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A Novel Semisynthetic Anion Receptor: Synthesis and Ion Recognition of (1-H-pyrrol-2-yl)-4-oxo-perezone

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Abstract: We describe the synthesis of the novel 2-(1,5-dimethyl-4-oxo-hexyl)-3-hydroxy-5-methyl-6-pyrrolyl-1,4-benzoquinone 2 from the natural product perezone 1. The anion–guest properties of the new compound were evaluated in the presence of fluoride, chloride, bromide and iodide tetrabutylammonium salts using 1H NMR titration techniques in deuterated dichloromethane or dimethylformamide. The title compound showed interesting colorimetric behavior in the presence of inorganic salts.

Keywords: Perezone, anion-guest, benzoquinone, pyrrolyl-quinone, ion-pair, quinone sensors.

1. INTRODUCTION

Much effort has been applied toward the synthesis of compounds that selectively recognize anions or cations for use in environmental, industrial, and biological chemical sensors. In medicine, for example, the quantitative and qualitative detection of anions is relevant to processes such as muscle contraction and anion gap function. For example, calcium is involved in biological processes, such as nerve impulse transmission, muscle contraction, and cell activity regulation. Aluminum is implicated in the development of Alzheimer´s disease. These examples highlight the importance of monitoring electrolytes in diagnostic and therapeutic medicine [1]. The development of naked-eye colorimetric anion sensors that do not require sophisticated instrumentation would have widespread utility.

Based on supramolecular concepts, anions can be selectively recognized by functional groups such as amides, ureas, thioureas, and some heterocycles such as imidazole, indole, or pyrrole [2]. Pyrroles, in particular, play an important role in the chemistry of heterocycle-based anion receptors. Dipyrroles or the macrocyclic calixpyrroles are effective and selective receptors for a variety of anionic species, such as fluoride, which is relevant to, for example, osteoporosis [3]. In general, the capacity of the host to recognize an anion lies in the host's ability to coordinate with the anion via Lewis acid, electrostatic, or hydrogen bonding interactions. Such interactions may be monitored by spectroscopic techniques, such as NMR, UV-vis spectroscopy, or X-ray diffraction.

Certain organic compounds can selectively recognize cations. In nature, a variety of cation-binding organic ligands are biologically important, including porphyrin, flavin, and quinones, to name a few [4]. A variety of synthetic cation receptors have been described as well. The most well-known class of such receptors includes the crown ethers, such as cryptands, podands, calixarenes, calixcrowns, which chelate metals [5-7]. Cation receptors containing non-ether groups, such as amides or carbonyl fragments, can also act as excellent cation guest recognizers [8].

Recently, a new class of ion receptors has attracted a great deal of interest by simultaneously coordinating both anionic and cationic guest species [8,9,10]. Such receptors bind to a salt as an associated ion pair. Such ditopic receptors for associated ion-pairs generally display strong binding constants [9-11]. The simultaneous binding of an ion pair species is potentially applicable to the removal of unwanted ions in industrial applications or in polluted water, in addition to clinical diagnosis or treatment approaches.

Electron-withdrawing groups bound to pyrrolyl compounds tend to increase the compound's binding affinity toward anions, such as fluoride [12]. Some quinones have been examined as possible cation or anion receptors [13-15], for example, benzoquinone has been reported to recognize an ion pair [16, 17]; however, pyrrole compounds as a group are the most widely studies class of anion receptors. To our knowledge, no pyrrolyl–quinone compounds have been described as selectively recognizing ions. As part of a general research program toward developing anion-recognizing compounds [18-20], we recently attempted to modify the natural product perezone **1** in an effort to obtain novel compounds capable of recognizing ions. Perezone **1,** a sesquiterpene quinone (2-(1,5-dimethyl-4-hexenyl)-3-hydroxy-5-methyl-1,4-benzoquinone) is an abundant natural product obtained from the roots of plants of the genus Perezia. This compound has been explored in a variety of chemical transformations and biological studies. Its antifeedant and phytotoxic activity [21], inhibition of ADP-induced platelet aggregation [22], promotion of the release of intra-mitochondrial

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Ca^{2+}[23], and induction of cytotoxicity through caspase-dependent or caspase-independent mechanisms have been reported [24]. To our knowledge, no reports have described perezone as an ion-recognizing compound.

From perezone **1**, we synthesized 2-(1,5-dimethyl-4-oxo-hexyl)-3-hydroxy-5-methyl-6-pyrrolyl-1,4-benzoquinone **2**, a candidate chemical sensor that we thought might be able to recognize ions. The compound included an anion-recognizing region (pyrrole as a hydrogen bond donor) and a cation-recognizing region that engaged in Lewis acid interactions via the carbonyl side chain. A redox-active quinone-based chromophore capable of undergoing an intensive change in color was introduced to include a signal-transducing portion of the molecule [25, 26]. (Fig. **1**) It is important to mention that *p*-quinone is widely used as a transducing unit in sensors.

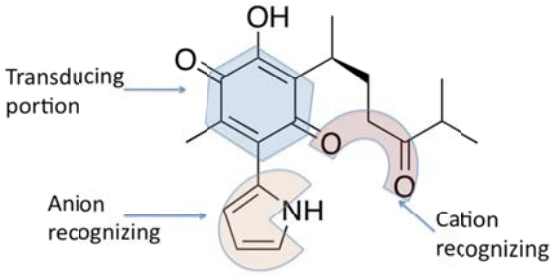


Fig. (1). Schematic representation of compound **2**, along with its anion recognition region (pyrrole hydrogen bond donor), cation recognition region (carbonyl side chain), and a p-quinone transduction region.

2. MATERIALS AND METHODS

Nuclear magnetic resonance spectra were recorded on a Varian Gemini 200 and Mercury 400. ^{1}H NMR spectra were recorded at 200 and 400 MHz and are reported as follows: chemical shift in ppm relative to TMS as an internal standard (for spectra obtained in $CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances). ^{13}C NMR spectra were recorded at 100 MHz, chemical shift in ppm relative to TMS from the solvent signal ($CDCl_3$ δ 77.0 ppm). The NMR experiments were measured in CD_2Cl_2 and DMF-d_6. All employed reagents were purchased from commercial sources. Reagents and solvents were of the highest quality available and used as received. TLC was performed on silica gel plates visualized either with a UV lamp at 254 nm. Flash chromatography was performed on Aldrich silica gel (70-230 Mesh).

2-(1,5-Dimethyl-4-oxo-hexyl)-3-hydroxy-5-methyl-[1,4]benzoquinone 4

To a solution of *2-(1,5-Dimethyl-4-hex-4-enyl)-3,5-dimethyl-1[1,4]benzoquinone* **1** (0.5 g, 2.0 mmol) dissolved in CH_2Cl_2 (4 ml) at 0°C was added 3-Chloroperbenzoic acid (0.35 g, 2.0 mmol). The mixture was allowed to warm up to room temperature and stirred for 16 hrs. The result solution was quenched by adding saturated aq $NaHCO_3$ (10 ml) and extracted with EtOAc (3 X 5 ml). The organic layers were then combined and dried (Na_2SO_4 anh). After concentration under reduced pressure, the crude product was purified by flash chromatography (Hex:EtOAc 8:2) to afford the title compound as a yellow solid; yield 0.32 g, 60%, mp 84 – 87°C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.07 (s, 1H), 6.50 (q, *J* = 1.6 Hz, 1H), 3.02 (m, 1H), 2.55 (m, 1H), 2.40 (dd, *J* = 9.4, 6.3 Hz, 1H), 2.32 (dd, *J* = 9.4, 5.6 Hz, 1H), 2.07 (d, *J* = 1.6 Hz, 3H), 1.99 (m, 1H), 1.86 (m, 1H), 1.23 (d, *J* = 7.1 Hz, 3H), 1.05 (dd, *J* = 6.9, 2.7, 6H)

^{13}C-NMR (101 MHz, $CDCl_3$): δ 214.5, 187.2, 184.1, 151.2, 140.6, 135.7, 123.5, 40.6, 38.9, 29.0, 27.9, 18.2, 18.1, 18.0, 14.7.

2-(1,5-Dimethyl-4-oxo-hexyl)-3-hydroxy-5-methyl-6-(1H-pyrrol-2-yl)-[1,4]benzoquinone 2

To a solution of **4** (0.2 g, 0.66 mmol) dissolved in CH_2Cl_2 (2.5 ml) was added pyrrol (0.1 ml, 1.45 mmol). The mixture was stirred for 2 min, then SiO_2 (1.0 g) was added and the solvent was removed under vacuum. The reaction was kept at room temperature for 16 h. The residue was purified by flash column chromatography (Hex:EtOAc 8:2) to give compound **2** as a blue solid; yield 0.11 g, 44%, mp 68 – 71°C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.99 (s, 1H), 7.45 (s, 1H), 7.12(td, *J* = 2.8, 1.3 Hz, 1H), 6.80 (m, 1H), 6.39 (dt, *J* = 3.9, 2.6 Hz, 1H), 3.11 – 3.00 (m, 1H), 2.56 (m, 1H), 2.39 (m, 2H), 2.31 (s, 3H), 2.11 – 1.99 (m, 1H), 1.94 – 1.82 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.05 (dd, *J* = 6.9, 2.6, 6H)

^{13}C-NMR (101 MHz, CDCl3): δ 214.5, 190.7, 183.0, 151.2, 133.4, 129.0, 126.3, 124.1, 122.1, 119.3, 110.6, 40.7, 39.0, 29.4, 28.2, 18.34, 18.3, 18.2, 14.4

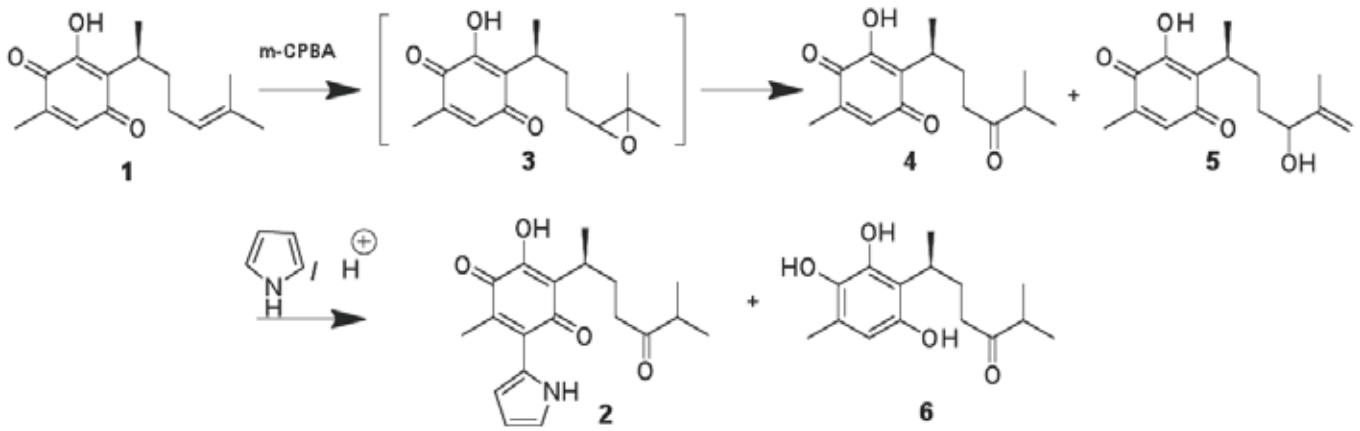
LR-MS(EI):m/z (rel int): 331([M+2], 12), 330([M+1],35), 329([M+], 100), 311(15), 244(58), 230(47). HR-MS (FAB+) 330.1708 (estimated, 330.1705).

NMR Studied on Host and Guest

The NMR experiments were measured in CD_2Cl_2 and DMF-d_6. The solution 0.01 M of **2** in deutered solvent was added with different equiv of solid tetrabutylammonium salts (F-, Cl-, Br- and I-) was recorded.

3. RESULTS AND DISCUSSION

The synthesis of compound 2 is shown in Scheme 1. Perezone **1** was reacted with *m*-CPBA to give the oxirane **3**, a precursor to the carbonyl which is at a strategic position on the molecule. It should be noted that oxiranes often undergo a rearrangement involving a 1,2-hydrogen migration to form aldehydes or ketones (Meinwald rearrangement) under Lewis acid or metal catalyzed conditions. Such reactions generally require high temperatures and long reaction times [27]. To our surprise, the epoxide **3** rearranged spontaneously to give the corresponding ketone **4** in the absence of solvent or catalyst. The corresponding allylic alcohol **5** was isolated from the reaction mixture as a byproduct, suggesting that the mechanism proceeded through a carbocation intermediate, possibly catalyzed by the quinone moiety.



Scheme 1. Synthesis of compound **2**.

To obtain the corresponding pyrrolyl–quinone **2,** compound **4** was reacted with pyrrole in the presence of a protic acid; however, the reaction was unsuccessful. Nucleophiles, such as amines or indoles, were incorporated into the perezone quinone ring by heating with $Zn(AcO)_2$ at 40°C for 48 h, or with NaH under reflux for 24 h [28, 29]. In an attempt to explore alternative green synthetic methods, the reaction was tested in the presence of non-toxic inexpensive silica gel. (Silanol groups are weakly acidic.) The silica gel proved to be an efficient catalyst, providing a recyclable surface for the alkylation of heterocyclic aromatic compounds [30-32]. The reaction was carried out efficiently at room temperature under solvent-free conditions over 12 h. The reaction mixture was eluted with CH_2Cl_2, and compound **2** was purified by column chromatography to obtain an amorphous purple solid with a 44% yield. Although no starting material was recovered, oxyhydroquinone **6** (reduced oxo-perezone) was isolated from the reaction mixture. When the reaction was carried out without silica gel, traces of the product did not appear until at 7 days after initiation. The new pyrrolyl–quinone compound was characterized by ^1H and ^{13}C NMR spectroscopy and by low-resolution and high-resolution mass spectrometry (LRMS and HRMS, respectively).

The anion–guest properties of **2** were evaluated in the presence of fluoride, chloride, bromide, and iodide tetrabutylammonium salts using 1H NMR titration techniques in deuterated dichloromethane at 298°K by following the induced shifts in the NH resonances upon complexation. The addition of fluoride first resulted in the disappearance of the quinone alcohol signal by adding 0.1 molar equivalents. Subsequently, the NH proton shift shifted at 10.5 ppm, indicating competition between the OH and NH groups for the formation of a hydrogen bond. The use of dimethyl formamide as a solvent yielded a maximum NH proton shift of 12.8 ppm. We assumed that DMF solvated the alcohol and prevented the formation of a complex with the anion, thereby paving the way to the NH pyrrole. The NH chemical shifts for the NMR spectra in DMF as a function of fluoride concentration are shown in (Fig. **2**). Interestingly, no proton shifts were observed in the presence of the other anions, indicating that compound **2** was selective for fluoride. This is interesting because fluorine has been accused of numerous human pathologies [33].

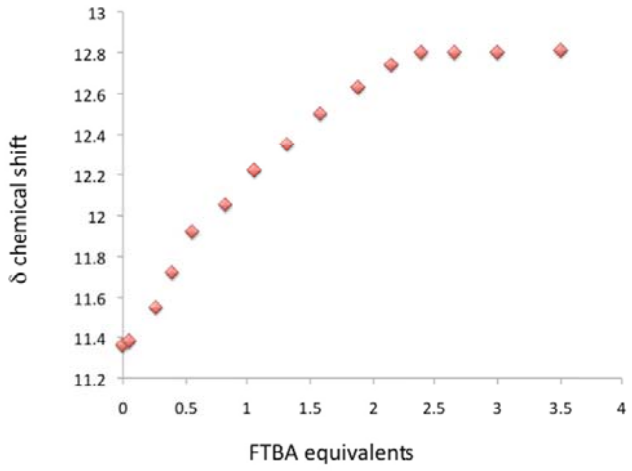


Fig. (2). ^1H NMR titration plot of compound **2** NH resonance upon addition of tetrabutylammonium fluoride dimethylformamide-d_7 at 298 K.

Compound **2** is expected to recognize anions via hydrogen-bonding and cations via Lewis acid interactions with the ketone and quinone carbonyl groups. With this in mind, we conducted preliminary complexation tests using inorganic salts. Filter paper was impregnated with compound **5** and immersed in a solution containing a test salt (0.1 M). This system permitted observation of the Lewis acid interactions via a change in color from purple to green ($Bi(NO_3)_3$), gray-green ($KMnO_4$), gray ($NaNO_2$), brown ($CuSO_4$), or yellow ($NaHCO_3$) (Fig. **3**).

4. CONCLUSION

In summary, a new fluoride-selective anion recognition system based on a pyrrolyl–quinone was easily obtained from the natural product perezone in two steps. The double bond was oxidized via oxirane rearrangement, followed by the chemoselective addition of pyrrole to the benzoquinone in good yields via an environmentally friendly, simple, and solvent-free approach. This last reaction remains under study, and we anticipate reporting the method as a generalized approach. The ion recognition properties are both interesting and useful for a variety of applications. The range of colors provided by compound **2** in the presence of aqueous

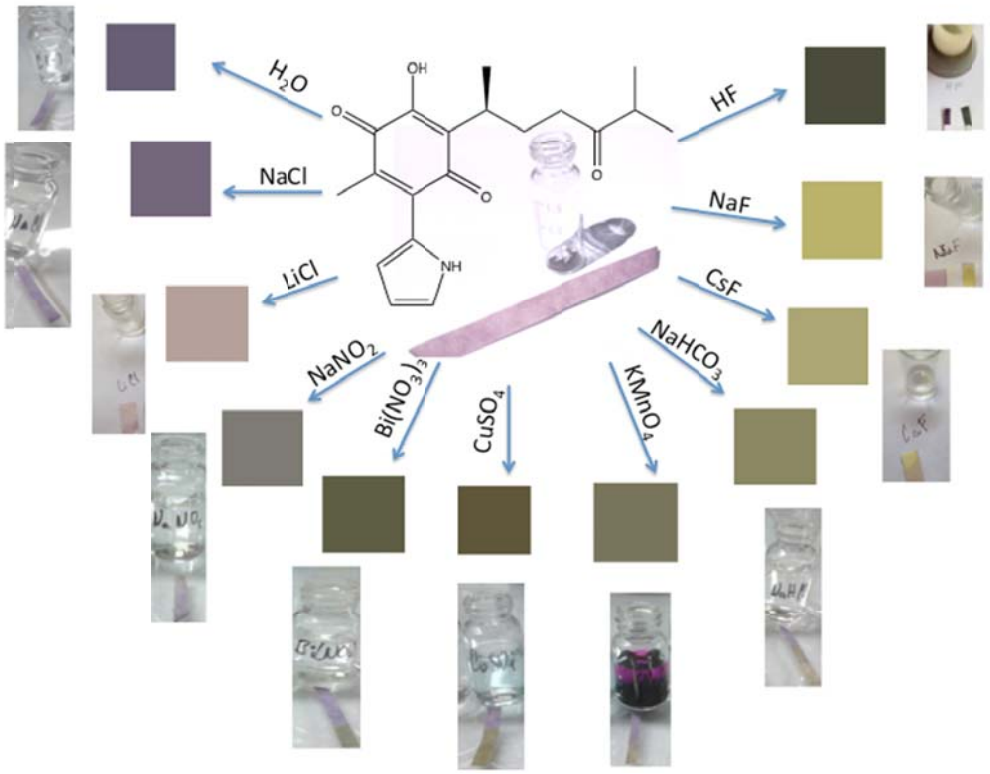


Fig. (3). Naked-eye colorimetric changes displayed by compound **2**, which had been impregnated into filter paper and exposed to different inorganic salts.

inorganic salts is large, and the colors correspond uniquely to each of the salts tested in this experiment. The chiral center in compound **2** may be useful for the detection of chiral ions.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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