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Knorr Cyclizations and Distonic Superelectrophiles

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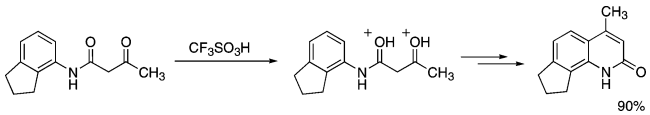
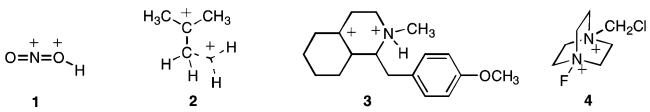


The acid-catalyzed Knorr cyclization has been studied by experimental and theoretical methods. The results of these studies indicate that β-ketoamides such as acetoacetanilide undergo diprotonation at the two carbonyl oxygen atoms to form distonic superelectrophiles. Direct observation of a dicationic superelectrophile was achieved by low-temperature ^{1}H, ^{15}N, and ^{13}C NMR from $FSO_3H-SbF_5-SO_2ClF$ solutions. In synthetic studies, the Brønsted superacid CF_3SO_3H is found to be an effective acid catalyst for the Knorr cyclization.

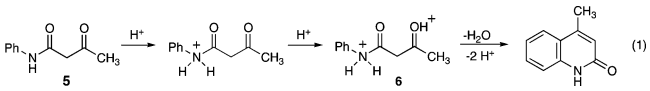
During the 1960s and 1970s, a number of cationic electrophilic reagents were shown to have greatly enhanced reactivities in the presence of superacids. This led to the concept of superelectrophilic activation, first proposed by Olah and coworkers in the mid-1970s.[1,2] Superelectrophiles can arise from the protosolvation of a cationic electrophile to generate a doubly electron deficient superelectrophile. Even partial protonation of an electrophile can lead to the superelectrophilic species. Superelectrophilic activation has also been shown to occur with various Lewis acids.[2]

Superelectrophiles are separated into two categories based on the distance between the charge centers.[2] *Gitionic* superelectrophiles are defined as species in which the two positive charge centers are separated by no more than one atom. *Distonic* superelectrophiles are defined as species in which the two positive charge centers are separated by two or more atoms. The protonitronium ion ($HONO^{2+}$, **1**) and the proto-*tert*-butyl



dication (**2**) are examples of gitionic superelectrophiles, while the ammonium-carbenium dication (**3**) and the electrophilic fluorinating agent, Selectfluor **4**, are typical distonic superelectrophiles.

In 1964, Staskun published a report describing his studies of the Knorr cyclization, a synthetic methodology used to prepare quinolin-2-ones.[3] This paper proposes a mechanism in which a distonic superelectrophile (**6**) triggers the cyclization chemistry (eq 1). Staskun noted that both the acid strength and the acid



quantity are important to the cyclization and he suggests that monocationic intermediates are not sufficiently reactive for the conversion. Remarkably, he demonstrates this superelectrophilic chemistry with both Brønsted and Lewis acids. Staskun's superelectrophilic dication mechanism has subsequently appeared in reviews and books on heterocyclic chemistry.[4] Although admirable as a predecessor of the general concept of superelectrophilic activation, Staskun's mechanism is questionable. At the time of this study, there was a considerable amount of uncertainty regarding the site of protonation on amides.[5] This question has been resolved over the years and in most cases oxygen is preferred over nitrogen as the site of protonation.

In the following paper, we examine the Knorr cyclization using experimental and theoretical methods. Both spectroscopic data and computational results indicate that an *O*,*O*-diprotonated species is the distonic superelectrophile involved in the Knorr cyclization. We also report the results from synthetic studies in which superacidic trifluoromethane-sulfonic acid (CF_3SO_3H, triflic acid) is found to be an outstanding acid catalyst for the Knorr cyclization.

With use of stable ion conditions and low-temperature NMR, a wide variety of onium ions have been directly observed and characterized.[6] However, superelectrophiles have been difficult to observe with NMR methods, due in part to their low equilibrium concentrations.[2a] Of the superelectrophiles that have been observed by NMR, most of these are distonic superelectrophiles. When acetoacetanilide (**5**) is studied under stable ion conditions, the data are consistent with the formation of *O*,*O*-diprotonated species (Table 1). In accord with basicity data (pK_a, acetone, -6.5 to -7.2; pK_a, *N*-phenylacetamide, -1 to -2)[7] and theoretical calculations (vide infra), the NMR data indicate that protonation occurs first at the amide group followed by protonation at the ketone. The signal at δ 168.8 in both CF_3CO_2H and FSO_3H can be assigned to the amide carboxonium carbon. In progressively more acidic media, the ketone carbonyl resonance is shifted from δ 204.3 in $CDCl_3$ downfield to a value of δ 237.5 in $SbF_5-FSO_3H-SO_2ClF$ solution. This ^{13}C NMR resonance is typical for protonated aldehydes and ketones.[8] The ^{15}N-labeled acetoacetanilide was also prepared and analyzed in

(1) Olah, G. A.; Germain, A.; Lin, H. C.; Forsyth, D. *J. Am. Chem. Soc.* **1975**, *97*, 2928.

(2) (a) Olah, G. A.; Klumpp, D. A. *Superelectrophiles and Their Chemistry*; Wiley: New York, 2008. (b) Olah, G. A.; Klumpp, D. A. *Acc. Chem Res.* **2004**, *37*, 211. (c) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767. (d) Olah, G. A.; Prakash, G. K. S.; Lammertsma, K. *Res. Chem. Intermed.* **1989**, *12*, 141.

(3) Staskun, B. *J. Org. Chem.* **1964**, *29*, 1153.

(4) Uff, B. C. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, UK, 1985; Vol. 2, p 425.

(5) Olah, G. A.; White, A. M.; O'Brien, D. H. *Chem. Rev.* **1970**, *70*, 561.

(6) Olah, G. A.; Laali, K. K.; Wang, Q.; Parkash, G. K. S. *Onium Ions*; Wiley: New York, 1998.

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TABLE 1. Results from the NMR Analysis of Acetoacetanilide (5) in Solutions of Varying Acidity

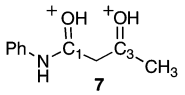
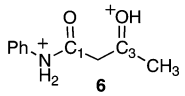
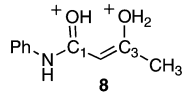
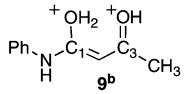
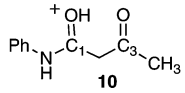
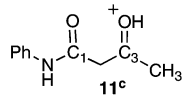
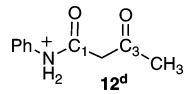
solvent	acidity, H_o	temp, °C	^{13}C signals,[a] δ	^{15}N signal,[a] δ
$CDCl_3$		25	30.7, 50.6, 120.3, 124.6, 128.9, 137.6, 164.4, 204.3	132.0 (doublet)
CF_3CO_2H	−2.7	−10	28.1, 46.3, 122.1, 127.3, 128.4, 132.7, 168.8, 209.3	144.1 (doublet)
FSO_3H	−15	−40	28.4, 42.9, 122.6, 129.3, 129.8, 130.1, 168.8, 220.6	150.9 (doublet)
FSO_3H, SbF_5 (1:1)	−24	−40	29.7, 44.9, 123.5, 126.9, 130.2, 131.7, 165.8, 237.5	162.3 (doublet)

[a] Superacidic samples were prepared with SO_2ClF as cosolvent; the ^{13}C external standard was d_6-acetone; the ^{15}N external standard was ^{15}N-labeled urea in d_4-methanol.

the superacidic solutions. If the *N*,*O*-diprotonated species (dication **6**) is generated as the superelectrophilic intermediate, then a triplet ^{15}N resonance should be visible in the ^{15}N NMR spectrum (assuming rapid proton exchange does not obscure ^{1}H−^{15}N coupling). In the strongest superacid used, SbF_5−FSO_3H−SO_2ClF, the ^{15}N resonance appears downfield at δ 162.3 as a doublet. The amide ^{15}N is significantly deshielded in SbF_5−FSO_3H−SO_2ClF, which is a consequence of the formation of the neighboring carboxonium ion (and increasing positive charge). On the basis of these data, it is proposed that acetoacetanilide (**5**) forms a significant equilibrium concentration of the *O*,*O*-diprotonated species (**7**). The ^{1}H NMR spectra of acetoacetanilide (**5**) were also obtained from superacidic media (FSO_3H, CF_3SO_3H, and SbF_5−FSO_3H solutions at −50 °C), and the spectra are consistent with the formation of dication **7**. In each of the superacid solutions, the spectra clearly show the methyl (CH_3), methylene (CH_2), amide (NH), and phenyl (C_6H_5) protons. The spectrum from FSO_3H is typical: δ 2.15 (3H), 3.85 (2H), 6.75−6.84 (5H), 9.35 (NH). The carboxonium proton(s) could not be observed, possibly due to fast exchange with the acid. With greater acidity, both the NH and the methylene peaks maintain the same intensity. This observation argues against the formation of *N*,*O*-diprotonated species (dication **6**) and any possible enol-type structures (vide infra).

Model calculations were performed on the protonated products from acetoacetanilide (**5**) to estimate the relative energies of the diprotonated species (**6**−**9**) and to compare experimental NMR chemical shift values with those from theory (Table 2).[9] Likewise, monocationic products (**10**−**12**) were also studied. At both the ab initio MP2/6-311++G(d,p) and density functional theory B3PW91/6-311++G(d,p) levels of theory,[10] the

TABLE 2. Calculated Relative Stabilities and NMR Data for Ions 6−12 at the MP2/6-311++G(d,p) Level (DFT Calculations, B3PW91/6-311++G(d,p) Level)[a]

	E_{rel} (kcal/mol)	^{15}N NMR, δ	^{13}C NMR, δ C_1	C_2	C_3	C_4
diprotonated ions						
 **7**	0.0	180 (193)	181 (168)	41 (45)	254 (246)	34 (38)
 **6**	8.5 (12.2)	107 (128)	181 (175)	46 (43)	253 (246)	34 (36)
 **8**	13.8 (15.0)	171 (162)	177 (175)	103 (103)	185 (246)	20 (22)
 **9**[b]	22.0 (20.4)	148 (162)	173 (158)	84 (90)	214 (202)	25 (28)
monoprotonated ions						
 **10**	0.0	158 (177)	189 (172)	38 (39)	223 (220)	31 (33)
 **11**[c]	10.7 (8.9)	141 (166)	180 (164)	40 (43)	253 (247)	30 (33)
 **12**[d]	12.6 (17.6)	98 (120)	169 (168)	45 (50)	219 (212)	32 (34)

[a] The ^{15}N signals are calculated in reference to NH_3 (gas phase); the ^{13}C signals are calculated in reference to $Si(CH_3)_4$. [b] Not a stable minimum, $-OH_2$ bonds set at a fixed length. [c] Not a stable minimum, −OH bond set at a fixed length. [d] Not a stable minimum, −NH bond set at a fixed length.

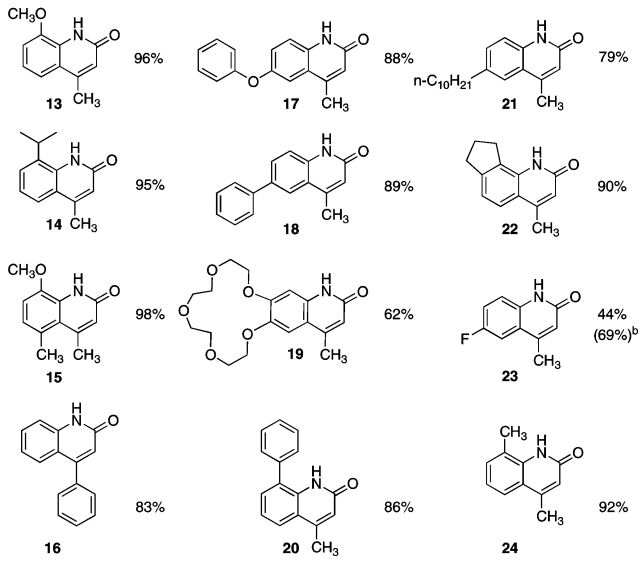
N,*O*-diprotonated species (**6**) and the *O*,*O*-diprotonated species (**7**) are found at energy minima (as determined by frequency calculations), with structure **6** being at least 8 kcal·mol^{-1} less stable than structure **7**. Although the enol-type structure (**8**) is at an energy minimum, it is about 14 kcal·mol^{-1} less stable than structure **7**. The isomeric enol-type structure (**9**) is not at an energy minimum, but rearranges upon optimization. ^{15}N and ^{13}C NMR GIAO data, calculated at the B3PW91/6-311++G(d,p)//B3PW91/6-311++G(d,p) and HF/6-311++G(d,p)//MP2/6-311++G(d,p) levels, indicate that the ^{15}N NMR resonances are diagnostic for N versus O protonation, as they vary sizably between **6** and **7** (65−75 ppm). The experimental spectrum from protonation of compound **5** in SbF_5−FSO_3H−SO_2ClF exhibits the ^{15}N resonance at δ 162.3, reasonably close to that predicted for the *O*,*O*-diprotonated species (**7**). The calculated values for ^{13}C resonances differ little for structures **6** and **7**, and therefore they are not as useful in distinguishing between N versus O protonation, but the calculated ^{13}C resonance for C_2 does appear to rule out the enol-type structure (**8**) as a major component of the equilibrium mixture in superacid. In comparing the calculated and experimental ^{13}C spectra for dication **7**, it is seen that both theoretical models predict the experimental spectrum fairly well. The density functional B3PW91 performs particularly well

(8) (a) Olah, G. A.; Rasul, G.; York, C. T.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 11211. (b) Klumpp, D. A.; Rendy, R.; Zhang, Y.; Gomez, A.; McElrea, A. *Org. Lett.* **2004**, *6*, 1789.

(9) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, A D.; Rabuck, K. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople. J. A. *Gaussian 98*, Revision A.11.4; Gaussian, Inc.: Pittsburgh, PA, 1998.

(10) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Wolinski, K.; Hinton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.

TABLE 3. Products and Yields from the Reactions of Acetoacetanilides with CF_3SO_3H at 25 °C

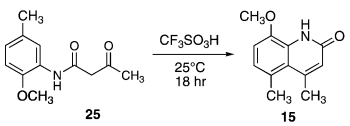


[a] Isolated yields of purified products; products were characterized by ^1H and ^{13}C NMR and high-resolution mass spectroscopy. [b] Reaction done with $CF_3SO_3H-SbF_5$.

in this regard. In the case of the monoprotonated products (**10**−**12**), only cation **10** (the amide carboxonium ion) is located at an energy minimum. Efforts to optimize structures **11** and **12** lead to isomerization (to **10**); however, with the O−H and N−H bond fixed, the potential energy and spectral data of **11** and **12** can be estimated. Most notably, the amide carbonyl protonation is favored by about 10 kcal·mol^{-1} over other sites of protonation. When the results of the above calculations are considered, two important conclusions can be made: monoprotonation occurs at the amide and the resulting intermediate (**10**) is unlikely to cyclize; both the predicted relative energies and ^{15}N NMR resonances support the presence of the distonic superelectrophile **7** as the superelectrophilic intermediate in the Knorr cyclization.[11]

The Knorr cyclizations are often done with strong mineral acids and elevated temperatures. For example, with H_2SO_4 or H_3PO_4 as the acid in Knorr cyclizations, it is necessary to use reaction temperatures in the range of 80−150 °C.[3,4] The involvement of diprotonated intermediates would of course necessitate the use of these forcing conditions. Over the years, it has been demonstrated that CF_3SO_3H is an effective superacid for promoting reactions involving dicationic, superelectrophilic species.[2a] A series of acetoacetanilides were prepared (from the respective anilines and diketene)[12] and reacted in CF_3SO_3H, producing good yields of the Knorr cyclization products **13**−**24** (Table 3). In general, the cyclizations are best accomplished with activated aryl-groups. Infrared spectroscopy indicated the quinolin-2-one structure to be the major component of the equilibrium mixtures of products **13**−**24** (C═O stretches at 1650−60 cm^{-1}). Efforts to extend this chemistry to deactivated aryl systems were not successful, although in the case of the fluoro-substituted acetoacetanilide, the product (**23**) yield increases modestly with the use of the stronger superacid system $CF_3SO_3H-SbF_5$ (10% mol SbF_5). At 25 °C, the cyclizations leading to **13** and **15** are found to be essentially complete within 30 min (20 equiv of CF_3SO_3H). The use of CF_3SO_3H leads to cyclizations at lower temperatures and in higher yields compared to H_2SO_4 or polyphosphoric acid. For example, compound **16** is prepared in 83% yield from 2-benzoylacetanilide at 25 °C in CF_3SO_3H, while the same product is formed in 20% and 30% yields from H_3PO_4 (140 °C) and H_2SO_4 (80−90 °C), respectively.[3]

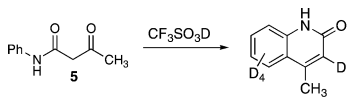
When compound **25** is reacted with decreasing quantities of CF_3SO_3H, the product yield decreases (eq 2). With 1.0 equiv



equiv. acid	yield
25	97%
2.5	86%
1.0	0%

(2)

of acid, no condensation product (**15**) is formed. In accord with Staskun's conclusion, the need for excess superacid suggests the involvement of diprotonated intermediates. Additionally, acetoacetanilide (**5**) was reacted in excess CF_3SO_3D and deuterium incorporation was not observed at the amide nitrogen (eq 3), as verified by ^{15}N NMR and mass spectral analyses. This indicates that protonation (deuteration) to form the *N*,*O*-diprotonated species (**6**) is not occurring.[13]



(3)

In conclusion, as Staskun observed, the Knorr cyclization generally requires heating with an excess of strong acid. This is consistent with the formation of the dicationic superelectrophilic species. When the present experimental and computational results are considered, the evidence clearly suggests the involvement of the *O*,*O*-diprotonated species (**7**) as the superelectrophile leading to Knorr products. While other diprotonated intermediates (i.e., enol-type structure **8**) cannot be rigorously excluded as the cyclization precursors, dication **7** is estimated to be at least 8 kcal·mol^{-1} more stable than other dications on the potential energy surface. Moreover, the NMR spectra indicate formation of *O*,*O*-diprotonated species (**7**) in superacidic solution. The superacid, CF_3SO_3H, is found to be an excellent acidic reagent for the Knorr cyclization. This is likely due to its ability to form the requisite diprotonated intermediates.

Experimental Section

Typical Synthetic Procedure. 4-Aminoindan (1.0 g, 7.5 mmol) is dissolved in 10 mL of anhydrous CH_2Cl_2 and 0.92 g of diketene (11 mmol) is added. The mixture is stirred at 25 °C for 2.5 h, followed by removal of the solvent under vacuum. The product (*N*-indan-4-yl-3-oxo-butyramide, 1.41 g, 6.5 mmol, 87%) is isolated by column chromatography (silica gel, 1:1 hexane:ether).

The *N*-indan-4-yl-3-oxo-butyramide (0.202 g, 0.92 mmol) is dissolved in 4 mL of dry CH_2Cl_2 and CF_3SO_3H (1.5 mL, 17 mmol) is slowly added to the solution (with stirring). The resulting mixture

(11) An *O*,*O*-diprotonated *β*-ketoamide was recently proposed by Schlosser and co-workers as an intermediate leading to the 2-methyl-4(1*H*)-quinolinones, see: Marull, M.; Lefebvre, O.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 54.

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(13) It is not presently clear if the aryl ring is deuterated prior to or after cyclization.

is stirred at 25 °C for ca. 15 h and then poured over 5−10 g of ice. The solution is extracted twice with $CHCl_3$, and the organic phase is washed twice with water and twice with brine solution, then dried with anhydrous sodium sulfate. Following column chromatography (1:1 hexane: ether), 8,9-dihydro-4-methyl-1*H*-cyclopenta[*h*]quinolin-2(7*H*)-one (**22**, 0.167 g, 0.84 mmol, 91%) is isolated as a white solid, mp 260−263 °C. ^{1}H NMR ($CDCl_3$) δ 10.13 (s, 1H) ,7.51 (d, 1H, J = 8 Hz), 7.14 (d, 1H, J = 8 Hz), 6.50 (s, 1H), 3.13 (t, 2H, J = 14 Hz), 3.08 (t, 2H, J = 14 Hz), 2.50 (s, 3H), 2.24−2.28 (mult, 2H). ^{13}C NMR ($CDCl_3$) δ 163.3, 149.3, 147.7, 134.8, 129.3, 123.1, 119.6, 118.9, 118.8, 33.6, 29.4, 25.0, 19.5. Low-resolution mass spectra (EI) *m*/*z* 199 (M+), 154, 115, 77, 44. HRMS calcd for $C_{13}H_{13}ON$ 199.0997, found 199.0996.

Computational Methods. All calculations were performed with the GAUSSIAN (G98) code.[9] Structures **6**−**12** were fully optimized without constraints at the HF/6-311++G(d,p) level, using several different starting geometries to explore the potential surface and ensure that the lowest energy conformation was selected. The lowest energy structures were examined by frequency analysis at this level, and demonstrated to be minima (no imaginary frequencies). The structures were then reoptimized by using the MP2 perturbation theory and B3PW91 density functional theory (DFT) models as coded in G98.[10] Relative energies (Table 2) were corrected with use of unscaled zero point energies (ZPEs) from the frequency analysis.

NMR calculations employed the gauge-independent atomic orbital (GIAO) approach. The models were selected to provide limited model testing.[14] It has been noted that DFT models provide little improvement over HF for NMR calculations, but that different structure models can affect NMR results;[15] thus the methods selected were B3PW91 for NMR based on a B3PW91-optimized structure (denoted B3PW91//B3PW91) as a DFT approach, and the analogously denoted HF//MP2 method as a PT approach. In addition, diffuse and polarization functions were included on the hydrogen atoms, as the optimizations suggested hydrogen bonding in the acetoanilide cations. Thus, the 6-311++G(d,p) basis set was used for all reported structures and NMR shift predictions. Cartesian coordinates for **6**−**12** at the MP2/6-311++G(d,p) level are available as Supporting Information.

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Note Added after ASAP Publication. In the version that was published ASAP on November 14, 2007, equation 2 contained an error, and also the paragraph above it had an incorrect compound number; the corrected version was published ASAP on November 16, 2007.

Supporting Information Available: General experimental details, characterization data and spectra, representative experimental procedures, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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