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Telluroxides Exhibit Hydrolysis Capacity

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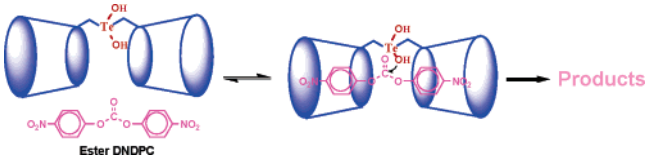

It has long been known that tellurium compounds are rather toxic to living organisms, and tellurium has not been found in natural biomacromolecules to date. The principles of telluride toxicity in biological processes are still controversial partly because of the lack of information on the biochemical features of tellurium. In this contribution, we report our finding for the first time that telluroxides exhibit hydrolysis capacity. For instance, 6,6′-telluroxy-bis(6-deoxy-β-cyclodextrin) acts as a hydrolase mimic and shows a significant rate acceleration of 106 000 for the hydrolysis of 4,4′-dinitrodiphenyl carbonate.

Introduction

The tellurium compounds have been proven to contain an extremely rich chemistry and are widely applied in many areas, such as metallurgy, chemicals, electronic conductors, and so on.[1] In addition to these applications, there is little information available on the biochemistry of tellurium compounds even now. It has long been known that tellurium compounds are rather toxic to living organisms, and tellurium has not been found in natural biomacromolecules, including DNA, RNA, proteins, sugars, and lipids. The principles of telluride toxicity in biological processes are still controversial partly because of the lack of information on the biochemical features of tellurium.[1a,2] Therefore, it is very important to explore new biological functions of metallic tellurium that can provide precious insights into biological processes. As we know, tellurium compounds have been used as preventive antioxidants and chemotherapeutic agents in the sense and realistically to simulate selenoenzyme glutathione peroxidases.[3] To our knowledge, however, in addition to the antioxidant function no other biological properties of tellurium compounds have been discovered thus far.

Since the hydrolytic cleavage of ester bonds is involved in many biological processes such as metabolic and signaling biochemical pathways, hydrolases are ubiquitous and essential for living organisms.[4] The simulation of hydrolase functions has been extensively studied by utilizing enzyme models in various structural types since the mechanisms of these reactions are known.[4,5] However, hydrolase mimics using telluroxide compounds is a novel and virgin area.

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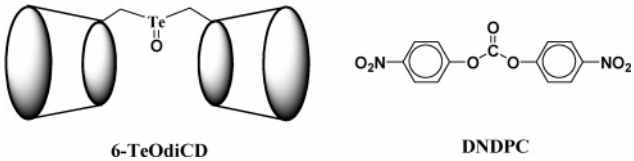
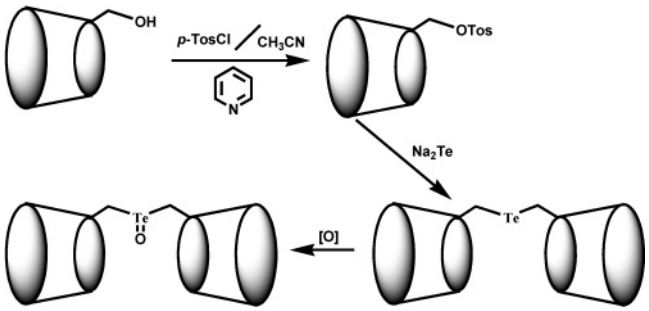
CHART 1



SCHEME 1



Herein, we report our new finding that telluroxides, in which tellurium(IV) acts as an active center, exhibit hydrolysis capacity efficiently for carbonate cleavage.

Results and Discussion

To demonstrate the fact that telluroxide compounds hydrolyze carbonate bonds, we selected 4,4′-dinitrodiphenyl carbonate (DNDPC) as a testing substrate (Chart 1). This substrate has hydrophobic groups at both ends and can aesthetically bind into the two cavities of cyclodextrin.[6] On the basis of understanding previous work,[5a,6] the ideal catalytic receptors could be achieved if the catalyst was a dimmer of cyclodextrin, in which a tellurium atom was attached at primary sides of cyclodextrins as a delicate linker. Thus, the desired telluroxide 6,6′-telluroxy-bis(6-deoxy-β-cyclodextrin) (6-TeOdiCD, Chart 1) was readily obtained from 6,6′-telluro-bis(6-deoxy-β-cyclodextrin) (6-TediCD) since the diorganyl telluride can be oxidized into the corresponding telluroxide by the mild oxidants.[3b−k,7] 6-TediCD was synthesized according to the literature procedure reported by Engman and co-workers.[2c] The detailed synthetic routes reported in previous literatures were illustrated in Scheme 1.

The catalytic capacities of these compounds were tested in the hydrolysis of substrate DNDPC in a 5% MeCN solution of Tris·HCl buffer (50 mM, pH 7.0) at 25 °C (Figure 1). On the basis of spectrophotometrical detection of product *p*-nitrophenol at 400 nm (ϵ = 8700 M^{-1} cm^{-1}, pH 7.0),[8] we determined the initial hydrolysis rates of DNDPC (50 μM) in the presence of various catalysts (5 μM) (Table 1). The initial rate of spontaneous cleavage of DNDPC (50 μM) was quite slow (v_{contr} = 0.0147 μM min^{-1}), but an obvious enhancement in the rate was observed when simple β-cyclodextrin was added (v_0 = 0.25 μM min^{-1}). In the presence of 6-TediCD, the initial rate (v_0 = 1.75 μM min^{-1}) was found only 7-fold higher than that of β-cyclodextrin. In contrast to β-cyclodextrin, it was practically reasonable that a better catalysis was observed for 6-TediCD owing to a much better hydrophobic binding for substrate.[6] In Table 1, it was worth noting that 6-TediCD has a 119-fold rate enhancement for DNDPC hydrolysis. Tastan and Akkaya recently also reported a similar observation that a cyclodextrin dimer showed a 150-fold rate enhancement for substrate DNDPC hydrolysis.[9] Apparently, the similar catalytic activities of the two cyclodextrin dimers should originate from their similar abilities for substrate binding. Importantly and interestingly, under the identical conditions telluroxide compound 6-TeOdiCD exhibited a dramatic rate enhancement (v_0 = 20.89 μM min^{-1}) with 1421-fold compared to the control reaction. To confirm the catalytic function of active center tellurium, we took bis(4-hydroxyphenyl) telluroxide (BHPTO) as a supplement and found that the small molecule BHPTO obviously promotes the hydrolysis reaction with a catalytic rate of 0.40 μM min^{-1}. However, no detectable catalytic activity of DNDPC hydrolysis was observed for the corresponding telluride bis(4-hydroxyphenyl) telluride.

To further assess the hydrolysis ability of telluroxide compound, a detailed kinetic study was undertaken. Saturation kinetics was observed, and the kinetic parameters for the hydrolysis reactions are shown in Table 2. These values were deduced from the Michaelis−Menten kinetics (Figure 2). Remarkable turnover numbers of k_{cat} = 30.6 min^{-1} were obtained for DNDPC hydrolysis catalyzed by 6-TeOdiCD. k_{cat}/

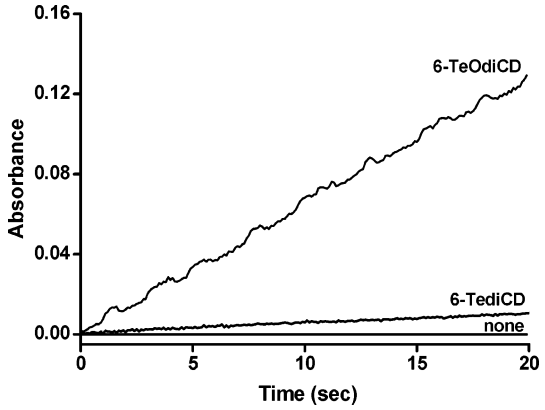


FIGURE 1. Plots of absorbance vs time during DNDPC (50 μM) hydrolysis in the presence of 6-TeOdiCD (5 μM), 6-TediCD (5 μM), and none.

TABLE 1. Initial Rates (v_0)[a] and Rate Accelerations (v_0/v_{contr}) for the Hydrolysis of DNDPC (50 μM) in the Presence of Various Catalysts (5 μM) in 5% MeCN Solution of Tris-HCl Buffer (pH 7.0) at 25 °C

catalyst	v_0 (μM min^{-1})	v_0/v_{contr}
6-TeOdiCD	20.89 ± 1.27	1421
6-TediCD	1.75 ± 0.12	119
β-cyclodextrin	0.25 ± 0.02	17
BHPTO[b]	0.40 ± 0.02	0.7

[a] The initial rates (v_0) were corrected for the control rate (v_{contr}) of DNDPC hydrolysis reaction, and values = means ± standard deviation. [b] In this assay, 10% MeOH was added and v_{contr} was then changed.

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TABLE 2. Kinetic Parameters[a] for the Hydrolysis of DNDPC in the Presence of 6-TeOdiCD (5 μM) and 6-TediCD (5 μM) in 5% MeCN Solution of Tris·HCl Buffer (pH 7.0) at 25 °C

catalyst	k_{uncat} (min^{-1})	k_{cat} (min^{-1})	K_m (mM)	k_{cat}/K_m (M^{-1} min^{-1})	k_{cat}/k_{uncat}
none	$(2.9 \pm 0.1) \times 10^{-4}$				
6-TeOdiCD		30.6 ± 3.2	0.29 ± 0.03	$(1.06 \pm 0.08) \times 10^5$	106000
6-TediCD		2.9 ± 0.1	0.12 ± 0.01	$(2.42 \pm 0.31) \times 10^4$	9860

[a] Values obtained from the Michaelis−Menten kinetics and standard deviation were enclosed.

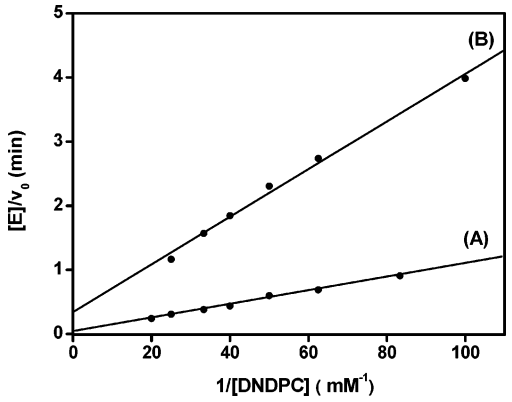


FIGURE 2. Lineweaver−Burk plots obtained for the 6-TeOdiCD (A) and 6-TediCD (B) model reaction in the presence of different substrate concentration [DNDPC] at pH 7.0 and 25 °C.

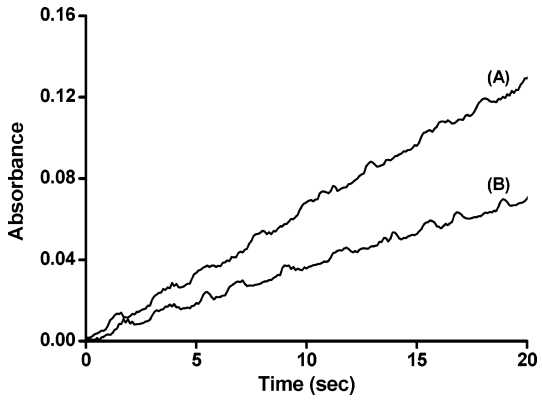


FIGURE 3. Plots of absorbance vs time (s) of 6-TeOdiCD-catalyzed hydrolysis reaction in the absence (A) or presence (B) of inhibitor DNPDS at pH 7.0 and 25 °C. The concentrations of inhibitor DNPDS and mimic 6-TeOdiCD both are 5 μM.

k_{uncat} was used to express the catalytic ability of hydrolase mimics. It showed in our case values up to 106 000. However, for 6-TediCD, the value of k_{cat}/k_{uncat} was found to be 9860 and at least 1 order of magnitude lower than that of 6-TeOdiCD. Furthermore, a much better catalytic efficiency k_{cat}/K_m for 6-TeOdiCD compared to 6-TediCD was obtained. These observations unambiguously demonstrated that catalytic site telluroxide group plays an essential role in the catalytic hydrolysis. Apparently, the large rate acceleration by our enzyme mimic 6-TeOdiCD originated from the combination of the binding sites (two hydrophobic cavities) and the catalytic site (telluroxide ligand). It is well-known that cyclodextrin dimers could show very strong binding for suitable ditopic substrates that could occupy both cyclodextrin cavities, and that, once the substrate was split in half by the catalytic group, the products would bind much more weakly.[6] As expected, we did not detect the signal of product inhibition. To observe the role of cyclodextrin cavities in our hydrolase model, we prepared a

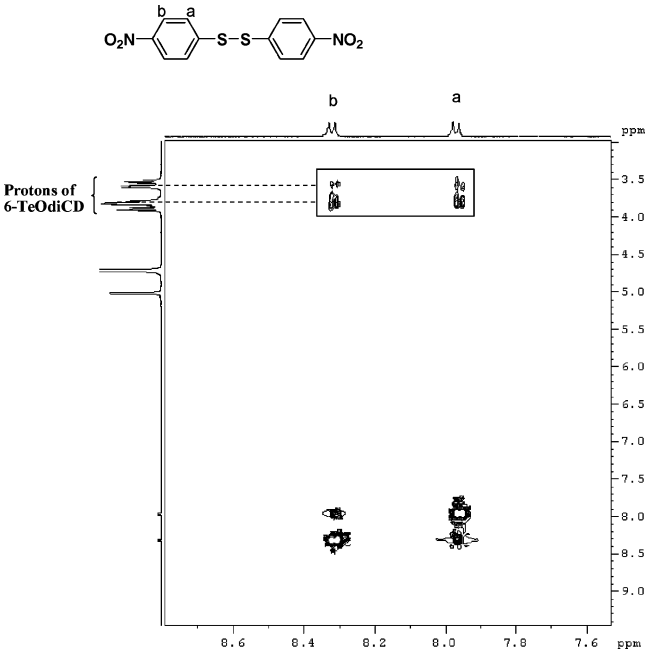


FIGURE 4. 2D NMR study of inclusion complexation of 6-TeOdiCD and inhibitor DNPDS.

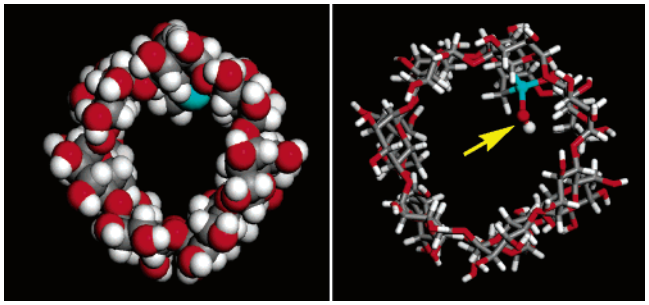


FIGURE 5. Side pictures of stable structure models of 6-TediCD (left) and 6-Te(OH)$_2$diCD (right) by molecular simulation.

substrate analogue di(*p*-nitrophenyl) disulfide (DNPDS). The 6-TeOdiCD-catalyzed hydrolysis of DNDPC can be significantly inhibited by DNPDS (Figure 3), strongly revealing the important role of substrate binding. To further confirm the above observation, the inclusion complexation of inhibitor DNPDS and 6-TeOdiCD was investigated by means of 2D NMR spectroscopy. In the 2D NMR spectrum (Figure 4), the interactions between the aryl protons of DNPDS and inside protons of cyclodextrin were found, indicating that DNPDS markedly inhibits the catalytic action of 6-TeOdiCD owing to the binding occupation of the cavity of cyclodextrin. Since telluride was converted into telluroxide, or even telluroxide hydrate,[7b] the swelled linker ligand should cause steric hindrance and therefore influence the substrate binding. We found that the association constants of 6-TeOdiCD and 6-TediCD for substrate DNDPC

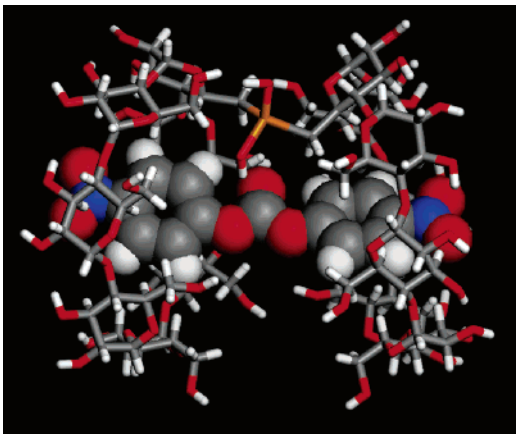
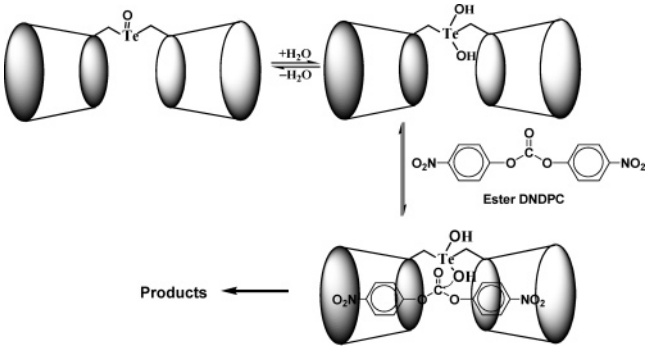


FIGURE 6. Structure model of inclusion complexation of 6-Te-$(OH)_2$diCD and substrate DNDPC.

SCHEME 2. Proposed Catalytic Mechanism of Hydrolase Model 6-TeOdiCD



are 3500 and 8500 M^{-1}, respectively. Furthermore, we also found that Michaelis constant K_m of 6-TeOdiCD was about 2.4-fold higher than that of 6-TediCD, revealing a relatively weaker substrate binding affinity for 6-TeOdiCD. Molecular modeling, as a useful and important tool for this experiment, gave an explicit illumination (Figure 5).

With respect to the mechanism of telluroxide-catalyzed hydrolysis reaction, some known information on tellurium chemistry as well as our above results together extruded the following reasonable explanation (Scheme 2).[1,3] The telluroxide compound readily binds and activates one water molecule and then forms a telluroxide hydrate,[7b] after which the resultant tellurium(IV)-activated hydroxyl group is capable of approaching and splitting the ester group of substrate and essentially performing the hydrolase functions. By using molecular modeling, we observed that the telluroxide hydrate 6-Te$(OH)_2$diCD can fully and strongly bind the substrate DNDPC (Figure 6).

Conclusions

In summary, we have successfully demonstrated that telluroxide compounds exhibit hydrolysis ability. In our case, both substrate binding and catalysis are very essential for the catalytic efficiency of hydrolase mimics. The discovery of novel biochemical features of tellurium compound will expand tellurium chemistry and possibly provide insights into biological systems. Further studies on the properties and reactivity of tellurium compounds hydrolyzing natural biomacromolecules are currently in progress.

Experimental Section

All chemicals were of the highest purity commercially available and were used without further purification. DNPDS was prepared by the oxidation of the corresponding thiol *p*-nitrophenylthiol (UV monitoring).

6,6′-Telluro-bis(6-deoxy-β-cyclodextrin). The compound 6-TediCD was synthesized according to previous procedure[2c] reported by Engman et al. with a minor modification. The aimed residue was purified on a column of Sephadex G-25 with distilled water as the eluent. The resulting solution was freeze-dried, and a pure sample 6-TediCD was obtained in 41% yield as a white powder. ^{1}H NMR (500 MHz, D_2O): δ 3.46−3.59 (m, 2-H, 4-H), 3.74−3.92 (m, 3-H, 5-H, 6-H), 4.96−5.02 (m, 1-H); ^{13}C NMR (500 MHz, D_2O): δ 60.0, 72.0, 72.3, 73.1, 81.7, 102.0; IR (cm^{-1}, KBr): υ 3340, 2928, 1626, 1140, 1079, 1030; MALDI-MS: calcd 2363.6, found 2363.3; Anal. Calcd for $C_{84}H_{138}O_{68}Te\cdot 12H_2O$: C, 39.07; H, 6.28. Found: C, 38.86; H, 6.01.

6,6′-Telluroxy-bis(6-deoxy-β-cyclodextrin). 6-TediCD (50 mg, 0.0212 mmol) was stirred with an equivalent molar of hydrogen peroxide in a diluted solution for 30 min. The mixture solution was freeze-dried, and then the residue was purified on a column of Sephadex G-25 with distilled water as an eluent. The resulting solution was freeze-dried, and a pure sample was obtained in 92% yield as a white powder. The final compound 6-TeOdiCD was confirmed by ^{1}H NMR (500 MHz, D_2O): δ 3.26−3.59 (m, 2-H, 4-H), 3.71−4.02 (m, 3-H, 5-H, 6-H), 4.91−5.12 (m, 1-H); ^{13}C NMR (500 MHz, D_2O): δ 60.7, 72.3, 72.5, 73.5, 81.5, 102.3; MALDI-MS: calcd 2379.6, found 2380.6.

4,4′-Dinitrodiphenyl Carbonate. To a stirred solution of *p*-nitrophenol (2.816 g, 20.16 mmol) and triethylamine (1.40 mL, 20.16 mmol) in dry THF (20 mL), triphosgene (0.50 g, 1.68 mmol) in dry THF (20 mL) was added dropwise in an ice bath. After 2 h, through filtering the triethylammoium salt, the solvent was removed and crude residue was purified by silica gel chromatography (dichloromethane as eluent). The product was obtained as a yellow powder with a yield of 42%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.75 (d, J = 9.0 Hz, 4H), 8.38 (d, J = 9.0 Hz, 4H); IR (cm^{-1}, KBr): υ 1768, 1521, 1267, 862; MALDI-MS: calcd 304.0, found 304.5.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and molecular modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

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