

A New Quadruple Hydrogen-Bonding Module Based on Five-Membered Heterocyclic Urea Structure

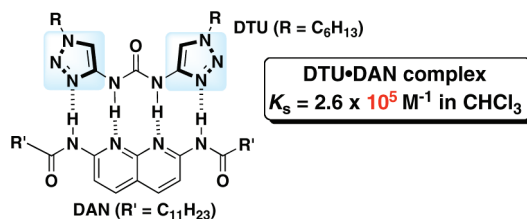
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ABSTRACT



N,N'-Di-4-triazolylurea (DTU) has developed as a new ADDA module and DTU forms a stable ADDA•DAAD heterocomplex with 2,7-diamido-1,8-naphthyridine (DAN) ($K_s = 2.6 \times 10^5 \text{ M}^{-1}$ in CHCl_3). The K_s value of the complex between DTU and DAN is 100-fold greater than that of the complex between *N,N'*-di-2-pyridylurea and DAN due to replacement of a pyridine ring with a 1,2,3-triazole ring.

Supramolecular architectures obtained by quadruple hydrogen-bonding modules with linear arrays have become an important research topic in supramolecular chemistry such as supramolecular polymers, nanofibers, and stimuli-responsive assemblies.¹ Among these quadruple hydrogen-bonded systems,¹ highly stable heterocomplexes with high selectivity can offer diversity and great potential in this field.^{2,3}

Zimmerman reported ADDA (A = hydrogen-bond acceptor, D = hydrogen-bond donor) modules inspired by a nucleobase. Ureidoguanine (UG)^{2a,b} and 7-deazaguanine urea (DeUG)^{2c,d} form highly stable ADDA•DAAD heterocomplexes with 2,7-diamido-1,8-naphthyridine (DAN)⁴ as the complementary DAAD module ($K_s > 10^7 \text{ M}^{-1}$ in CDCl_3), and exhibit weak self-association (K_{dim} for UG $\approx 2.3 \times 10^2 \text{ M}^{-1}$ and K_{dim} for DeUG $= 8.8 \times 10^2 \text{ M}^{-1}$ in CDCl_3).⁵ Their conformers with ADDA arrays can be well-preorganized with the use of an intramolecular hydrogen bond,⁶ and other unfavorable conformers and tautomers are disfavored. The

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(1) For reviews, see: (a) Zimmerman, S. C.; Corbin, P. S. *Struct. Bonding (Berlin)* **2000**, 96, 63. (b) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5. (c) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, 101, 4071. (d) Wilson, A. J. *Soft Matter* **2007**, 3, 409. (e) Dankers, P. Y. W.; Meijer, E. W. *Bull. Chem. Soc. Jpn.* **2007**, 80, 2047. (f) de Greef, T. F. A.; Meijer, E. W. *Nature* **2008**, 453, 171. (g) de Greef, T. F. A.; Smulders, M. M. J.; Wolfs, M.; Schenning, A. P. H. J.; Sijbesma, R. P.; Meijer, E. W. *Chem. Rev.* **2009**, 109, 5687. (h) Lee, C. C.; Grenier, C.; Meijer, E. W.; Schenning, A. P. H. J. *Chem. Soc. Rev.* **2009**, 38, 671.

(2) (a) Park, T.; Zimmerman, S. C.; Nakashima, S. *J. Am. Chem. Soc.* **2005**, 127, 6520. (b) Park, T.; Todd, E. M.; Nakashima, S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2005**, 127, 18133. (c) Ong, H. C.; Zimmerman, S. C. *Org. Lett.* **2006**, 8, 1589. (d) Kuykendall, D. W.; Anderson, C. A.; Zimmerman, S. C. *Org. Lett.* **2009**, 11, 61.

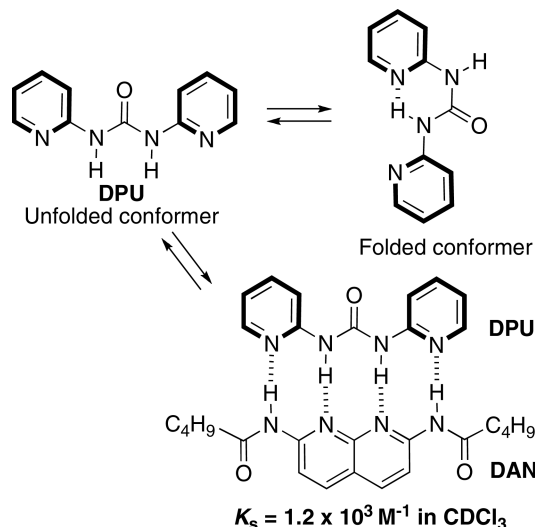
(3) With regard to application to a supramolecular polymer, it has been suggested that the ideal association constant for useful degrees of polymerization is comparable to or greater than $\sim 10^5 \text{ M}^{-1}$ in CHCl_3 .^{1d–g}

(4) (a) Ligthart, G. B. W. L.; Ohkawa, H.; Sijbesma, R. P.; Meijer, E. W. *J. Org. Chem.* **2006**, 71, 375. (b) Todd, E. M.; Quinn, J. R.; Park, T.; Zimmerman, S. C. *Isr. J. Chem.* **2005**, 45, 381.

(5) While ureidopyrimidinone (UPy) and deazapterin (DeAP) can provide ADDA arrays and form highly stable heterocomplexes with DAN ($K_s > 10^7 \text{ M}^{-1}$), these systems compete with highly stable self-associated dimers with DDAA arrays ($K_{\text{dim}} > 10^7 \text{ M}^{-1}$), see: (a) Ligthart, G. B. W. L.; Ohkawa, H.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2005**, 127, 810. (b) de Greef, T. F. A.; Ercolani, G.; Ligthart, G. B. W. L.; Meijer, E. W.; Sijbesma, R. P. *J. Am. Chem. Soc.* **2008**, 130, 13755. (c) de Greef, T. F. A.; Ligthart, G. B. W. L.; Lutz, M.; Spek, A. L.; Meijer, E. W.; Sijbesma, R. P. *J. Am. Chem. Soc.* **2008**, 130, 5479. (d) Wang, X.-Z.; Li, X.-Q.; Shao, X.-Q.; Zhao, X.; Deng, P.; Jiang, X.-K.; Li, Z.-T.; Chen, Y.-Q. *Chem.—Eur. J.* **2003**, 9, 2904. (e) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, 120, 9710.

utility of the **UG•DAN** complex has been demonstrated in supramolecular block copolymers and supramolecular polymer blends.⁷

Scheme 1



As another type of ADDA module, *N,N'*-di-2-pyridylurea (**DPU**) has been studied in detail (Scheme 1).⁸ Unfortunately, the K_s value of **DPU** with **DAN** ($K_s = 1.2 \times 10^3 \text{ M}^{-1}$ in CDCl_3) is much lower than the predicted value since **DPU** prefers to form a folded conformer, which is stabilized by intramolecular hydrogen-bonding.^{8,9} Therefore, the intramolecular hydrogen-bonding of **DPU** in the folded conformer must be broken prior to the complexation with **DAN**.

We have been interested in development of quadruple hydrogen-bonding modules based on five-membered heterocyclic urea structures because these have a clear advantage over 2-pyridylurea structures in regard to providing linear multiple hydrogen-bonding arrays.¹⁰ We considered that six-membered heterocyclic ureas such as 2-pyridylurea structures would be destabilized as a result of steric repulsion due to the shorter distance between 3-H in the pyridine ring and the oxygen on the urea carbonyl substitute. Thus, their conformational equilibrium was biased toward the folded conformer that was stabilized by the intramolecular hydrogen-bonding. In contrast, some five-membered heterocyclic ureas,

(6) A hydrazide-based ADDA module reported by Li is also well-preorganized with the use of intramolecular hydrogen-bonding and exhibits highly stable ADDA•DAAD heterocomplexes with **DAN** ($K_s = 6.0 \times 10^5 \text{ M}^{-1}$ in CDCl_3) and weak self-association ($K_{\text{dim}} = 5.5 \times 10^1 \text{ M}^{-1}$ in CDCl_3), see: Zhao, X.; Wang, X.-Z.; Jiang, X.-K.; Chen, Y.-Q.; Li, Z.-T.; Chen, G.-J. *J. Am. Chem. Soc.* **2003**, *125*, 15128.

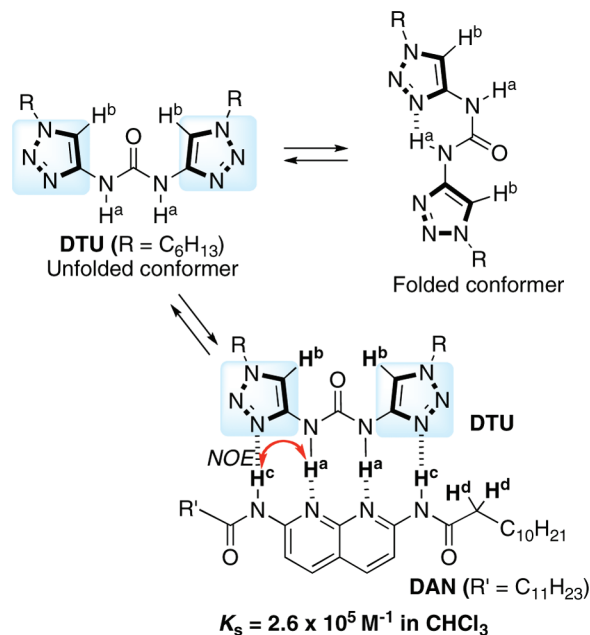
(7) (a) Park, T.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2006**, *128*, 13986. (b) Park, T.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2006**, *128*, 14236. (c) Park, T.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2006**, *128*, 11582.

(8) (a) Corbin, P. S.; Zimmerman, S. C.; Thiessen, P. A.; Hawryluk, N. A.; Murray, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 10475. (b) Singha, N. C.; Sathyanarayana, D. N. *J. Chem. Soc., Perkin Trans. 2* **1997**, 157. (c) Luning, U.; Kühl, C.; Uphoff, A. *Eur. J. Org. Chem.* **2002**, 4063. (d) Sudha, L. V.; Sathyanarayana, D. N. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1647.

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(10) Hisamatsu, Y.; Fukumi, Y.; Shirai, N.; Ikeda, S.; Odashima, K. *Tetrahedron Lett.* **2008**, *49*, 2005.

Scheme 2



such as 4-oxazolylurea derivatives, were capable of forming unfolded conformers, since the unfavorable interactions in six-membered heterocyclic ureas are reduced in five-membered heterocyclic ureas.¹⁰ Recently, we applied our concept to development of a new DDAA module, ureidoimidazo[1,2-a]pyrimidine (**Uimp**).¹¹ This module forms a highly stable homodimer ($K_{\text{dim}} > 1.1 \times 10^5 \text{ M}^{-1}$ in CDCl_3) without competition from undesired hydrogen-bonded dimers.

In this paper, we report *N,N'*-di-4-triazolylurea (**DTU**) as a new ADDA module based on a five-membered heterocyclic urea structure (Scheme 2). The 1,2,3-triazole ring system in **DTU** is easily synthesized via the Huisgen 1,3-dipolar cycloaddition, which is known as the click reaction.¹² To the best of our knowledge, **DTU** is the first example of an ADDA module that forms a highly stable heterocomplex with **DAN** ($K_s = 2.6 \times 10^5 \text{ M}^{-1}$ in CHCl_3) without preorganization of its conformation by intramolecular hydrogen-bonding. The K_s value of **DTU•DAN** complex is 100-fold greater than that of **DPU•DAN** complex due to replacement of the pyridine ring with the 1,2,3-triazole ring.

DTU was easily synthesized in four steps from commercially available reagents (Scheme 3). Triazole **1** was prepared in a one-pot synthesis via the Huisgen 1,3-dipolar cycloaddition from 1-hexylbromide in 92% yield,¹³ and hydrolysis to give acid **2** in 89% yield. **DTU** was then prepared from **2** via the Curtius rearrangement with diphenylphosphoryl azide (DPPA) in 60% yield.¹⁴

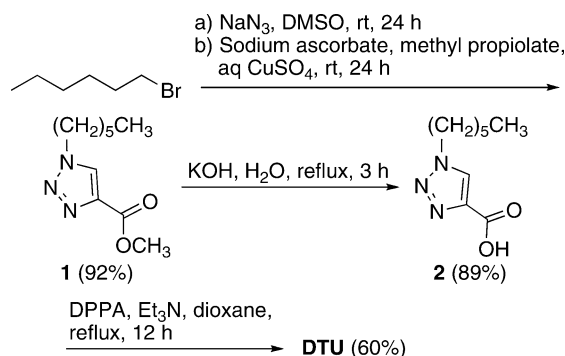
(11) Hisamatsu, Y.; Shirai, N.; Ikeda, S.; Odashima, K. *Org. Lett.* **2009**, *11*, 4342.

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Scheme 3. Synthesis of DTU



First, the self-association of **DTU** was investigated by ^1H NMR. In a dilution study of **DTU** in CDCl_3 from 45 mM to 0.40 mM, NH^a and CH^b proton signals were shifted upfield, respectively. This indicated the self-association of **DTU** in CDCl_3 by intermolecular hydrogen bonds involving NH^a protons. The change in the chemical shift ($\Delta\delta$) of NH^a between 45 mM and 1.0 mM was 0.72 ppm, and the NH^a broadened below 1.0 mM. The change in the chemical shift ($\Delta\delta$) of CH^b from 45 mM to 0.40 mM was 0.13 ppm and the K_{dim} value was determined to be $(7.1 \pm 0.6) \times 10^2 \text{ M}^{-1}$ by the nonlinear least-squares curve-fitting method.^{15,16} When the CDCl_3 solution of **DTU** (10 mM) was cooled from 25 to -50°C , both NH^a ($\Delta\delta = 0.76$ ppm) and CH^b ($\Delta\delta = 0.10$ ppm) proton signals showed downfield shifts that were consistent with self-association. Furthermore, the splitting of NH^a and CH^b proton signals, which indicated the folded conformer,^{8a,10} was not observed. Similar variable-temperature ^1H NMR spectra were obtained in a dilute concentration of **DTU** (0.80 mM). On the other hand, the major conformer of **DPU** is the folded one.⁸ Indeed, in the ^1H NMR spectra of **DPU** in CDCl_3 , proton signals of urea NH and aromatic 3-H in the pyridine ring disappear due to broadening at 25°C , and two pairs of split proton signals of the urea NH and 3-H were observed at -40°C , since these protons are not equivalent in the folded conformer.^{8a} These results suggested the minimal contribution of the formation of folded **DTU** dimer¹⁷ and the proposed major dimeric structure of **DTU** should be unfolded one (see Supporting Information).

Next, the formation of a heterocomplex between **DTU** and the complementary DAAD module **DAN** was monitored by ^1H NMR spectroscopy in CDCl_3 (Figure 1). At a 1:1 ratio of **DTU** (10 mM) and **DAN** (10 mM), a significant downfield shift was observed for the urea NH^a of **DTU** ($\Delta\delta = 1.88$ ppm) and the amide NH^c of **DAN** ($\Delta\delta = 3.82$ ppm). These

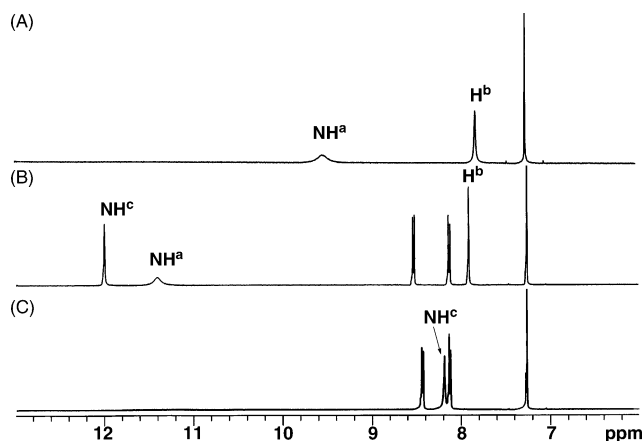


Figure 1. Partial ^1H NMR spectra (500 MHz) of (A) **DTU** (10 mM), (B) **DTU** (10 mM) + **DAN** (10 mM), and (C) **DAN** (10 mM) at 25°C in CDCl_3 .

changes in the chemical shift support the formation of a **DTU**•**DAN** complex via multiple hydrogen bonds involving NH^a and NH^c protons. The stoichiometry of the complex between **DTU** and **DAN** was confirmed to be 1:1 by a Job plot.¹⁸ NOE contact was observed between the NH^a of **DTU** and NH^c of **DAN**. In addition, the ESI mass spectrum shows molecular ion peaks of **DTU**•**DAN** (m/z : 887.6 [**DTU** + **DAN** + H^+]). These results strongly indicate that **DTU** forms a quadruple hydrogen-bonded heterocomplex with **DAN** by ADDA•DAAD arrays, as shown in Scheme 2. The formation of a **DTU**•**DAN** complex was also supported by the DFT calculation at the B3LYP method with a 6-31+G** basis set. The distance of hydrogen-bonding $\text{NH}^a \cdots \text{N}$ and $\text{NH}^c \cdots \text{N}$ was estimated to be 2.1 Å and 2.0 Å, respectively. When **DAN** (1.0 mM) was titrated with **DTU** (0 – 3.0 equiv) by ^1H NMR, significant downfield shifts were observed for both the NH^c ($\Delta\delta = 3.9$ ppm) and CH^d ($\Delta\delta = 0.26$ ppm) proton signals and these were almost saturated upon the addition of 1.0 equiv of **DTU**. In a dilution study of a 1:1 mixture of **DTU** and **DAN** from 20 mM to 0.4 mM,² no clear changes were observed in the chemical shift values of NH^a and NH^c proton signals.¹⁹ This shows that the **DTU**•**DAN** complex persists at a low concentration.

We investigated the binding property in the **DTU**•**DAN** complex by UV/vis spectroscopy in CHCl_3 at 25°C (Figure 2). Upon the addition of **DTU** (0 – 3.0 equiv) to **DAN** (20 μM), the absorption intensity of **DAN** at 353 and 370 nm increased with an isosbestic point at 349 nm. Based on the change in the absorption intensity at 353 nm, the stability constant of a 1:1 complex between **DTU** and **DAN** was determined to be $(2.6 \pm 0.2) \times 10^5 \text{ M}^{-1}$ by the nonlinear least-squares curve-fitting method.^{15,20} The K_s value of **DTU** with **DAN** is 100-fold greater than that of **DPU** ($K_s = 1.2$

(15) Connors, K. A. *Binding Constants*; Wiley: New York, 1987.

(16) When we tried to determine the K_{dim} value of **DTU** based on chemical shift changes of urea NH^a proton signals at the concentration from 1.0 mM to 45 mM, the K_{dim} value gave large error due to insufficiency of the chemical shift data at lower concentration range (<1 mM).

(17) The K_{dimer} value of **DTU** was higher than those for general folded dimers with DA•AD arrays ($K_{\text{dim}} < 3 \times 10^2 \text{ M}^{-1}$ in CDCl_3)^{6,8a} see: (a) EArcher, A.; Gong, H.; Krische, M. J. *Tetrahedron* **2001**, 57, 1139. (b) McGhee, A. M.; Kilner, C.; Wilson, A. J. *Chem. Commun.* **2008**, 344. (c) Lafitte, V. G. H.; Aliev, A. E.; Horton, P. N.; Hursthouse, M. B.; Bala, K.; Golding, P.; Hailes, H. C. *J. Am. Chem. Soc.* **2006**, 128, 6544.

(18) Job, P. *Ann. Chim. Appl.* **1928**, 9, 113.

(19) For a 1:1 mixture of **DTU** and **DAN** at a concentration of less than 0.4 mM, the NH^a proton signal of **DTU** disappeared due to broadening. Assuming that there is less than 10% dissociation at 0.4 mM, the K_s value of **DTU**•**DAN** was estimated to be a lower limit of $1.1 \times 10^5 \text{ M}^{-1}$.²

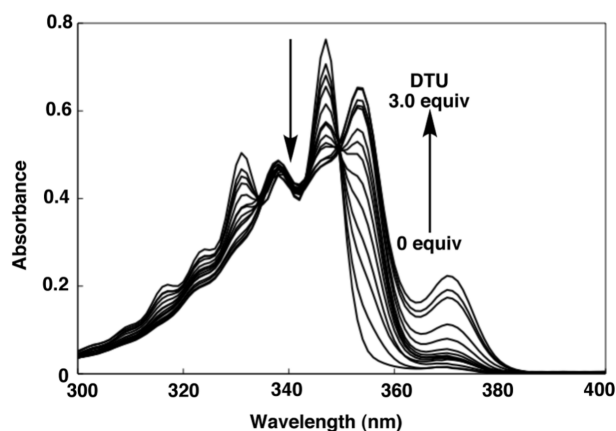


Figure 2. Changes in the absorption spectra of **DAN** (20 μM) in CHCl_3 at 25 $^\circ\text{C}$ upon addition of **DTU** (0–3.0 equiv).

$\times 10^3 \text{ M}^{-1}$ in CDCl_3) by replacement of the pyridine ring with the 1,2,3-triazole ring.

To predict the ΔG values of linear multiple hydrogen-bonded complexes, Zimmerman developed a formula based on an empirical method.²¹ This formula takes into account several variables including intramolecular hydrogen bonds that are broken before complexation (e.g., 2-pyridylureas).⁸ The ΔG_{298} value calculated for **DTU**•**DAN** complex from the formula was estimated to be $-7.0 \text{ kcal mol}^{-1}$, when the variable for the intramolecular hydrogen bond was not used.

(20) Due to small absorption intensity changes (370 nm) of **DAN** at the lower concentration range of **DTU** (<1.0 equiv), it was difficult to determine the K_s value.

(21) Quinn, J. R.; Zimmerman, S. C.; Del Bene, J. E.; Shavitt, I. J. *Am. Chem. Soc.* **2007**, 129, 934.

(22) DADD•ADAA arrays exhibit low affinity ($K_s < 10^3 \text{ M}^{-1}$ in CHCl_3) since DADD modules contain 2-pyridylurea structures, see: (a) Taubitz, J.; Lüning, U. *Eur. J. Org. Chem.* **2008**, 5922. (b) Quin, J. R.; Zimmerman, S. C. *Org. Lett.* **2004**, 6, 1649.

This calculated ΔG_{298} value was similar to the experimental value ($\Delta G_{298} = -7.4 \text{ kcal mol}^{-1}$). This supports the notion that **DTU** is suitable for use as an ADDA module and preorganization is not needed to give a linear ADDA array.

In conclusion, we have developed a new ADDA module based on the five-membered heterocyclic urea structure. *N,N'*-Di-4-triazolylurea (**DTU**) forms a highly stable ADDA•DAAD complex with **DAN** ($K_s = 2.6 \times 10^5$ in CHCl_3) without preorganization. Due to replacement of the pyridine ring with a 1,2,3-triazole ring, the K_s value of **DTU**•**DAN** complex is 100-fold greater than that of **DPU**•**DAN** complex. This result shows that the 1,2,3-triazole system via the click reaction is useful for obtaining components of multiple hydrogen-bonding modules. Our concept would contribute to development of promising quadruple hydrogen-bonding modules without the competition of undesired folded conformers and tautomers. Since limited examples of DADD modules have been reported,^{8c,22} we are currently studying the development of novel DADD module based on the five-membered heterocyclic urea structure.

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Supporting Information Available: Details of the synthesis and characterization for all new compounds, the complexation studies by NMR measurements, ESI-MS measurement and DFT calculation. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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