-dihydro-4-pyridyl)-8-trifluoroacetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-1,2-dicarboxylate. A second five-membered heterocyclic ring was formed through attack of the N_b nitrogen to the 2-position of the indole ring system. Short intramolecular distances between the non-bonded electronegative atoms (O and F) and between fluorine and a benzene ring, are attributed to tight packing of the molecules in the crystal structure.

We have previously found that N_b-methoxycarbonyl-L-tryptophan methyl ester (**1**) reacts readily with trifluoroacetic acid anhydride (TFAA) in trifluoroacetic acid with cyclisation and concurrent trifluoroacetylation to give the diastereoisomeric products **2** and **3** in the ratio 14:1 (Scheme 1).[1] When TFAA in pyridine was used instead, the main product **4** (Fig. 1) displayed NMR spectra resembling those of **2** and **3** but with a number of additional lines indicating incorporation of the pyridine ring into the product.[2] Mass spectroscopy (peak matching corresponding to $C_{23}H_{19}F_6N_3O_6$, found $m/z = 547.1179$, error 1 mmu) indicated the presence of two trifluoroacetyl groups and one ring derived from dihydropyridine. Although a thorough investigation of all reaction products had been performed[2] the diastereoisomer of **4** was not detected. Obviously a regio- and stereo-specific reaction had occurred in pyridine in contrast with the reaction in trifluoroacetic acid. It is probable that the latter reaction is stepwise involving an ion-pair while the former implies the participation of the adduct TFAA·pyridine.[3] The main objective of the X-ray analysis was to determine the exact structure of compound **4**.

X-Ray crystallographic structure determination

Data collection. Low-temperature data were collected on an Enraf-Nonius CAD4 diffractometer with Cu $K\alpha$ radiation. A graphite crystal was used as the monochromator. The initial orientation matrix and cell parameters were determined from 22 reflections $40.49° < \theta < 44.22°$. 6416 reflections were measured on a transparent beam-formed crystal with $\omega/2\theta$ scans covering the octants hkl, $hk\bar{l}$ and $\bar{h}\bar{k}l,\bar{h}\bar{k}\bar{l}$ from 1–75 deg (Table 1).

Data reduction. The Blessing data reduction package DREADD[4] was used for the data reduction and error

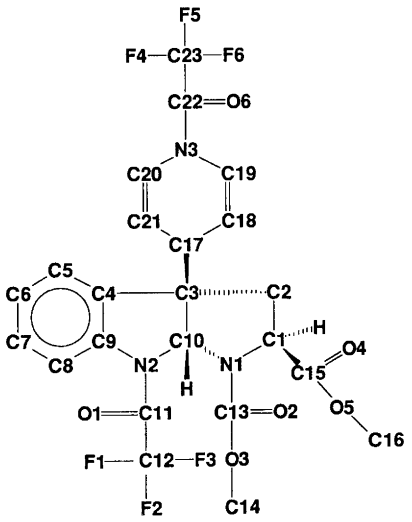
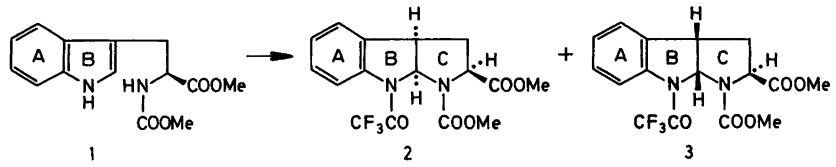


Fig. 1. The atomic labelling system and the configuration of **4** as determined by X-ray analysis.

* To whom correspondence should be addressed.



Scheme 1.

analysis. The space group was determined from the systematic absent reflections as derived from the diffractometer list. The reflections were corrected for Lorentz polarisation. Since the initial structure refinement showed the need for an extinction correction, the decay corrections were weighted by intensity. The decay differed substantially for the three intensity-control reflections; 002 [max. 5481(50), min. 4749(64)], 020 [max. 2576(22), min. 2466 (22)], 210 [max. 2470(21), min. 2406(21)]. Due to this, an anisotropic decay correction was applied. The data were corrected for absorption.[5] The transmission factors were between 0.897 and 0.628. The data were averaged with normal probability down-weighting of outliers. 4700 unique reflections with $R_{int} = 0.030$ were obtained from 3324 reflections measured once and 1376 reflections measured two or more times. 4656 of the unique reflections were observed [$F \geq 4\sigma(F)$].

Structure solution. The direct method facility of SHELXS-86[6] was applied for the structure solution. XMOL[7] was used as a graphical interface to the list of starting coordinates suggested by SHELXS-86. The indole system, the trifluoroacetyl groups and the methoxycarbonyl groups were immediately recognizable. The subsequent difference electron density map revealed the remaining non-hydrogen atoms in the structure.

Refinement. The SHELXL-93[8] full matrix least-squares refinement on F^2 was used for the refinement process. In order to assess the validity of subsequent hydrogen assignments and their possible degrees of freedom, every tenth reflection was omitted from the refinement procedure and used for a test data set to produce R_{Test}^{Free} values, as recommended by Brunger.[9] The difference electron density map calculated after anisotropic refinement of the non-hydrogen atoms displayed electron density from hydrogens. At this stage the R-values based on $F[F \geq 4\sigma(F)]$ were $R = 0.0514$ and $R_{Test}^{Free} = 0.0531$. Three different levels of freedom for the hydrogens were tested in the subsequent refinement. In all three cases the iso-

Table 1. Crystal data and structure refinement.

Empirical formula	$C_{23}H_{19}F_6N_3O_6$
Formula weight	547.41 g mol^{-1}
Temperature	122.0(5) K
Wavelength	Cu $K\alpha$
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a=8.964(2) Å
	b=14.404(2) Å
	c=17.673(5) Å
Volume	2282.0(8)^3
Z	4
Density (calculated)	1.593 Mg m^{-3}
Absorption coefficient	1.299 mm^{-1}
F(000)	1120
Crystal size	0.15×0.47×0.20 mm
θ range for data	3.96–74.97°
Index ranges	$-11 \leq h \leq 11$, $-12 \leq k \leq 18$, $-21 \leq l \leq 22$
Reflections collected	6416
Independent reflections	4700 [R(int)=0.030]
Data/restraints/parameters	4700/0/346
Goodness-of-fit on F^2	1.048
Final R* indices [$F \geq 4\sigma(F)$][a]	$R1$=0.0332, $wR2$=0.0897
R indices (all data)[a]	$R1$=0.0335, $wR2$=0.0900
Absolute structure parameter	−0.10(9)
Extinction coefficient	0.0045(3)
Largest diff. peak and hole in electron difference map	0.265 and −0.225 e Å^{-3}

[a] $R1$ is the residual based on F and $R2$ the residual based on F^2. The weights are given by

$$w = 1/[\sigma^2(F_o^2) + (0.0590P)^2 + 0.68P]$$

where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$.

tropic displacement parameters of the methyl-hydrogens were constrained to 1.5 times the equivalent isotropic displacement parameter of the atom to which they were bonded. The corresponding value was 1.2 for all other hydrogens. A riding model refinement with distances and angles fixed yielded $R = 0.0344$ and $R_{\text{Test}}^{\text{Free}} = 0.0359$.

A refinement with fixed angles and bond distances as variables resulted in $R = 0.0344$ and $R_{\text{Test}}^{\text{Free}} = 0.0362$, and with both angles and distance as variables the values were $R = 0.0339$ and $R_{\text{Test}}^{\text{Free}} = 0.0366$. The increase in $R_{\text{Test}}^{\text{Free}}$ indicates that the information content in the data was insufficient for a refinement of the hydrogen positions. The riding model with fixed distances and angles was used for the hydrogens in the subsequent refinement. The C–H distances were set at 0.98 Å for methyl-hydrogens and 0.95 Å for ethyl-hydrogens. The C–H distance used for aromatic hydrogens was 0.95 Å. The SHELXL-93 weighting scheme parameters were iterated to convergence. The final values of R and $R_{\text{Test}}^{\text{Free}}$, before merging of the work and test data sets for final refinements on all reflections, were $R = 0.0332$ and $R_{\text{Test}}^{\text{Free}} = 0.0348$. The final difference electron-density map showed no special features. The trifluoromethyl groups were well defined: one in an eclipsed conformation and one in a staggered. The final atomic coordinates are listed in Table 2. The choice of stereoisomer was confirmed by the Flack[10] absolute structure parameter, which was 0 to within one standard deviation.

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}
C(1)	7644(2)	6793(1)	6938(1)	16(1)
C(2)	7723(2)	6400(1)	7749(1)	17(1)
C(3)	6482(2)	6919(1)	8168(1)	15(1)
C(4)	6872(2)	7921(1)	8343(1)	15(1)
C(5)	8091(2)	8267(1)	8737(1)	19(1)
C(6)	8160(2)	9220(1)	8879(1)	23(1)
C(7)	7030(2)	9803(1)	8625(1)	24(1)
C(8)	5805(2)	9466(1)	8225(1)	21(1)
C(9)	5755(2)	8517(1)	8091(1)	16(1)
C(10)	5246(2)	7051(1)	7574(1)	15(1)
C(11)	3262(2)	8311(1)	7531(1)	17(1)
C(12)	1944(2)	7648(1)	7367(1)	20(1)
C(13)	5496(2)	7428(1)	6217(1)	18(1)
C(14)	6032(2)	7865(1)	4963(1)	28(1)
C(15)	8175(2)	6059(1)	6381(1)	17(1)
C(16)	7502(2)	4792(1)	5622(1)	31(1)
C(17)	5939(2)	6415(1)	8903(1)	18(1)
C(18)	4789(2)	6983(1)	9314(1)	20(1)
C(19)	3361(2)	6745(1)	9374(1)	20(1)
C(20)	3881(2)	5244(1)	8826(1)	20(1)
C(21)	5317(2)	5462(1)	8750(1)	20(1)
C(22)	1300(2)	5741(1)	9143(1)	21(1)
C(23)	694(2)	4802(1)	8854(1)	26(1)
N(1)	6070(1)	7047(1)	6858(1)	16(1)
N(2)	4618(1)	7974(1)	7732(1)	15(1)
N(3)	2807(2)	5889(1)	9094(1)	19(1)
O(1)	2923(1)	9127(1)	7552(1)	26(1)
O(2)	4199(1)	7670(1)	6147(1)	28(1)
O(3)	6545(1)	7500(1)	5684(1)	22(1)
O(4)	9470(1)	5950(1)	6231(1)	24(1)
O(5)	7056(1)	5543(1)	6110(1)	22(1)
O(6)	418(1)	6301(1)	9394(1)	28(1)
F(1)	1106(1)	7979(1)	6821(1)	35(1)
F(2)	2237(1)	6769(1)	7207(1)	36(1)
F(3)	1110(1)	7633(1)	7997(1)	45(1)
F(4)	−779(1)	4793(1)	8919(1)	36(1)
F(5)	1035(2)	4659(1)	8131(1)	46(1)
F(6)	1228(1)	4093(1)	9255(1)	43(1)

Discussion

Description of the structure. The structure of **4** (Figs. 1 and 2), as determined by the X-ray analysis, includes the presence of a second heterocyclic five-membered ring (C) formally derived from attack of the N_b nitrogen on the C = C bond of ring B as in the reaction sequence leading to **2** and **3** outlined in Scheme 1. However, as evidenced by the simultaneous attachment of the *N*-trifluoroacetylpyridine fragment this addition had been initiated by the presence of the reagent derived from TFAA in pyridine.

Bond lengths and angles are listed in Table 3. Loss of aromatic character of the B ring is reflected in the elongation of the carbon–carbon bonds compared with typical single-bond distances. The *N*-trifluoroacetyldihydropyridine unit is connected to C(3) through tetrahedrally coordinated C(17). H(17) was clearly visible in the difference electron-density map. This attachment disrupts the aromatic system of the pyridine ring and localised double bonds are formed between C(18)–C(19) and C(20)–C(21). The formation of the second heterocyclic ring and the attachment of the *N*-trifluoroacetyldihydropyridine group create two new chiral centres at C(3) and C(10). The absolute configurations of the chiral centres are C(1), *S*; C(3), *R* and C(10), *S*.

The two trifluoroacetyl groups form amides to N(2) of the indole system and N(3) of the dihydropyridine ring. Both amide systems are almost planar and N(2)–C(11) [1.356(2) Å] and N(3)–C(22) [1.370(2) Å] are shortened indicating partial double-bond character. The C(12) atom deviates by 0.012 Å from the mean plane of C(12)C(11)O(1)N(2) and (C23) by 0.001 Å from the mean plane of C(23)C(22)O(6)N(3). The carbamate group N(1)O(3)C(13)O(2) can also be considered planar with a distance of N(1) from the mean plane of the remaining atoms of 0.005 Å and a C(13)–N(1) distance of 1.359(2) Å. These features are typical of resonance delocalisation resulting in *cis–trans* isomerism in solution of compounds of this type as demonstrated by NMR techniques.[1–3] The N(2) trifluoroacetyl group adopts a conformation with the carbonyl oxygen O(1) towards the C(8)–H hydrogen as also found in another *N*-trifluoroacetylindole.[11] Since the *cis–trans* ratio in solution of compounds **2** and **3** is close to 1:1[1] this conformational preference does not reflect different steric requirements of the trifluoromethyl vs. the CO group but is either coincidental or due to crystal effects.

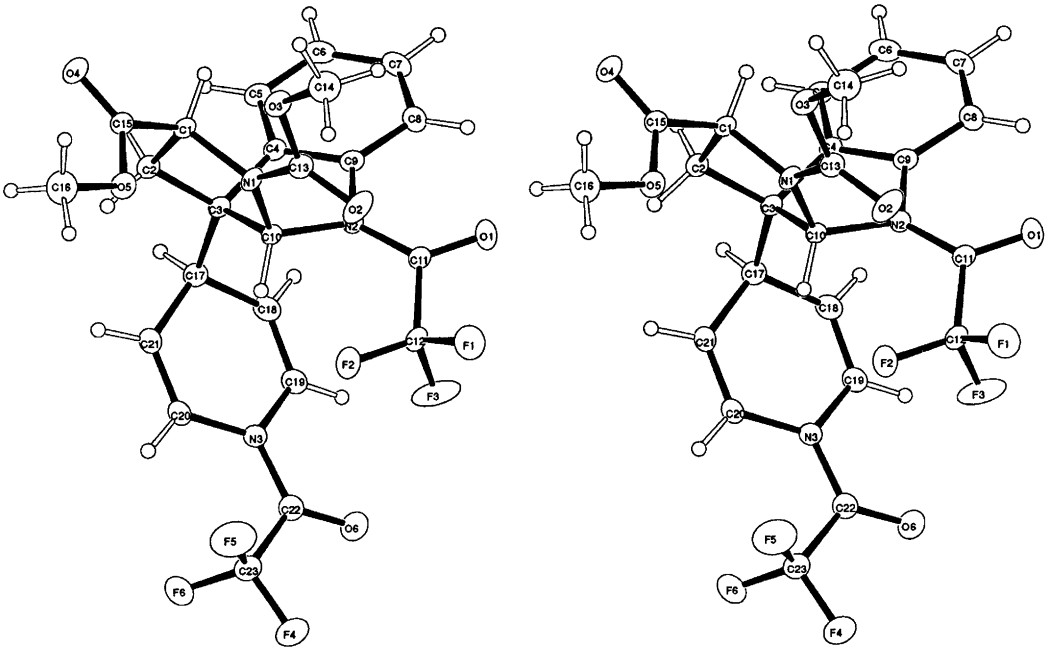


Fig. 2. ORTEP[24] drawing of **4**. Ellipsoids drawn at the 50% probability level.

Configuration and non-bonded interactions. The torsion angles are given in Table 4. The aromatic character of the pyrrole ring has been removed by the cyclisation resulting in two *cis*-fused enveloped-shaped rings B and C. The atoms C(10), C(3) and N(2) of the B ring are twisted out from the indole mean plane as demonstrated by the torsion angle C(4)–C(3)–C(10)–N(2) of −25.2(14)°. The torsion angle N(1)–C(1)–C(2)–C(3) of −28.9(14)° shows the puckering of the C ring to be a little higher. A search of the Cambridge Structural Database[12] revealed 32 structures with similar ring systems including three fused rings, one of these[13] very similar to **4**. Both *cis* and *trans* configurations of the junction between B and C rings were found although the *cis* configuration is the most common. The average of the torsion angle C(9)–N(2)–C(10)–N(1) defining the relative position of the B and C rings was 106.3° for the *trans* configurations vs. −116.6° for *cis*, as compared with −84.57(14)° in compound **4**. The angle between the least-squares planes of the indole plane and the C ring is 78.00(5)°, almost perpendicular to the indole system.

The methoxycarbonyl group connected to C(1) adopts an *exo* configuration relative to the surface of the condensed rings in contrast with the findings for all other similarly substituted hexahydropyrroloindoles where an *endo* configuration is adopted.[14] This has led to the suggestion that the *endo* configuration allows a non-bonding interaction between the ester group and the aromatic system,[14] but this hypothesis was subsequently invalidated.[15] The present result supports the proposal that the stability of *endo* and *exo* configurations in gas-phase is not widely different and that the preferred configuration in their synthesis is determined mainly by van der Waals forces and solvation.[15]

The *N*-trifluoroacetyldihydropyridine moiety is *exo* to the condensed ring system with a torsion angle C(10)–C(3)–C(17)–C(18) of −63.9(2)° with the electronegative atoms F(3) and O(6) at an interatomic distance of only 3.188(2) Å. The pyridine ring is bent towards the trifluoroacetyl group containing F(3) as illustrated by an angle of 12.72(12)° between the mean planes of the pyridine fragments C(17)–C(18)–C(21) and C(18)–C(21)–C(19)–C(20)–N(3). These unexpected findings could be due to a tight packing of the molecules (calculated density 1.593 Mg m^{-3}) in the crystal (Fig. 3). Moreover, F(5) from the eclipsed trifluoroacetyl group on the pyridine ring displays a short intermolecular contact to the benzene ring of a neighbouring molecule. The distance from the least-squares plane through the benzene ring to F(5) is 3.494(2) Å and to the carbon atoms in the benzene ring is in the range 3.56–4.07 Å. This is probably also due to tight packing in the crystal. Other unexplained short distances involving trifluoromethyl groups have been described.[16]

In trifluoroacetamides, the trifluoromethyl group often adopts conformations, relative to the N–C=O group, eclipsed with either O or with N.[11,17,18] In **4** the trifluoroacetyl group at the pyridine nitrogen has the trifluoromethyl group almost eclipsed to oxygen [torsional angle F(4)–C(23)–C(22)–O(6) 1.8(2)°] while it is closer to nitrogen in the other trifluoroacetyl group [torsional angle F(2)–C(12)–C(11)–N(2) −19.6(2)°]. To our knowledge, the reason for this preference for eclipsed conformations has never been explained. High-resolution microwave in-

Table 3. Bond lengths (Å) and angles (deg).

C(1)–N(1)	1.465(2)	N(1)–C(1)–C(15)	114.34(13)	C(19)–C(18)–C(17)	124.0(2)
C(1)–C(15)	1.521(2)	N(1)–C(1)–C(2)	103.07(12)	C(18)–C(19)–N(3)	122.2(2)
C(1)–C(2)	1.541(2)	C(15)–C(1)–C(2)	109.39(12)	C(21)–C(20)–N(3)	122.4(2)
C(2)–C(3)	1.532(2)	C(3)–C(2)–C(1)	103.77(12)	C(20)–C(21)–C(17)	123.7(2)
C(3)–C(4)	1.518(2)	C(4)–C(3)–C(2)	113.29(12)	O(6)–C(22)–N(3)	124.3(2)
C(3)–C(10)	1.539(2)	C(4)–C(3)–C(10)	100.80(11)	O(6)–C(22)–C(23)	118.2(2)
C(3)–C(17)	1.564(2)	C(2)–C(3)–C(10)	104.61(12)	N(3)–C(22)–C(23)	117.48(14)
C(4)–C(5)	1.388(2)	C(4)–C(3)–C(17)	110.14(12)	F(4)–C(23)–F(5)	108.2(2)
C(4)–C(9)	1.391(2)	C(2)–C(3)–C(17)	113.64(12)	F(4)–C(23)–F(6)	107.7(2)
C(5)–C(6)	1.397(2)	C(10)–C(3)–C(17)	113.59(12)	F(5)–C(23)–F(6)	108.1(2)
C(6)–C(7)	1.390(3)	C(5)–C(4)–C(9)	120.41(14)	F(4)–C(23)–C(22)	109.25(14)
C(7)–C(8)	1.393(2)	C(5)–C(4)–C(3)	128.63(14)	F(5)–C(23)–C(22)	111.9(2)
C(8)–C(9)	1.388(2)	C(9)–C(4)–C(3)	110.85(13)	F(6)–C(23)–C(22)	111.6(2)
C(9)–N(2)	1.433(2)	C(4)–C(5)–C(6)	118.5(2)	C(13)–N(1)–C(10)	121.81(12)
C(10)–N(1)	1.465(2)	C(7)–C(6)–C(5)	120.3(2)	C(13)–N(1)–C(1)	123.15(12)
C(10)–N(2)	1.471(2)	C(6)–C(7)–C(8)	121.8(2)	C(10)–N(1)–C(1)	113.74(12)
C(11)–O(1)	1.215(2)	C(9)–C(8)–C(7)	117.1(2)	C(11)–N(2)–C(9)	123.97(13)
C(11)–N(2)	1.356(2)	C(8)–C(9)–C(4)	121.98(14)	C(11)–N(2)–C(10)	128.06(13)
C(11)–C(12)	1.546(2)	C(8)–C(9)–N(2)	129.45(14)	C(9)–N(2)–C(10)	107.77(12)
C(12)–F(1)	1.314(2)	C(4)–C(9)–N(2)	108.50(13)	C(22)–N(3)–C(20)	126.06(14)
C(12)–F(2)	1.324(2)	N(1)–C(10)–N(2)	111.10(12)	C(22)–N(3)–C(19)	117.22(14)
C(12)–F(3)	1.341(2)	N(1)–C(10)–C(3)	103.08(11)	C(20)–N(3)–C(19)	116.62(14)
C(13)–O(2)	1.220(2)	N(2)–C(10)–C(3)	104.91(11)	C(13)–O(3)–C(14)	115.14(13)
C(13)–O(3)	1.336(2)	O(1)–C(11)–N(2)	124.2(2)	C(15)–O(5)–C(16)	115.10(13)
C(13)–N(1)	1.359(2)	O(1)–C(11)–C(12)	114.35(14)		
C(14)–O(3)	1.452(2)	N(2)–C(11)–C(12)	120.86(13)		
C(15)–O(4)	1.201(2)	F(1)–C(12)–F(2)	107.66(14)		
C(15)–O(5)	1.337(2)	F(1)–C(12)–F(3)	107.29(14)		
C(16)–O(5)	1.440(2)	F(2)–C(12)–F(3)	105.79(14)		
C(17)–C(18)	1.504(2)	F(1)–C(12)–C(11)	110.52(13)		
C(17)–C(21)	1.506(2)	F(2)–C(12)–C(11)	118.65(13)		
C(18)–C(19)	1.330(2)	F(3)–C(12)–C(11)	106.33(13)		
C(19)–N(3)	1.419(2)	O(2)–C(13)–O(3)	125.23(14)		
C(20)–C(21)	1.332(2)	O(2)–C(13)–N(1)	124.1(2)		
C(20)–N(3)	1.419(2)	O(3)–C(13)–N(1)	110.70(13)		
C(22)–O(6)	1.213(2)	O(4)–C(15)–O(5)	124.9(2)		
C(22)–N(3)	1.370(2)	O(4)–C(15)–C(1)	122.43(14)		
C(22)–C(23)	1.545(2)	O(5)–C(15)–C(1)	112.58(13)		
C(23)–F(4)	1.325(2)	C(18)–C(17)–C(21)	109.19(13)		
C(23)–F(5)	1.329(2)	C(18)–C(17)–C(3)	111.20(13)		
C(23)–F(6)	1.333(2)	C(21)–C(17)–C(3)	112.91(13)		

vestigations of simple trifluoroacetamides failed to allow determination of the potential barrier because of lack of fine structure attributed to rapid intramolecular vibrational relaxation.[19] In crystalline trifluoroacetamide, rotational disorder of the CF_3 group is observed[20] attributed to a small potential barrier with several minima. Moreover, in methyl trifluoroacetate, the potential barrier of the CF_3 group is very small[21] allowing the predominant conformation to result from the operation of otherwise negligible interactions. For example, the interaction between the dipoles of C^+-F^- and $N^+=C-O^-$ might stabilize the conformation with fluorine eclipsed with nitrogen. In acetamide[22,23] the conformational changes from gas phase to solid state can be explained entirely by the electrostatic lattice forces.

Acknowledgements. We thank Flemming Hansen for assistance in the experimental crystallographic work and Dr. Sine Larsen for helpful discussions of the crystal

Table 4. Torsion angles (deg).

C(2)–C(1)–C(15)–O(4)	−85.3(2)
C(3)–C(10)–N(1)–C(1)	8.5(2)
C(4)–C(3)–C(10)–N(2)	−25.2(14)
C(5)–C(4)–C(3)–C(2)	−56.1(2)
C(7)–C(8)–C(9)–N(2)	176.8(2)
C(9)–N(2)–C(10)–N(1)	−84.6(14)
C(10)–C(3)–C(4)–C(9)	16.7(2)
C(10)–C(3)–C(17)–C(18)	−63.9(2)
C(12)–C(11)–N(2)–C(9)	−161.9(14)
C(18)–C(19)–N(3)–C(20)	7.4(2)
C(18)–C(19)–N(3)–C(22)	−176.0(2)
C(21)–C(20)–N(3)–C(22)	175.5(2)
N(1)–C(1)–C(2)–C(3)	−28.9(14)
N(1)–C(13)–O(3)–C(14)	177.6(1)
N(3)–C(20)–C(21)–C(17)	−3.0(3)
N(3)–C(19)–C(18)–C(17)	4.4(3)
O(1)–C(11)–N(2)–C(9)	8.9(3)
O(2)–C(13)–N(1)–C(10)	−11.6(3)
F(2)–C(12)–C(11)–N(2)	−19.6(2)
F(4)–C(23)–C(22)–O(6)	1.8(2)

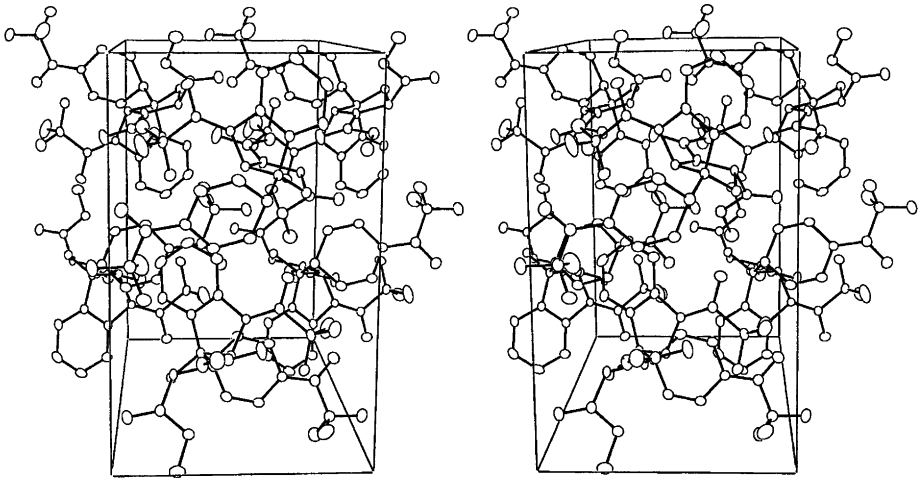


Fig. 3. ORTEP drawing showing the molecular packing of **4** in the crystal viewed down the *c*-axis.

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