Structural studies of reagents for peptide bond formation: Crystal and molecular structures of HBTU and HATU

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SUMMARY

X-ray structure determinations of HBTU and HATU, well-known reagents for peptide bond formation, show that the solid-state structures of these compounds differ markedly from those commonly presented in the literature. The solid-state structures are isomers of the N,N,N',N'-tetramethyluronium salt formulation commonly written for HBTU and HATU. HBTU and HATU, obtained either directly from synthesis or from CH_3CN solution, crystallize as the guanidinium N-oxide isomers. Both compounds crystallize in nearly identical conformations, despite marked differences in crystal packing.

INTRODUCTION

The success of the chemical synthesis of peptides, performed either in solution or in solid-phase, relies on an efficient combination of protecting groups and coupling reagents [1]. The introduction of 1-hydroxybenzotriazole (HOBt) as an additive for peptide bond formation was a significant improvement [2]. HOBt may be used in conjunction with carbodiimide or active esters, such as pentafluorophenyl (Pfp) esters. These mediated couplings form the corresponding OBt active esters, which react rapidly with the amine component to yield the peptide bond. Alternatively, the in situ formation of OBt esters may be accomplished with uronium salts, O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate or tetrafluoroborate (HBTU or TBTU), which incorporate an OBt moiety [3]. This uronium salt-mediated activation occurs faster than with carbodiimide or Pfp ester methods.

Recently, a pyridinium derivative of HOBt, 7-aza-1-hydroxybenzotriazole (HOAt), as well as the corresponding uronium salt, O-(7-aza-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), have been described as

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an excellent condensing additive and reagent, respectively [4]. HATU has been shown to be clearly superior in terms of coupling efficiency for coded amino acids as well as for unnatural hindered amino acids, and in the suppression of racemization in both solution and solid-phase methods [5]. This overwhelming enhancement in reactivity led us to initiate an investigation to determine possible structural differences between HATU and HBTU.

MATERIALS AND METHODS

Materials

HBTU was obtained from Richelieu Biotechnologies (Saint-Hyacinthe, Quebec). HATU, commercially available from Biosearch Corporation, was prepared from HOAt and tetramethylchloroformadinium hexafluorophosphate [3b,4].

X-ray powder diffraction measurements

X-ray powder diffraction measurements were carried out on a high-resolution Rigaku powder diffractometer in the Department of Materials Science and Engineering at MIT, Cambridge, MA. CuKα radiation (λ = 1.54178 Å; Rigaku IU300 rotating anode generator, 60 kV, 300 mA) was used. X-ray powder measurements were performed on two samples each of HBTU ((i) as delivered from Richelieu; (ii) recrystallized from acetonitrile) and HATU ((i) as obtained by the

published synthetic procedure from CH_2Cl_2 [3b,4]; (ii) recrystallized from acetonitrile). Only those peaks with a relative intensity larger than 2.5% of the maximum are reported here. Data reported below are d-spacings (in Å) with relative intensity in parentheses.

HATU (i): 12.302 (12.7), 8.717 (10.8), 6.573 (6.7), 6.348 (49.0), 6.155 (100.0), 5.840 (8.1), 5.542 (23.1), 5.414 (22.2), 4.913 (10.3), 4.757 (3.7), 4.526 (10.2), 4.367 (2.8), 4.180 (21.4), 4.103 (33.2), 3.799 (27.3), 3.748 (10.0), 3.582 (12.4), 3.507 (16.1), 3.191 (13.6), 3.022 (3.0), 2.982 (8.2), 2.917 (8.4), 2.703 (5.1), 2.371 (2.8). This pattern is in excellent agreement with the powder pattern of HATU calculated [6] from the results of the X-ray single-crystal structure determination described below.

HATU (ii): The powder diffraction pattern of this sample matches that of HATU (i). However, five additional low-intensity peaks appear in this pattern that are not present in the pattern of HATU (i), nor do they correspond to any d-spacings calculated from the results of the single-crystal work: 10.722 (1.9), 7.993 (1.1), 5.224 (1.3), 4.849 (1.7), 4.048 (3.4). These results suggest that recrystallization of HATU from acetonitrile leads to introduction of a few percent of a crystalline polymorph, an isomer or a degradation product.

HBTU (i): The pattern for this sample corresponded well to that of HBTU (ii), with no significant differences. Since the pattern for HBTU
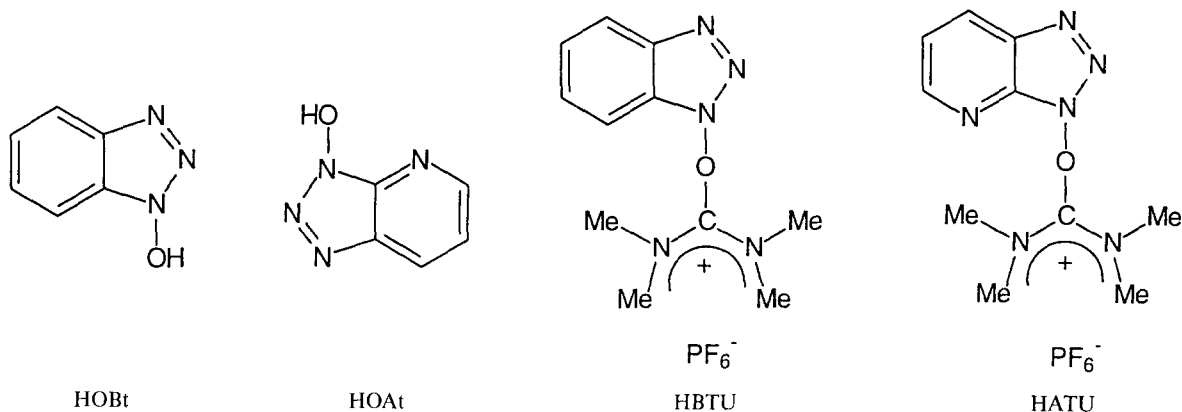

HOBt   HOAt   HBTU   HATU

TABLE 1
DATA FOR THE X-RAY DIFFRACTION STUDIES OF HBTU AND HATU

Compound	HBTU, $[C_{11}H_{16}ON_5^+][PF_6^-]$	HATU, $[C_{10}H_{15}ON_6^+][PF_6^-]$
Crystal data at 21(1) °C		
Crystal system	triclinic[a]	monoclinic
Space group	P$\bar{1}$ [C_i^1; no. 2]	P2_1/n [C_{2h}^5; no. 14]
a (Å)	13.069(5)	13.508(4)
b (Å)	7.446(3)	7.158(2)
c (Å)	8.784(4)	17.597(5)
α (deg)	103.92(4)	90
β (deg)	100.25(4)	110.01(3)
γ (deg)	89.13(4)	90
V (Å^3)	816.1(13)	1598.7(17)
Z	2	4
Crystal size (mm)	0.46 × 0.59 × 0.71	0.13 × 0.21 × 0.67
Formula weight	379.25	380.235
ρ_{calc} (g cm^{-3})	1.543	1.580
ρ_{obs} (g cm^{-3})	1.52(1)	1.54(2)
μ (cm^{-1}) (MoK$\bar{\alpha}$)	2.34	2.27

Cell constant determination

Seven pairs of ± (*hkl*) and refined 2θ, ω, χ values in the range $23 \le |2\theta| \le 25°$ (λ(MoK$\bar{\alpha}$) = 0.71073 Å)

Measurement of intensity data[b]

Radiation	MoK$\bar{\alpha}$, graphite monochromator	
Reflections measured	+*h*, ±*k*, ±*l* (3.5° ≤ 2θ ≤ 45°)	+*h*, +*k*, ±*l* (3.5° ≤ 2θ ≤ 50°)
Scan type, speed	ω, vble, 3.91–14.65°/min	ω, vble, 2.93–8.37°/min
Scan range	2.2°; 2.0° offset in ω for bkgd	1.1°; 1.1° offset in ω for bkgd
No. of reflections measured	2240; 2127 in unique set	2933; 2806 in unique set
Standard reflections; period	04$\bar{3}$, 11$\bar{5}$, 7$\bar{2}$0; 100	0 0 10, 80$\bar{4}$, 14$\bar{2}$; 100
Weighting of reflections	Tukey–Prince weights	As before, p = 0.040[c]
R_{av}	0.018 (*0kl* reflections)	0.012 (*0kl* reflections)
No. of data used in refinement	1851 [I > 1.96σ(I)]	2153 [I > 1.96σ(I)]
No. of refined parameters	318	277
Solution	SHELXS-86, difference-Fourier	SHELXS-86, difference-Fourier
Refinement[d]	Full-matrix least squares	Full-matrix least squares
Anisotropic displacement parameters	All nonhydrogen atoms	All nonhydrogen atoms
Isotropic displacement parameters	hydrogen atoms	hydrogen atoms
R	0.0504	0.0383
R_w	0.0578	0.0476
SDU	1.09	1.59
R (*all* reflections)	0.062	0.062
Final difference map	5 peaks, 0.16–0.19e$^-$/Å^3 near F atoms; other peaks random, range −0.08 to +0.15e$^-$/Å^3	10 peaks, 0.21–0.36e$^-$/Å^3 near F atoms; other peaks random, range −0.33 to +0.21e$^-$/Å^3

[a] The reduced cell was produced by the program TRACER (S.L. Lawton, Mobil Oil Company, Paulsboro, NJ, 1967): a = 8.784, b = 13.069, c = 7.446 Å; α = 90.87, β = 103.92, γ = 79.75°.

[b] Foxman, B.M., Goldberg, P.L. and Mazurek, H., Inorg. Chem., 20 (1981) 4368; all computations were carried out using the SHELXS-86, MolEN (HATU) and CRYSTALS (HBTU) programs.

[c] Corfield, P.W.R., Doedens, R.J. and Ibers, J.A., Inorg. Chem., 6 (1967) 197.

[d] $R_{av} = \Sigma|I - I_{av}|/\Sigma I$; $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R_w = (\Sigma w[|F_o| - |F_c|]^2/\Sigma w|F_o|^2)^{1/2}$; $SDU = (\Sigma w[|F_o| - |F_c|]^2/(m - n))^{1/2}$, where m is the number of observations and n is the number of parameters.
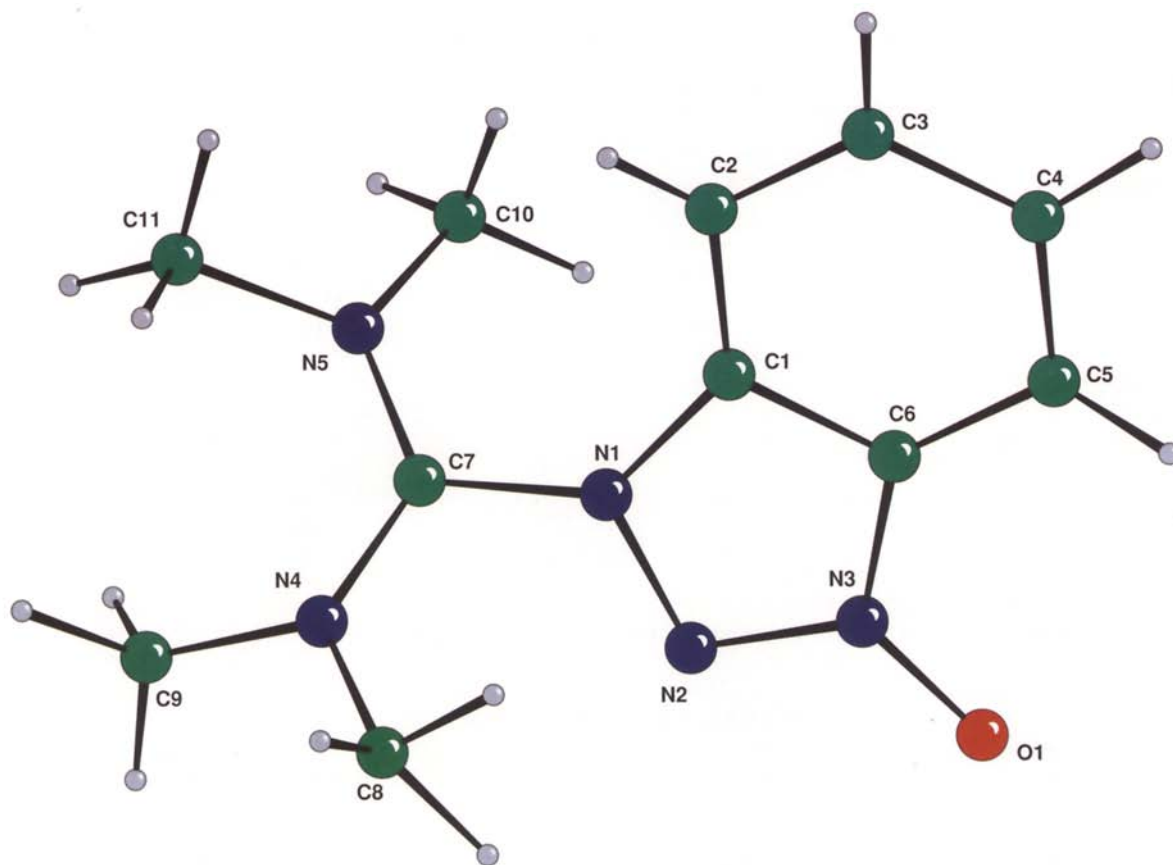
Fig. 1. Molecular structure of HBTU, showing atom labelling scheme.

(ii) is of somewhat better quality, those data are given here.

HBTU (ii): 8.403 (3.2), 7.702 (2.7), 6.525 (3.0), 6.430 (6.9), 6.232 (100.0), 5.626 (4.8), 5.414 (7.3), 4.881 (13.2), 4.813 (7.5), 4.716 (3.7), 4.288 (25.4), 4.203 (17.1), 4.088 (3.0), 3.799 (7.7), 3.729 (12.1), 3.565 (4.1), 3.326 (2.6), 3.218 (2.5), 3.087 (5.6), 2.769 (2.6). This pattern is in excellent agreement with the powder pattern of HBTU calculated [6] from the results of the X-ray single-crystal structure determination described below.

X-ray structure determination

Crystals of HBTU and HATU were grown by slow evaporation of acetonitrile solutions; each crystal was selected after examination by polarized light microscopy and mounted on a Pyrex fiber affixed to a brass pin. Each crystal was transferred to a Supper No. 455 goniometer and optically centered on a Syntex P2₁ diffractometer. Measurements on the diffractometer were performed as described previously [7,8]. For both structures, a summary of experimental details and measurements is presented in Table 1. The analytical scattering factors of Cromer and Waber were used; real and imaginary components of anomalous scattering were included in the calculations [9]. The X-ray structure determination of HBTU was complicated by the presence of disorder in the hexafluorophosphate anion. The final disorder model involves two orientations of the anion, related to one another by a 45° rotation

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about one pair of *trans*-fluorine atoms. Refinement of the occupancies of two sets of F_4 groups (F3 through F6 and F31 through F61), with the occupancies constrained to sum to 1.0, led to 0.53 (1) as the occupancy for atoms F3 through F6. There was no evidence for any disorder in the cation. Refinement of the structure of HATU proceeded smoothly. All hydrogen atoms were located and refined for both structures. The C-H bond distances in HBTU varied from 0.88 to 1.09 (4) Å with an average of 0.96 Å. For HATU, the C-H bond distances varied from 0.86 to 1.02 (4) Å with an average of 0.94 Å. Atomic coordinates and selected bond distances and angles for HBTU and HATU are listed in Tables 2–5. Anisotropic

displacement parameters for the ordered atoms in HBTU and HATU lie in normal ranges for structures determined at room temperature and containing hexafluorophosphate anions (0.04–0.10 Å^2 for HBTU and 0.04–0.15 Å^2 for HATU). In order to obtain reliable information regarding the thermal motion of these molecules, structure determination at low temperature (not currently available to us) is required. Nonetheless, the goal of this study – the unambiguous determination of the structures of HATU and HBTU – has been achieved. Tables of anisotropic displacement parameters as well as observed and calculated structure amplitudes are available from the authors [10].
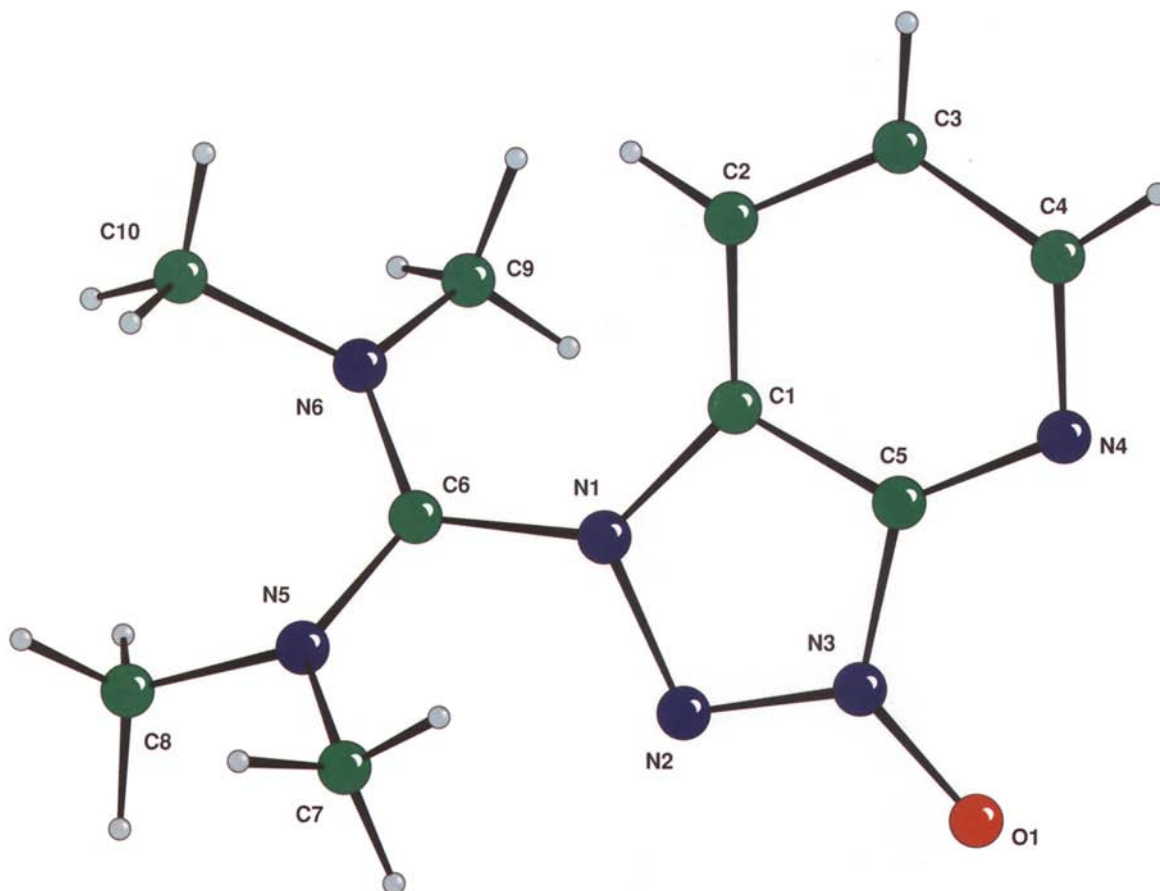

Fig. 2. Molecular structure of HATU, showing atom labelling scheme.

RESULTS AND DISCUSSION

The molecular structures of the cations in HBTU and HATU are shown in Figs. 1 and 2, respectively. The most striking feature, common to both structures, is that HBTU and HATU are guanidinium N-oxide salts, rather than uronium salts. This unanticipated result requires reformulation of the structures commonly presented by our group [4,5a] as well as by others [3,5c]. Inspection of Tables 3 and 5 reveals that both molecules are nearly isodimensional, except for the distances to N4, the pyridine nitrogen atom in HATU. Both molecules are well represented as guanidinium N-oxide cations, as shown. Thus, the N2–N3 distance in each molecule is quite short

HBTU (X = CH)
HATU (X = N)
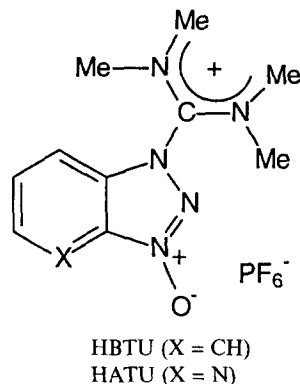
(1.308(3) and 1.311(3) Å for HBTU and HATU, respectively). The N3–O1 distances (1.273(3) and 1.259(3) Å) are consistent with the N–O distance of 1.267(2) Å observed in 3-(N^{α}-tritylmethionyl)-

TABLE 2
ATOMIC COORDINATES FOR HBTU[a,b]

Atom	x	y	z	B_{eq} (Å^2)
P1	0.16122 (7)	0.3619 (1)	0.8297 (1)	4.48
F1	0.1985 (4)	0.2449 (6)	0.9509 (5)	10.86
F2	0.1321 (3)	0.4896 (6)	0.7092 (5)	10.45
F3	0.2171 (9)	0.252 (2)	0.699 (1)	8.31
F4	0.0876 (7)	0.491 (2)	0.9352 (8)	8.54
F5	0.0585 (6)	0.268 (1)	0.727 (1)	8.82
F6	0.2540 (7)	0.486 (2)	0.921 (2)	10.15
F31	0.2758 (7)	0.358 (2)	0.793 (2)	7.57
F41	0.0592 (8)	0.323 (2)	0.880 (3)	10.15
F51	0.145 (1)	0.160 (1)	0.723 (1)	11.21
F61	0.178 (2)	0.535 (1)	0.948 (1)	10.80
O1	−0.4743 (2)	1.2375 (3)	0.6496 (3)	4.63
N1	−0.3295 (2)	0.8760 (3)	0.7065 (3)	3.06
N2	−0.3421 (2)	1.0403 (3)	0.6589 (3)	3.57
N3	−0.4354 (2)	1.0908 (3)	0.6827 (3)	3.51
N4	−0.1491 (2)	0.8824 (3)	0.7492 (3)	3.48
N5	−0.2440 (2)	0.6055 (3)	0.6288 (3)	3.21
C1	−0.4165 (2)	0.8284 (4)	0.7598 (3)	2.76
C2	−0.4412 (2)	0.6834 (4)	0.8214 (4)	3.34
C3	−0.5370 (3)	0.6870 (5)	0.8636 (4)	3.88
C4	−0.6071 (3)	0.8293 (5)	0.8467 (4)	3.99
C5	−0.5825 (2)	0.9728 (5)	0.7871 (4)	3.77
C6	−0.4852 (2)	0.9674 (4)	0.7442 (3)	2.97
C7	−0.2365 (2)	0.7843 (4)	0.6949 (3)	2.88
C8	−0.1404 (3)	1.0516 (5)	0.8786 (5)	4.37
C9	−0.0535 (3)	0.8289 (7)	0.6868 (6)	5.12
C10	−0.3326 (3)	0.5209 (5)	0.5054 (4)	3.96
C11	−0.1634 (4)	0.4768 (6)	0.6676 (5)	4.69

[a] Atoms refined using anisotropic displacement parameters in this table and in Table 4 are given in the form of the isotropic equivalent displacement parameter, defined as: $1.33[a^2B_{11} + b^2B_{22} + c^2B_{33} + ab \cdot \cos \gamma \cdot B_{12} + ac \cdot \cos \beta \cdot B_{13} + bc \cdot \cos \alpha \cdot B_{23}]$.

[b] Numbers in parentheses in this and the following tables are estimated standard deviations in the least significant digit.

TABLE 3
SELECTED BOND LENGTHS AND ANGLES FOR HBTU

Bond length (Å)

O1-N3	1.273 (3)	N4-C7	1.315 (4)	C1-C2	1.384 (4)
N1-N2	1.383 (3)	N4-C8	1.470 (4)	C1-C6	1.375 (4)
N1-C1	1.386 (4)	N4-C9	1.465 (4)	C2-C3	1.365 (4)
N1-C7	1.392 (4)	N5-C7	1.316 (4)	C3-C4	1.408 (5)
N2-N3	1.308 (3)	N5-C10	1.469 (4)	C4-C5	1.363 (5)
N3-C6	1.393 (4)	N5-C11	1.464 (4)	C5-C6	1.386 (4)

Bond angle (°)

N2-N1-C1	111.6 (2)	C8-N4-C9	115.5 (3)	C3-C4-C5	121.4 (3)
N2-N1-C7	118.5 (2)	C7-N5-C10	122.3 (3)	C4-C5-C6	115.6 (3)
C1-N1-C7	129.8 (2)	C7-N5-C11	122.8 (3)	N3-C6-C1	106.2 (2)
N1-N2-N3	104.1 (2)	C10-N5-C11	114.8 (3)	N3-C6-C5	130.5 (3)
O1-N3-N2	121.7 (3)	N1-C1-C2	133.8 (3)	C1-C6-C5	123.3 (3)
O1-N3-C6	125.3 (3)	N1-C1-C6	105.1 (2)	N1-C7-N4	117.8 (3)
N2-N3-C6	113.0 (2)	C2-C1-C6	121.1 (3)	N1-C7-N5	116.6 (2)
C7-N4-C8	122.2 (3)	C1-C2-C3	116.1 (3)	N4-C7-N5	125.5 (3)
C7-N4-C9	122.3 (3)	C2-C3-C4	122.5 (3)		

benzotriazole-1-oxide [11]. A slightly longer distance, 1.303(2) Å, was observed for the analogous bond length in benzotriazole-1-oxide [12]; in that structure the oxygen atom participates as an acceptor atom in a bifurcated hydrogen bond to two water molecules.

TABLE 4
ATOMIC COORDINATES FOR HATU

Atom	x	y	z	B_{eq} (Å^2)
P1	0.75466 (5)	0.80888 (9)	0.94141 (3)	3.77
F1	0.6649 (1)	0.8024 (2)	0.85552 (9)	6.58
F2	0.8443 (1)	0.8159 (3)	1.02777 (9)	6.78
F3	0.7080 (1)	0.9980 (2)	0.96104 (9)	6.19
F4	0.6824 (1)	0.6934 (2)	0.9785 (1)	6.96
F5	0.8274 (1)	0.9236 (2)	0.90425 (9)	6.43
F6	0.8019 (1)	0.6199 (2)	0.9217 (1)	7.28
O1	1.2160 (2)	1.3119 (2)	0.8002 (1)	7.47
N1	1.1149 (1)	0.8918 (2)	0.8160 (1)	3.26
N2	1.1019 (2)	1.0766 (3)	0.7908 (1)	4.35
N3	1.1978 (2)	1.1442 (3)	0.8125 (1)	4.84
N4	1.3774 (1)	1.0336 (4)	0.8778 (1)	6.53
N5	0.9501 (1)	0.7974 (3)	0.7298 (1)	3.54
N6	1.0251 (1)	0.6607 (2)	0.8570 (1)	3.27
C1	1.2202 (1)	0.8478 (3)	0.8527 (1)	3.34
C2	1.2760 (2)	0.6881 (3)	0.8862 (1)	4.29
C3	1.3829 (2)	0.7108 (4)	0.9153 (2)	6.03
C4	1.4293 (2)	0.8800 (5)	0.9096 (2)	7.73
C5	1.2739 (2)	1.0087 (3)	0.8509 (1)	4.34
C6	1.0267 (1)	0.7800 (3)	0.8002 (1)	2.97
C7	0.9668 (2)	0.8616 (4)	0.6561 (1)	4.71
C8	0.8395 (2)	0.7633 (4)	0.7219 (2)	4.98
C9	1.0714 (2)	0.7042 (4)	0.9435 (1)	4.39
C10	0.9731 (2)	0.4778 (3)	0.8363 (2)	4.71

TABLE 5
SELECTED BOND LENGTHS AND ANGLES FOR HATU

Bond length (Å)

O1-N3	1.259 (3)	N4-C4	1.322 (4)	N6-C9	1.468 (3)
N1-N2	1.387 (2)	N4-C5	1.326 (3)	N6-C10	1.472 (3)
N1-C1	1.382 (2)	N5-C6	1.320 (2)	C1-C2	1.385 (3)
N1-C6	1.383 (3)	N5-C7	1.465 (3)	C1-C5	1.367 (3)
N2-N3	1.311 (3)	N5-C8	1.473 (3)	C2-C3	1.367 (3)
N3-C5	1.406 (3)	N6-C6	1.320 (3)	C3-C4	1.383 (5)

Bond angle (°)

N2-N1-C1	111.3 (2)	C6-N5-C8	121.1 (2)	C2-C3-C4	121.6 (2)
N2-N1-C6	118.8 (2)	C7-N5-C8	115.3 (2)	N4-C4-C3	124.8 (2)
C1-N1-C6	129.8 (2)	C6-N6-C9	122.5 (2)	N3-C5-N4	125.9 (2)
N1-N2-N3	104.7 (2)	C6-N6-C10	121.2 (2)	N3-C5-C1	106.6 (2)
O1-N3-N2	122.2 (2)	C9-N6-C10	116.3 (2)	N4-C5-C1	127.4 (2)
O1-N3-C5	125.9 (2)	N1-C1-C2	135.2 (2)	N1-C6-N5	118.6 (2)
N2-N3-C5	111.8 (2)	N1-C1-C5	105.4 (2)	N1-C6-N6	117.3 (1)
C4-N4-C5	112.4 (2)	C2-C1-C5	119.3 (2)	N5-C6-N6	124.2 (2)
C6-N5-C7	123.5 (2)	C1-C2-C3	114.4 (2)		

Despite the fact that HBTU and HATU are not isomorphous, the molecules crystallize in nearly identical conformations; this is immediately obvious from inspection of Figs. 1 and 2. Their respective torsion angles differ slightly: N2-N1-C6-N5 = 39.7° (HATU); N2-N1-C7-N4 = 47.0° (HBTU) and N2-N1-C6-N6 = −140.9° (HATU); N2-N1-C7-N5 = −132.4° (HBTU). The crystal structures of HBTU and HATU are shown in Figs. 3 and 4, respectively. For HBTU (Fig. 3), the structure consists of infinite stacks of cations; within each stack there are two types of centrosymmetric, head-to-tail 'dimers'. One type of dimeric interaction occurs in the center of the unit
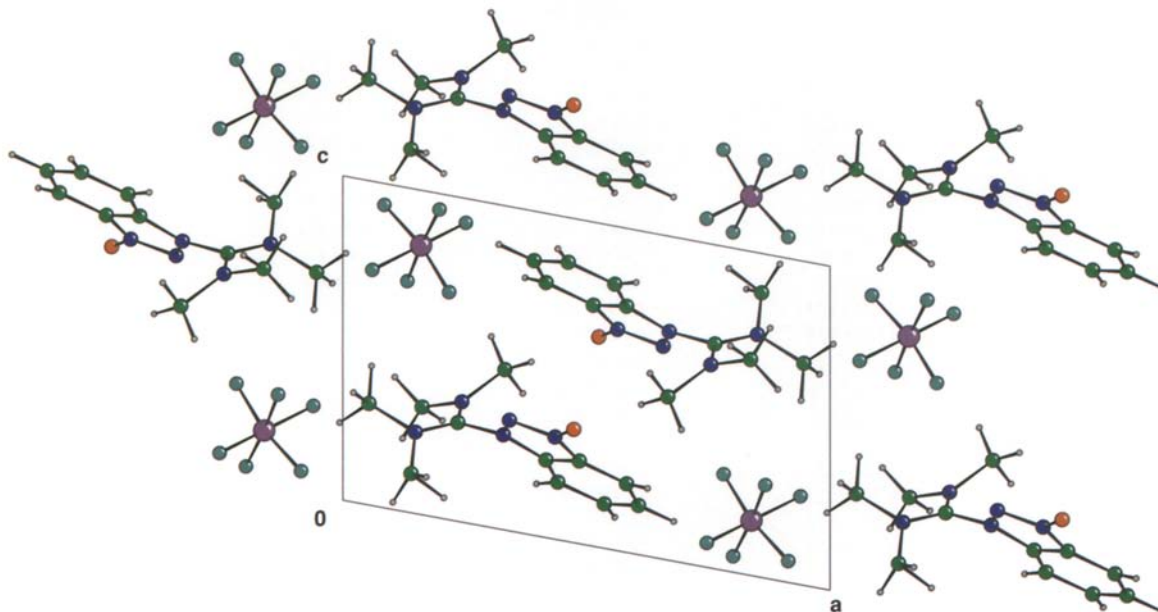

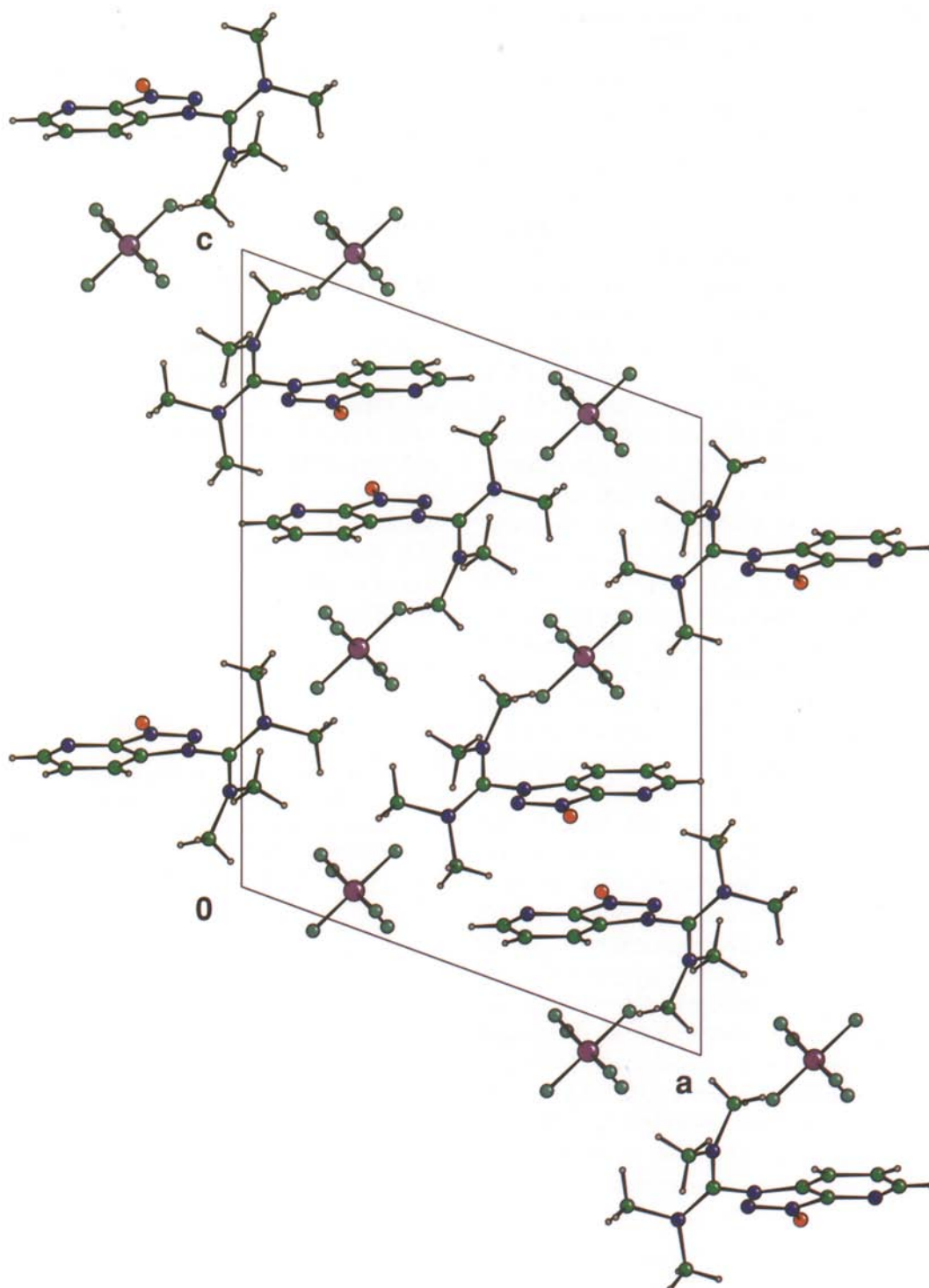Fig. 3. View of the unit cell of HBTU, projected down the crystallographic *b* axis.

Fig. 4. View of the unit cell of HATU, projected down the crystallographic *b* axis.

cell outline in Fig. 3: the triazole rings are overlapped, with a short N3···N3[$-1-x$, $2-y$, $1-z$] contact of 3.32 Å. Above this, the second, weaker dimeric interaction involves overlap of the benzene rings, with the shortest contact being C4···C6[$-1-x$, $2-y$, $2-z$], 3.54 Å. Molecules of HATU are arranged along the cell diagonal, as shown in Fig. 4. However, rather than an infinite stack of dimeric interactions, the cations crystallize as isolated 'dimer pairs'. The pairs are further apart than those in HBTU; the shortest contact between the planar portions of symmetry-related molecules is N3···C2[$5/2-x$, $1/2+y$, $3/2-z$], 3.65 Å. The phenomenon of two nearly isosteric molecules which crystallize in different packing arrangements is likely a reflection of subtle differences in the influence of electrostatic effects and weak hydrogen bonds. In HBTU, there are two probable hydrogen bonds to the oxygen atom, C10-H101···O1[$-1-x$, $2-y$, $1-z$], with C···O = 3.36 Å and C-H···O = 165.4°, and a weaker interaction, C10-H103···O1[x, $y-1$, z], with C···O = 3.58 Å and C-H···O = 168.0°. In HATU, there is a hydrogen bond from C2-H21···O1[x, $y-1$, z] with C···O = 3.06 Å and C-H···O = 132.1°, and a weaker interaction, C7-H72···N4[$5/2-x$, $y-1/2$, $3/2-z$] with C···N = 3.34 Å and C-H···N = 123.3°.

X-ray powder diffraction data indicate that synthetic HATU [3b,4] (from CH_2Cl_2) and HATU recrystallized from acetonitrile have identical powder patterns; these match the powder pattern calculated from the single-crystal data. Synthetic HBTU (Richelieu) and HBTU recrystallized from acetonitrile again have identical powder diffraction patterns which match that of the pattern calculated from the single-crystal data. These data provide compelling evidence that HATU and HBTU are guanidinium N-oxide salts in the solid state. Clearly, recrystallization of these species does not result in a rearrangement.

CONCLUSIONS

In conclusion, the results presented here require a new formulation for the uronium salts used as valuable reagents for peptide synthesis. These experiments strongly suggest that a reexamination of the solution structures of these molecules is in order. Further experiments are underway in our laboratories to search for polymorphs of these and related molecules, and to determine the detailed role that these molecules play in peptide bond formation.

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