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Supramolecular acid/base catalysis *via* multiple hydrogen bonding interaction

Koji Ohsaki, Katsuaki Konishi* and Takuzo Aida*

Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan. E-mail: aida@macro.t.u-tokyo.ac.jp

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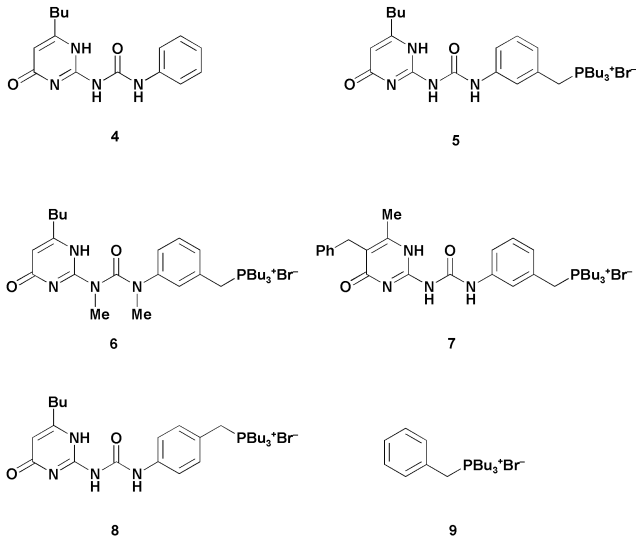
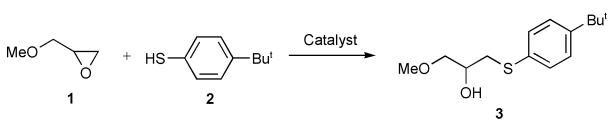
2-Ureidoisocytosine bearing a phosphonium ion functionality self-assembles in an anti-parallel manner, to exhibit a cooperative acid/base catalysis for the ring-opening reaction of an epoxide.

Catalysis *via* noncovalent interactions is one of the interesting subjects in supramolecular chemistry,[1] for which utilisation of multiple hydrogen-bonding interactions may be promising, as they possibly allow well-defined spatial arrangements of certain functionalities.[2,3] However, examples so far reported have focused on the binding of substrates to the catalytically active sites.[4] Herein we report a novel supramolecular catalysis, where a multiple hydrogen-bonding interaction is utilised for the spatial assembly of weakly acidic and basic functionalities to construct a catalytically active site.



4 **5** **6** **7** **8** **9**

The reaction we chose is the ring-opening of glycidyl methyl ether (**1**) with 4-*tert*-butylthiophenol (**2**) (Scheme 1), where acid and base functionalities are expected to activate **1** and **2**, respectively. As the self-assembling motif, we chose 2-ureidoisocytosine (2-ureido-4-pyrimidone, Fig. 1),[5] to which a "phosphonium ion" functionality was attached (**5**, **7**, **8**).[6,7] Phosphonium salts as weak Lewis acids have been reported to activate epoxides for the reaction with thiols.[8] Similarly to parent 2-phenylureidoisocytosine (**4**),[5] these phosphonium ion-appended derivatives in $CDCl_3$ formed quadruply hydrogen-bonded dimers (Fig. 1). For example, the ^1H NMR spectrum of **5** (20 mM) at 25 °C showed three NH signals at a low magnetic



1 **2** **3**

Scheme 1

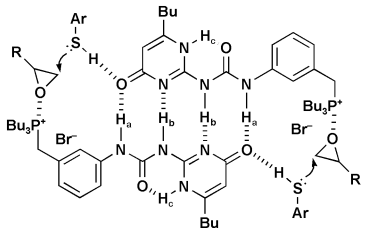


Fig. 1 A proposed mechanism for the catalysis of **5** in ring-opening of epoxide with thiol; cooperation of phosphonium ion (acid) and C(4)=O (base) functionalities by self assembly through multiple hydrogen-bonding interactions.

region (δ 12.89, 12.31 and 12.15), characteristic of the hydrogen-bonded dimer of 2-ureidoisocytosine.[5] On the other hand, the 5-H proton of **5**, which is informative of the dimerization equilibrium,[5] showed a signal predominantly at δ 5.92 due to dimeric **5** with a negligibly weak signal at δ 5.78 (< 1%) assignable to the monomeric form. In the dimeric form of **5**, the phosphonium ion functionality and the weakly Lewis-basic oxygen atom of the C(4)=O functionality, located on the other side of the molecule, are in proximity to each other (Fig. 1), so that they can serve cooperatively for acid/base catalysis.

Typically, the reaction of **1** (200 mM) and **2** (240 mM) was investigated in $CDCl_3$ at 50 °C,[9] where no uncatalyzed reactions took place. In the presence of **5** (20 mM), the ring-opening reaction of **1** took place smoothly to give 3-(4-*tert*-butylphenylthio)-1-methoxypropane-2-ol (**3**) in 78% yield based on **1** in 150 h (Fig. 2(b), ●).[10] Although a phosphonium salt such as **9** alone promoted the reaction,[8] the yield of the ring-opened

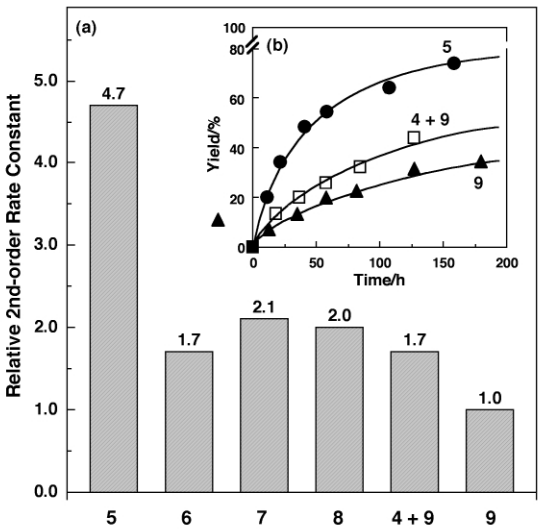


Fig. 2 (a) Relative second-order rate constants of the reaction between **1** (200 mM) and **2** (240 mM) in the presence of **5**–**9** (20 mM) and an equimolar mixture of **4** and **9** (each 20 mM) in $CDCl_3$ at 50 °C. (b) Time courses of the reaction in the presence of **5** (●), an equimolar mixture of **4** and **9** (□), and **9** (▲).

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product (**3**) after 180 h was only 32% (▲) under otherwise identical conditions to the above. The second-order rate constant of the reaction in the presence of **5** ($k_{2(5)}$) was determined to be 6.8×10^{-2} mol^{-1} h^{-1}, which is 4.7-times larger than that with **9** alone as catalyst ($k_{2(9)} = 1.4 \times 10^{-2}$ mol^{-1} h^{-1}) (Fig. 2(a)). On the other hand, non-functionalized 2-phenylureidoisocytosine (**4**) alone did not give rise to the ring-opening reaction, but was capable of assisting the phosphonium salt-mediated reaction. For example, in the presence of an equimolar amount of **4** with respect to **9** (each 20 mM), the ring-opening reaction proceeded 1.7-times faster ($k_{2(4/9)} = 2.4 \times 10^{-2}$ mol^{-1} h^{-1}) (Fig. 2(a) and (b), □) than that with **9** alone as catalyst. Similarly to **4**, a *N*-methylated derivative of **5** (**6**), which is unable to form a hydrogen-bonded dimer, showed a low rate enhancement with a ratio $k_{2(6)}/k_{2(9)}$ of 1.7 (Fig. 2(a)). However, it is obvious that the cooperative effects of such ureidoisocytosine derivatives are less explicit than that observed for the dimeric form of **5**, where the C(4)=O functionality is located in proximity to the phosphonium ion functionality. In connection with these observations, a ^{1}H NMR saturation transfer experiment was conducted for a mixture of **2** (200 mM) and **4** (200 mM) in $CDCl_3$ at 50 °C. When the S-H proton of **2** (δ 3.50) was irradiated, the signal due to N-H_a of **4** was decreased to 70% in intensity (Fig. 3), while the intensities of the other two NH signals (H_b, H_c) remained unchanged. Therefore, thiol **2** is most likely hydrogen-bonded with the C(4)=O functionality of **4**, thereby allowing a facile proton exchange between S-H and N-H_a.

Taking all the above observations into account, the catalysis by the 2-ureidoisocytosine/phosphonium salt system is considered to involve a dual mode activation of the substrates, where the epoxide is activated by the phosphonium salt as Lewis acid, while the C(4)=O functionality as Lewis base assists ionization of the thiol through the hydrogen-bonding interaction. The large rate enhancement with **5** appears to be due to the dimerization of **5** in an anti-parallel fashion (Fig. 1), which allows a proximal orientation of the Lewis-acidic and basic activation sites.

In relation to the above mechanism, we found that the orientation of the phosphonium group and the steric bulk around the C(4)=O functionality are both important for achieving a high catalytic activity. For example, a regioisomer of **5** (**8**), bearing a phosphonium ion at the *para* position of the terminal aryl group, was much less effective as catalyst, where the rate enhancement ($k_{2(8)}/k_{2(9)} = 2.0$, Fig. 2(a)) was similar to those observed for monomeric **6** and by non-functionalized **4** externally added to the system. Use of a 5-benzyl derivative of **5** (**7**), which suffers a steric hindrance around the C(4)=O functionality, again resulted in only a small acceleration with a $k_{2(6)}/k_{2(9)}$ value of 2.1 (Fig. 2(a)). Although these reference systems may cause some non-specific effects due to the difference in, *e.g.*, polarity from **5**, their obviously low activities support the proposed mechanism of the ring-opening reaction catalyzed by **5** (Fig. 1).

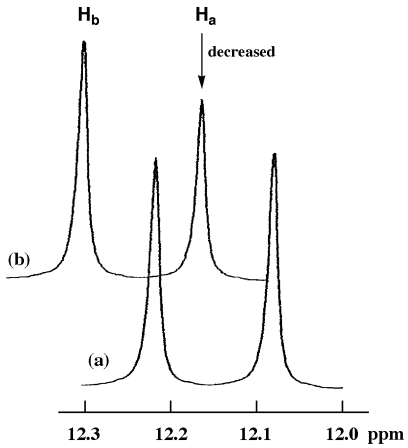

Fig. 3 ^{1}H NMR spectra of (a) a mixture of **2** and **4** (each 200 mM) in $CDCl_3$ at 50 °C and (b) that upon irradiation at the S-H signal (δ 3.50).

In conclusion, we have demonstrated a conceptually new supramolecular catalysis, where a complementary hydrogen-bonding interaction of 2-ureidoisocytosine is utilised for the construction of a catalytically active site consisting of acidic and basic functionalities, allowing a dual mode activation the substrates.

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Notes and references

1 J. L. Atwood and J.-M. Lehn (eds.), *Comprehensive Supramolecular Chemistry*, Pergamon, New York, 1996; A. J. Kirby, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 707.

2 G. A. Jeffery and W. S. Saenger, *Hydrogen Bonding in Biological Structures*, Springer, Heidelberg, 1994; G. M. Whitesides, E. E. Simanek, J. P. Mathias, C. T. Seto, D. N. Chin, M. Mammen and D. M. Gordon, *Acc. Chem. Res.*, 1995, **28**, 37; M. M. Conn and J. Rebek Jr., *Chem. Rev.*, 1997, **97**, 1647.

3 T. J. Murray and S. C. Zimmerman, *J. Am. Chem. Soc.*, 1992, **114**, 4010; V. Jubian, R. P. Dixon and A. D. Hamilton, *J. Am. Chem. Soc.*, 1992, **114**, 1120; J. Sartorius and H.-J. Schneider, *Chem. Eur. J.*, 1996, **2**, 1446; F. H. Beijer, R. P. Sijbesma, J. A. J. M. Vekemans, E. W. Meijer, H. Kooijman and A. L. Spek, *J. Org. Chem.*, 1996, **61**, 6371; J. Kang and J. Rebek Jr., *Nature*, 1997, **385**, 50; P. S. Corbin and S. C. Zimmerman, *J. Am. Chem. Soc.*, 1998, **120**, 9710.

4 T. R. Kelly, G. J. Bridger and C. Zhao, *J. Am. Chem. Soc.*, 1990, **112**, 8024; G. von Kiedrowski, B. Wlotzka, J. Helbing, M. Matzen and S. Jordan, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 423; E. A. Wintner, M. M. Conn and J. Rebek Jr., *Acc. Chem. Res.*, 1994, **27**, 198; B. Wang and I. O. Sutherland, *Chem. Commun.*, 1997, 1495; S. J. Howell, N. Spencer and D. Philp, *Org. Lett.*, 2002, **4**, 273.

5 R. P. Sijbesma, F. H. Beijer, L. Brunsveld, B. J. B. Folmer, J. H. K. K. Hirschberg, R. F. M. Lange, J. K. L. Lowe and E. W. Meijer, *Science*, 1997, **278**, 1601; F. H. Beijer, R. P. Sijbesma, H. Kooijman, A. L. Spek and E. W. Meijer, *J. Am. Chem. Soc.*, 1998, **120**, 6761.

6 **5**, **7**, and **8** were prepared from 6-alkylisocytosines (ref. 5) by three steps involving the reaction with the corresponding chloromethylphenylisocyanates (R. A. Michelin, G. Facchin and P. Uguagliati, *Inorg. Chem.*, 1984, **23**, 961), followed by quarternarisation of the resulting 2-(chloromethylphenylureido)isocytosines with Bu_3P and subsequent anion exchange with aqueous NaBr. **6** was prepared from **5** by lithiation with lithium bis(trimethylsilylamide), followed by alkylation with MeI.

7 **5**: Mp 105–106 °C. ^{1}H NMR (270 MHz; $CDCl_3$), δ 12.89 (s, 1H, 1-H), 12.31 (s, 1H, 2-NHCO), 12.15 (s, 1H, CON*H*C_6H_4), 7.60 (m, 2H, C_6H_4), 7.25 (m, 2H, C_6H_4), 5.92 (s, 1H, 5-H), 4.15 (d, $C_6H_4CH_2P$), 2.49 (t, 6-$CH_2C_3H_7$, 2H), 2.40 (br, P$CH_2C_3H_7$, 6H), 1.63 (m, 6-$CH_2CH_2C_2H_5$, 2H), 1.38 (m, 6-$C_2H_4CH_2CH_3$, 2H), 1.49 (br, $PCH_2CH_2C_2H_5$ and $PC_2H_4CH_2CH_3$, 12H), 0.95 (m, overlapped, $PC_3H_6CH_3$ and 6-$C_3H_6CH_3$, 12H). Anal. calc. for $C_{28}H_{46}BrN_4O_2P{\cdot}H_2O$: C, 56.09; H, 8.07; N, 9.34, found: C, 56.21; H, 7.85; N, 9.31%. **6**: Mp 86–90 °C. ^{1}H NMR (270 MHz; $CDCl_3$), δ 12.80 (s, 1H, 1-H), 7.60–7.20 (m, 4H, C_6H_4), 5.56 (s, 1H, 5-H), 4.15 (d, $C_6H_4CH_2P$), 2.50–0.90 (m, overlapped, 6-C_4H_9 (9H), PC_4H_9 (27H), NCH_3 (6H)). FAB-HRMS (*m*/*z*): calc. for $[M - Br]^+$ ($C_{30}H_{50}N_4O_2P$): 529.3671, found: 529.3672. **7**: Mp 132–133 °C. ^{1}H NMR (270 MHz; $CDCl_3$), δ 12.83 (s, 1H, 1-H), 12.38 (s, 1H, 2-NHCO), 12.07 (s, 1H, CON*H*C_6H_4), 7.51 (m, 2H, C_6H_4), 7.25 (m, 5H, C_6H_5), 7.24 (m, 2H, C_6H_4), 4.56 (d, 2H, $C_6H_4CH_2P$), 2.28 (br, $CH_2C_3H_7$, 6H), 2.10 (s, 3H, 6-CH_3), 1.47 (br, $CH_2CH_2C_2H_5$ and $C_2H_4CH_2CH_3$, 12H), 0.91 (t, $C_3H_6CH_3$, 9H). Anal. calc. for $C_{32}H_{46}BrN_4O_2P{\cdot}H_2O$: C, 59.35; H, 7.50; N, 8.65, found: C, 59.10; H, 7.55; N, 8.38%. **8**: Mp 115–116 °C. ^{1}H NMR (270 MHz; $CDCl_3$), δ 13.06 (s, 1H, 1-H), 12.19 (s, 1H, 2-NHCO), 12.08 (s, 1H, CON*H*C_6H_4), 7.51 (d, 2H, C_6H_4), 7.25 (d, 2H, C_6H_4), 5.85 (s, 1H, 5-H), 4.41 (d, $C_6H_4CH_2P$), 2.48 (t, 6-$CH_2C_3H_7$, 2H), 2.27 (br, P$CH_2C_3H_7$, 6H), 1.67 (m, 6-$CH_2CH_2C_2H_5$, 2H), 1.43 (m, 6-$C_2H_4CH_2CH_3$, 2H), 1.46 (br, $PCH_2CH_2C_2H_5$ and $PC_2H_4CH_2CH_3$, 12H), 0.95 (m, overlapped, $PC_3H_6CH_3$ and 6-$C_3H_6CH_3$, 12H). FAB-HRMS (*m*/*z*): calc. for $[M - Br]^+$ ($C_{28}H_{46}N_4O_2P$): 501.3358, found: 501.3358.

8 T. Iizawa, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 597.

9 The reaction was followed by ^{1}H NMR spectroscopy, and the second-order rate constant (k_2) was obtained according to the equation $([\mathbf{1}]_0 - [\mathbf{2}]_0)k_2t = \ln(([\mathbf{1}] \times [\mathbf{2}]_0)/([\mathbf{1}]_0 \times [\mathbf{2}]))$.

10 ^{1}H NMR spectroscopy showed that **5** and **7**–**9** in the ring-opening reaction of **1** with **2** are all in the dimeric forms.