2-Pyridone and 3-oxo-1,2,6-thiadiazine-1,1-dioxide derivatives: a new class of hydrogen bond equivalents of uracil

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Summary

Hydrogen bond complex stability between adenine (A) and hydrogen bond equivalents of uracil: 2-pyridone derivatives (U_{X2O}^X) and 3-oxo-1,2,6-thiadiazine-1,1-dioxide derivatives (U_{SO2}^X) was studied, and as the result, the hydrogen bond energy of U_{X2O}^X-A and a complex of UX_{SO2}^X-A, was about 1.5 kcal/mol more stable than that of the corresponding adenine-uracil derivatives complex, respectively. The energy difference between the imide tautomer and enol tautomer was smaller than those of uracil derivatives. U_{SO2}^F can form a stable complex with A, and its imide tautomer is stable.

Introduction

The Watson–Crick type base pair formation is fundamental for the molecular recognition of nucleic acid [1]: the processes of transcription from DNA to mRNA [2], and of translation from mRNA to protein *via* tRNA [3] are based on the formation of the Watson-Crick type base pairs. Watson-Crick type base pair formation has attracted widespread attention *i. e.*, it has been applied to construction of artificial supermolecular systems [4–9], to template synthesis [10], and to antisense technology [11–13]. These applications are based on the selective hydrogen bond formation of nucleic acid bases, so a molecule which is able to selectively form a stable complex is needed. As is well-known, the adenine (A)-uracil (U)/thymine (T) base pair is less stable than the guanine (G)-cytosine (C) base pair; thus, hydrogen bond equivalents of U/T are highly demanded for the applications described above.

We report herein a molecular design of a hydrogen bond equivalent of uracil, and computational evaluation of the equivalents.

Jorgensen *et al.* proposed secondary interactions in multiply hydrogen-bonded complexes [14, 15]. In the A-U base pair, the *exo*-cyclic oxygen atom at the 2-position in U does not form a hydrogen bond, but Jorgensen's proposal suggests that the electrostatic interaction between this oxygen atom reduces the total stability of the A-U base pair (Figure 1). It is expected that the stability of the complex should be improved by removing the 2-position oxygen. To remove the oxygen, the 1-position nitrogen in U must be substituted to carbon, because the backbone structure (ribose in RNA, for example) should be bound at the position. As a result, 2-pyridone derivatives (U_{X2O}^X, Figure 1) are expected to be a potent hydrogen bond equivalent of uracil.

On the other hand, we have already reported *ab initio* molecular orbital study on the substitution effect on hydrogen bond energies for base pair formation between nucleic acid base analogues [16–20]. The results of our previous report show the stability of the base pair is sensitive to the substitutions on the bases, and in the case of uracil derivatives (U^X) [16, 20], U^X possessing a stronger electron-withdrawing group (EWG) forms a more stable base pair. Based on the results, the carbonyl group on the 2-position of uracil can be substituted by a more electron-withdrawing sulfonyl group. Accordingly, 3-oxo-1,2,6-thiadiazine-1,1-dioxide derivatives (U_{SO2}^X, Figure 1) are also ex-

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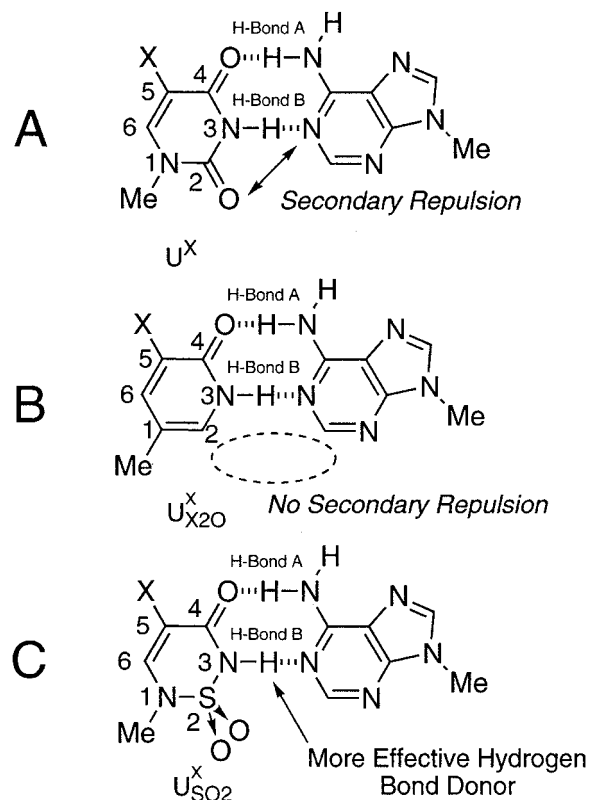E-mail: t-uchimaru@aist.go.jp

Figure 1. Hydrogen bond formation of uracil (U), 2-Pyridone (U_{X2O}) and 3-oxo-1,2,6-thiadiazine-1,1-dioxede (U_{SO2}) derivatives with adenine (A).

Figure 2. ΔE^{HB} (kcal/mol) of each U^X, U^X_{X2O} and U^X_{SO2}. *: See Ref.27-29.

pected to be a potent hydrogen bond equivalent of uracil.

Hereafter, we refer to the position numbers of these heterocycles as the corresponding uracil position numbers (Figure 1), not the IUPAC position numbers. Additionally, the substitution effect on the hydrogen bond stability of the 'base pair' complex between A and these uracil equivalents was evaluated.

Methods

In most theoretical studies, the hydrogen bond energies of the Watson–Crick type base pairs were evaluated at the second-order Møller–Plesset (MP2) [21] level of theory using double-ζ basis sets with polarization [22]. We already reported an *ab initio* study regarding the basis set effect on the calculated hydrogen bond energies of the Watson-Crick type base pairs at the MP2 levels of theory [23]. The values of hydrogen bond energies of the A–U and G–C base pairs, evaluated at the computational levels of MP2/6-
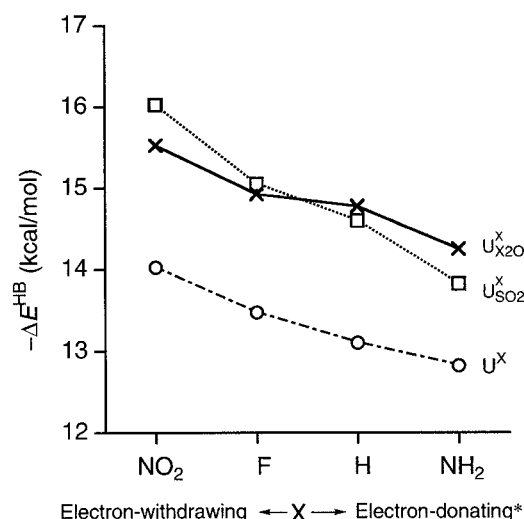
31+G(2d′,p′) [24] //HF/6-31G(d,p) (−13.16 kcal/mol for the A–U base pair and −26.08 kcal/mol for the G–C base pair), were in excellent agreement with the values calculated at MP2/6-311++G(3df,p)//HF/6-311++G(3d,p) (−13.48 kcal/mol for the A–U base pair and −26.58 kcal/mol for the G–C base pair). Thus, in the present work, a basis set effect was evaluated using MP2/6-31+G(2d′,p′)//HF/6-31G(d,p) level calculations. The basis set superposition error (BSSE) for hydrogen bond energies was corrected by using the counterpoise method [25]. We refer to the molecular interaction energy with BSSE correction as ΔE^{HB}. $\Delta\Delta E$ was defined as the substitution effect on ΔE^{HB} comparing the U–A base pair. C_s symmetry was assumed except for U^X_{SO2} and U^X_{SO2}–A. All theoretical calculations were carried out using the GAUSSIAN 98 program [26].

Results and discussion

In the present work, hydrogen bond stability and substitution effect on the stability of four U^X_{X2O} and U^X_{SO2} were studied, and compared to those of the corresponding U^X. Table 1 shows the results of theoretically estimated ΔE^{HB} and ΔE (kcal/mol) of each U^X, U^X_{X2O} and U^X_{SO2}. As expected, ΔE^{HB} of U^X_{X2O} was about 1.5 more negative than that of the corresponding U^X. Improvement of the complex stability by deletion of the *exo*-cyclic oxygen atom on the 2-position in U should be mainly considered as the effect of canceling

Table 1. ΔE^{HB}, BSSE and $\Delta\delta E$ (kcal/mol) of each U^X, U_{X2O}^X and U_{SO2}^X (MP2/6-31+G(2d$'$,p$'$)//HF/6-31G(d,p) level of theory).

X	U_{X2O}^X			U_{SO2}^X			U^X		
	ΔE^{HB}	BSSE	$\Delta\Delta E$	ΔE^{HB}	BSSE	$\Delta\Delta E$	ΔE^{HB}	BSSE	$\Delta\Delta E$
NO$_2$	−15.5	2.2	−2.4	−16.0	3.0	−2.9	−14.0	2.4	−0.9
F	−14.9	2.1	−1.8	−15.1	2.8	−1.9	-13.5	2.2	−0.4
H	−14.8	2.0	−1.7	−14.6	2.7	−1.5	-13.1	2.1	–
NH$_2$	−14.3	2.0	−1.1	−13.8	2.7	−0.7	-12.8	2.2	+0.3
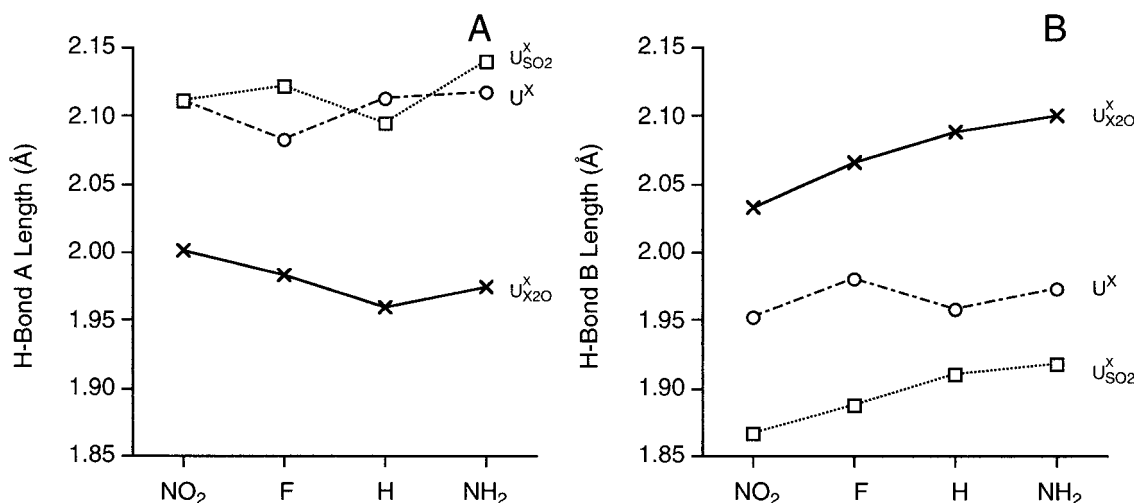
Figure 3. Hydrogen bond length of U^X, U_{X2O}^X and U_{SO2}^X.

the electrostatic repulsion of the 2-position oxygen in U and the 1-position nitrogen in A.

It is considered that deletion of the *exo*-cyclic oxygen atom on the 2-position in U enriches the electron density of the heterocyles: H-Bond A should be enforced and H-Bond B should be weakened. Thus, the importance of H-Bond A should be larger in the U_{X2O}^X–A base pair than in the corresponding U^X–A base pair. This corresponds to the smaller range of the ΔE^{HB} depending on the 5-position substitution of the U_{X2O}^X–A base pair than that of the U^X–A base pair (Figure 2). Table 2 shows the hydrogen bond length (Å) and atomic charges (e) of ^4O and ^3H in the Mulliken, CHelpG [30] and NPA [31] methods. H-Bond A length of the U_{X2O}^X–A base pair was shorter than that of the U^X–A base pair and the U_{SO2}^X–A base pair, while H-Bond B length of the U_{X2O}^X–A base pair was longer than that of the U^X–A base pair and the U_{SO2}^X–A base pair (Figure 3) [32]. A relationship was noted between the atomic charge and the substitution

group in the Mulliken and NPA methods, but not in the ChelpG method. Figure 4 shows the change in the atomic charge depending on the substitution group in the Mulliken method. U_{X2O}^X has a more negative charge in ^4O, and a less positive charge in ^3H comparing the other two heterocyclic groups. The atomic charge in ^4O became less negative by introduction of EWG, and the atomic charge in ^3H became more positive by introduction of EWG. Nevertheless, U_{X2O}^X possessing stronger EWG on the 5-position formed a more stable base pair with A, the same as the substitution effect in U^X, and U_{X2O}^X possessing an EDG on the 5-position forms a less stable base pair with A. Thus, H-Bond B is more important than H-Bond A in the U_{X2O}^X–A base pair, the same as in the U^X–A base pair.

ΔE^{HB} of the U_{SO2}^X–A base pair was about 1.5 kcal/mol more negative than that of the corresponding U^X–A base pair. H-Bond A length of the U_{SO2}^X–A base pair was longer than that of the U_{X2O}^X–A base pair, and almost the same as that of the U^X–A
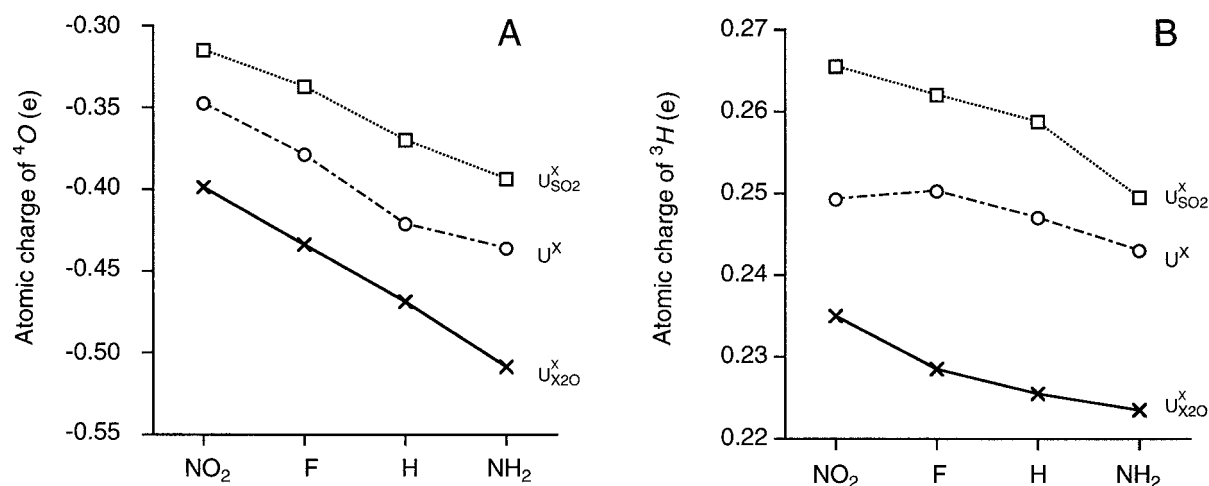
Figure 4. Atomic charges (e) of ^4O and ^3H in the Mulliken method at the level of HF/6-31+G(2d′,p′)//HF/6-31G(d,p) calculation.
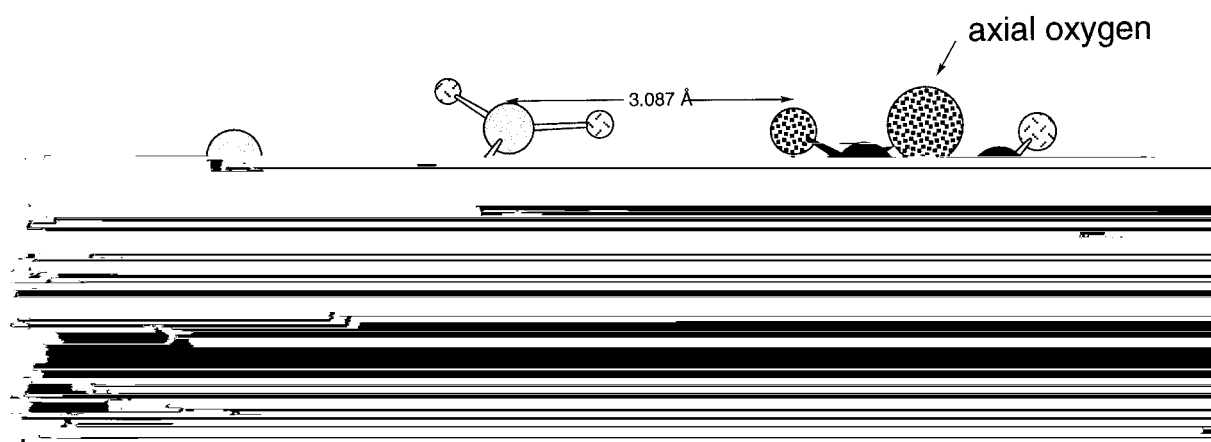

Figure 5. HF/6-31G(d,p) Optimized structure of U_{SO2}–A base pair.

base pair. H-Bond B length of the U_{SO2}^X–A base pair was shorter than that of the U^X–A base pair and the U_{X2O}^X–A base pair (Figure 3). U_{SO2}^X has a less negative charge in ^4O, and a more positive charge in ^3H compared with the other two heterocyclic groups (Figure 4). The atomic charge in ^4O became less negative by introduction of EWG, and the atomic charge in ^3H became more positive by introduction of EWG. In the case of the U_{SO2}^X–A base pair, the importance of H-Bond B should be larger than that of U^X–A and U_{X2O}^X–A. Therefore, the range of the ΔE^{HB} depending on the 5-position substitution of the U_{SO2}^X–A base pair was larger than that of the U^X–A base pair and U_{X2O}^X–A base pair. ΔE^{HB} of the U_{SO2}^{NO2}–A base pair was the most negative in the present study.

Figure 5 shows the optimized structure of U_{SO2}–A base pair. One of the oxygen atoms of the sulfonyl group is located in almost the same plane of the hydrogen bond formation. Considering the fact that secondary interaction between the sulfonyl oxygen and the 1-position nitrogen of adenine should occur, however, the effect of enforcing the acidity of the 3-position proton overcomes the effect of the secondary interaction. The other oxygen atom of the sulfonyl group arises axial from the plane.

Tautomerism of these hydrogen bond equivalents should be considered to achieve highly selective molecular recognition (Figure 6), because the enol tautomer (Figure 6B) is the hydrogen bond equivalent of cytosine [33]. Table 3 shows the energy difference between the tautomers. Positive value shows that the imide tautomer is stable. We already reported that the imide tautomer (Figure 6A) is much more stable (over 10 kcal/mol) in both gas-phase and the aqueous-phase,

Table 2. Hydrogen bond length (Å) and atomic charges (e) of ^4O and ^3H in three methods using 6-31+G(2d',p') basis set (HF density was used for Mulliken method and MP2 density was used for CHelpG and NPA methods).

	X	U_{X2O}^X				U_{SO2}^X				U^X			
		Length	Mulliken	ChelpG	NPA	Length	Mulliken	ChelpG	NPA	Length	Mulliken	ChelpG	NPA
^4O or H-Bond A	NO2	2.001	−0.49	−0.54	−0.50	2.110	−0.32	−0.40	−0.35	2.111	−0.50	−0.56	−0.52
	F	1.983	−0.53	−0.57	−0.53	2.121	−0.34	−0.43	−0.38	2.082	−0.52	−0.59	−0.54
	H	1.959	−0.58	−0.63	−0.59	2.095	−0.37	−0.47	−0.42	2.113	−0.54	−0.61	−0.57
	NH2	1.974	−0.54	−0.61	−0.55	2.140	−0.39	−0.51	−0.44	2.116	−0.55	−0.64	−0.58
^3H or H-Bond B	NO2	2.033	0.44	0.34	0.38	1.867	0.27	0.24	0.25	1.952	0.48	0.46	0.46
	F	2.066	0.46	0.34	0.40	1.887	0.26	0.23	0.25	1.981	0.43	0.45	0.46
	H	2.088	0.44	0.33	0.37	1.910	0.26	0.23	0.25	1.958	0.47	0.45	0.46
	NH2	2.101	0.37	0.34	0.39	1.918	0.25	0.22	0.24	1.973	0.47	0.45	0.46

A: Imide tautomers   B: Enol tautomer

U^X

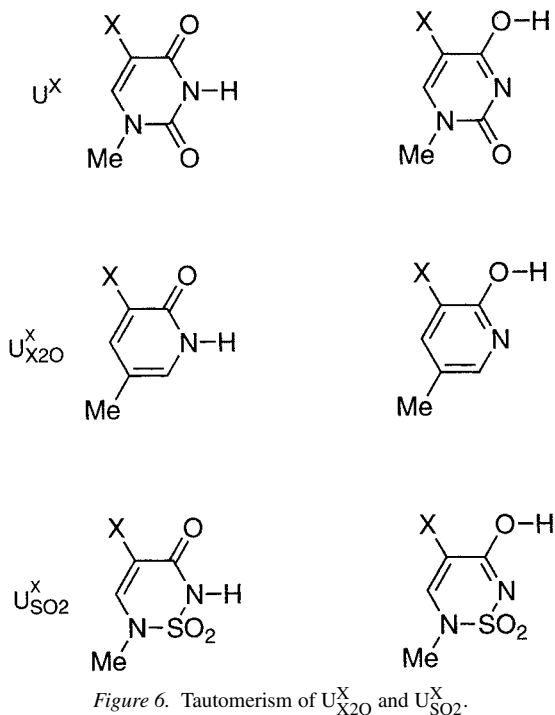U_{X2O}^X

U_{SO2}^X

Figure 6. Tautomerism of U_{X2O}^X and U_{SO2}^X.

Table 3. Energy difference between the tautomers (kcal/mol).

X	U_{X2O}^X	U_{SO2}^X
NO2	−3.4	−1.0
F	−2.8	+1.5
H	−3.1	−0.1
NH2	+0.3	+4.7

in the case of U^X [34]. Unexpectedly, in almost all derivatives, except U_{SO2}^F, U_{SO2}^{NH2}, and U_{X2O}^{NH2}, the enol tautomer of the derivatives was more stable or equally stable in the gas-phase. Thus, it is important to evaluate not only the stability of the hydrogen bond but also the equilibrium of the tautomers, when we change the heterocyclic system. Our calculation suggests that imide tautomer of is U_{SO2}^F stable. From the result of the energy difference of the tautomers, the imide/enol ratio should be about 12/1, for the U_{SO2}^F. U_{SO2}^F can form a stable complex with A. Thus, our present study suggests that U_{SO2}^F is the most promising hydrogen bond equivalent of uracil. Recently, Lan *et al.* reported that duplex stability of the DNA, which contains U_{X2O}^{Me} instead of T, was decreased compared with normal

DNA-duplex stability [35, 36]. They concluded that the reason for the decrease of the stability should be the removal of the minor groove hydration in U_{X2O}^{Me} containing the DNA-duplex, by deletion of the 2-position oxygen, which locates on the minor groove of the DNA-duplex. The duplex stability is dependent not only on the base pair hydrogen bond stability but also other various factors, *e.g.*, minor groove hydration, stacking of the bases, conformation of the sugars, *etc*. However, if the structure of the backbone is drastically altered, *e.g.*, in PNA [37–39], hydrogen bond stability of U_{X2O} and U_{SO2} derivatives can be expected.

Conclusion

The hydrogen bond complexes U_{X2O}^{X}–A and U_{SO2}^{X}–A were both more stable than the hydrogen bond complexes between uracil derivatives and adenine. The imide tautomer of U_{SO2}^{F} is more stable than the enol tautomer of U_{SO2}^{F}. Thus, U_{SO2}^{F} is a potent hydrogen bond equivalent of uracil.

Acknowledgments

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