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Understanding the Structure/Reactivity of Aminium/Uronium Salts as Coupling Reagents in Peptide Synthesis[1]

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Abstract

Coupling reagents based on onium (aminium/uronium) salts based on HOBt and HOAt are more frequently used in solid-phase peptide synthesis than the classical carbodiimide methods. The structure of the carbon skeleton has a determining role in the efficiency of the reagent for the activation step. Simple theoretical calculations using the AM1 semiempirical Hamiltonian as implemented in the MOPAC program provide a rational way to correlate the reactivity of different aminium/uronium salts with the structure of the carbon skeleton.

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Keywords: AM1 method, amide bond formation, MOPAC, solid-phase peptide synthesis, uronium salts

Peptide coupling methods derived from onium (aminium/uronium and phosphonium) salts based on 1-hydroxybenzotriazole (HOBt)[2] and 1-hydroxy-7-azabenzotriazole (HOAt)[3] are becoming incorporated in synthetic strategies more frequently than the classical carbodiimide methods.[4]

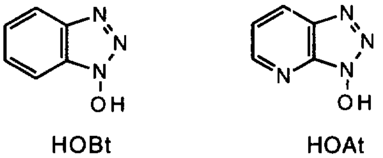

Figure 1. Structures of additives HOBt and HOAt

In a recent study, we have correlated the reactivity of various onium salts derived from HOXt (X=A,B), with the structure of the reagents in question.[5] Thus, we have confirmed that the aza derivatives are more reactive than the parent benzotriazole derivatives in both activation and coupling. Furthermore, the structure of the carbon skeleton has a determining role in the efficiency of the reagent for the activation step. Thus, pyrrolidino derivatives

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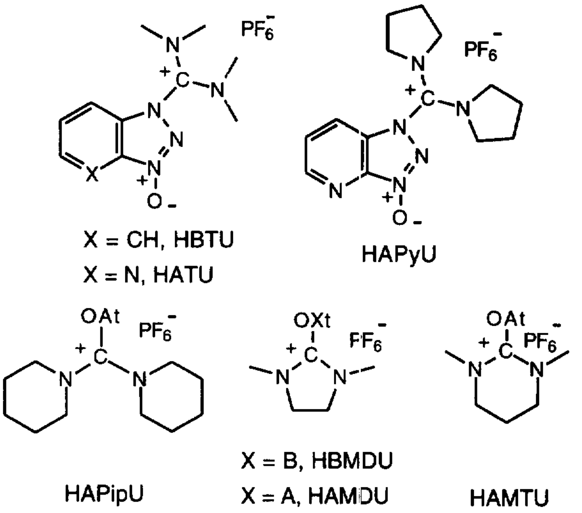
(HAPyU) appear to be reagents of choice relative to the piperidino (HAPipU) analogs or those derived from trialkylamines (HATU), being both dihydroimidazole derivatives (HAMDU and HBMDU), and HAMTU practically inefficient. These three reagents are clearly unstable in DMF in the presence of base (DIEA) and they decompose before achieving the activation of the carboxylic acid.



X = CH, HBTU
X = N, HATU

HAPyU

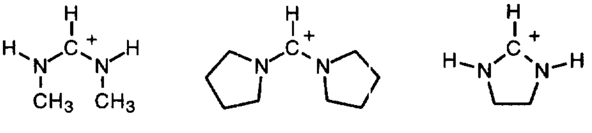
HAPipU

X = B, HBMDU
X = A, HAMDU

HAMTU

Figure 2. Structures of reagents used in this study[6]

In order to explain qualitatively the behavior of the activated species considered above towards nucleophiles, some theoretical calculations were carried out using the AM1 semi-empirical Hamiltonian[7],[8] for gas phase reactions as implemented in the MOPAC program.[9] Due to the large dimensions of the molecules studied, the calculations were carried out on simplified systems corresponding to HXTU, HXPyU, and HXMDU which are shown in Figure 3. The reaction studied was the addition of water to the three carbocation models to give the corresponding alcohol and a proton.



HXTUm HXPyUm HXMDUm

Figure 3. Structures of the models used for the theoretical calculations ("m" signifies model)

The AM1 model for the three cation patterns, HXTUm, HXPyUm and HXMDUm, gave planar geometrical structures. The analysis of the wave function for these three molecules revealed that the lone electron pairs associated with each nitrogen atom were delocalized within the atoms N-C-N, giving an allyl radical anion character to these three molecules.

In the reaction of a water molecule with these three cation patterns in the gas phase, the corresponding transition state structures are presented in Figure 4. The calculated energy barriers were 102.8 kcal mol^{-1} for HXTUm, 56.9 kcal mol^{-1} for HXPyUm, and 44.0 kcal mol^{-1} for HXMDUm. These calculations are consistent with the experimental results presented above. What is the reason for these discrepancies in the energy barriers? For the HXMDUm case in the transition state, both amino groups present strong pyramidalization (126° and 127°); whereas for HXTUm case at the transition state, one amino function has a pyramidalization of 138°, whereas the other was almost planar (178°). For the HXTUm and due to this planarization, the electrons of the two nitrogen atoms of these amino functions were delocalized between the nitrogen atoms and the carbocation. Consequently, the cabocation, which is at the center of the reaction, contains some important electron density which impedes nucleophilic attack. For the HXMDUm transition state, due to the strong pyramidalization of both amino functions the two lone electron pairs are localized on each nitrogen atom, and the carbocation comprises a very small electron density allowing rapid nucleophilic attack at this position. HXPyUm stands between the two above models since both amino functions present in the transition state give a pyramidalization of 123° and 135°. As seen in Fig. 4, this transition state is much closer to that of HXMDUm than to the HXTUm transition state. This explains that energy barriers of HXMDU and HXPyU are quite close.

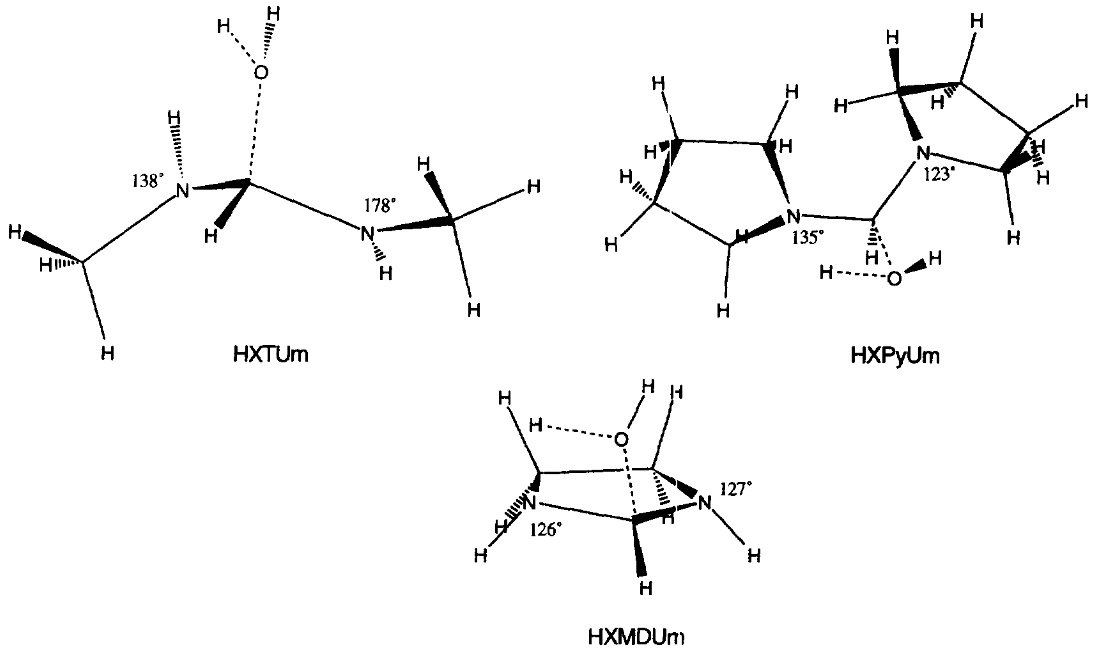


Figure 4. Transition state structures for the reaction of water with model onium-type molecules in the gas phase (numbers signify pyramidalization angles)

In conclusion, the reactivity of aminium/uronium salts is governed by two opposing effects namely: π-electron delocalization between the N–C–N atoms and the strain within the carbon skeleton. Nucleophilic attack will be disfavoured by increasing π-electron delocalization. On the other hand if the optimal disposition of the carbon skeleton causes a reduction in this electronic delocalization, then nucleophilic attack will be favoured.

The use of theoretical methods has provided a reasonable explanation for the experimental results. In the future, a combination of both theoretical and experimental methods should lead to the rational design of more effective reagents.[10]

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References and notes

[1] Abbreviations used for amino acids and the designations of peptides follow the rules of the IUPAC-IUB Commission of Biochemical Nomenclature in *J. Biol. Chem.* **1972**, *247*, 977-983. The following additional abbreviations are used: DIEA, *N,N*-diisopropylethylamine; DMF, *N,N*-dimethylformamide; HAMDU, *O*-(7-azabenzotriazol-1-yl)-1,3-dimethyleneuronium hexafluorophosphate; HAMTU, *O*-(7-azabenzotriazol-1-yl)-1,3-trimethyleneuronium hexafluorophosphate; HAPipU; *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate; HAPyU, 1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene) pyrrolidinium hexafluorophosphate *N*-oxide; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-yl-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; HBMDU, *O*-(benzotriazol-1-yl)-1,3-dimethyleneuronium hexafluorophosphate; HOAt, 7-aza-1-hydroxybenzotriazole (3-hydroxy-3*H*-1,2,3-triazolo-[4,5-*b*]pyridine]; HOBt, 1-hydroxybenzotriazole.

[2] König, W., Geiger, R. *Chem. Ber.* **1970**, *103*, 788-798.

[3] Carpino, L.A. *J. Am. Chem. Soc.* **1993**, *115*, 4397-4398.

[4] (a) Albericio, F., Carpino, L.A. In *Methods in Enzymology, Solid-Phase Peptide Synthesis* (Fields, G.B., ed), Academic Press, Orlando (FL), **1997**, *289*, 104-126. (b) Humphrey, J.M., Chamberlin, A.R. *Chem. Rev.* **1997**, *97*, 2243-2266.

[5] Albericio, F., Bofill, J.M., El-Faham, A., Kates, S.A. *J. Org. Chem.* **1998**, *63*, 9678-9683.

[6] X-ray analysis has shown that HATU, HBTU, and HAPyU crystallize in the form of the aminium salts; see: (a) Abdelmoty, I., Albericio, F., Carpino, L. A., Foxman, B. M. , Kates, S. A. *Lett. Pept. Sci.* **1994**, *1*, 52-67; (b) Henklein, P., Costisella, B., Wray, V., Domke, T., Carpino, L. A., El-Faham, A., Kates, S. A., Abdelmoty, A., Foxman, B. M. In *Peptides 1996. Proceedings of the 24th European Peptide Symposium* (Ramage R. & Epton, R. eds.), Mayflower Worldwide Ltd, Birmingham, pp. 465 - 466, 1997. For those compounds for which X-ray data have not yet been obtained, generic structural representations are shown. For these reagents, traditional nomenclature has arbitrarily been retained.

[7] Dewar, M.J.S., Zoebisch, E.G., Healy, E.F. , Stewart, J.J.P. *J. Am. Chem. Soc.* **1985**, *107*, 3902 - 3909.

[8] It has been showed that this Hamiltonian is appropiate for this type of systems. See ref. 7 and Fabian, WMF. *Z. Naturforsch., A: Phys. Sci.* **1990**, *45*, 1328-1334.

[9] (a) Stewart, J.J.P. *QCPE Bull.* **1983**, *3*, p. 101; (b) Olivella, S. *QCPE Bull.* **1984**, *4*, p. 109.

[10] For an elegant example of the combination of both theoretical and experimental methods in the development of chemical methods for the synthesis of oligodeoxyribonucleotides, see Wada, T., Sato, Y., Honda, F., Kawahara, S., Sekine, M. *J. Am. Chem. Soc.* **1997**, *119*, 12710 - 12721.