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"Supramolecular Circuitry": Three Chemiluminescent, Cucurbit[7]uril-Controlled On/Off Switches

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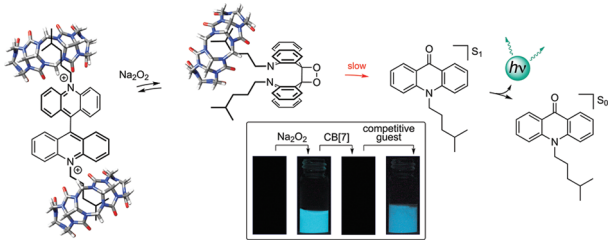
ABSTRACT



Three Cucurbit[7]uril-controlled chemiluminescent on/off switches based on the lucigenin motif have been synthesized. Light emission is triggered upon addition of sodium peroxide, interrupted or dimmed in the presence of Cucurbit[7]uril, and restored upon injection of a competitive guest. The process, which can be mimicked by a simple resistor-capacitor circuit, is rationalized by examining the role of the macrocyclic host on the network of equilibria involved in the chemiluminescent process.

There is an ongoing effort in the supramolecular community to replicate biological recognition mechanisms with smaller, less complex organic guests and hosts; one of these mechanisms is the thermodynamically or kinetically controlled stabilization of reactive species, intermediates, and otherwise unstable conformations within the pocket of a larger host.[1] While the stabilizations of cyclobutadiene[2a] and benzyne[2b] into hemicarcerands are now classical supramolecular landmarks, recent examples of intermediate stabilization also include the controlled encapsulation of isoimides,[3a] hemiaminals,[3b] and hemiacetals.[3c]

In this study, we wanted to assess whether a member of the cucurbituril family of macrocycles (CB[*n*]) could allosterically affect a network of equilibria between several reactive species, by interacting selectively with subunits remote from the reaction centers. CB[*n*]s are pumpkin-shaped macrocycles that have generated tremendous interest in the past 10 years due to their exceptional recognition properties;[4] they bear *n* glycoluril motifs linked by methylene bridges, two hydrophilic carbonylated portals, and a hydrophobic cavity and display the strongest noncovalent

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interaction ever measured toward selected guests[4c,d] (see Figure 1 for the structure of CB[7]).

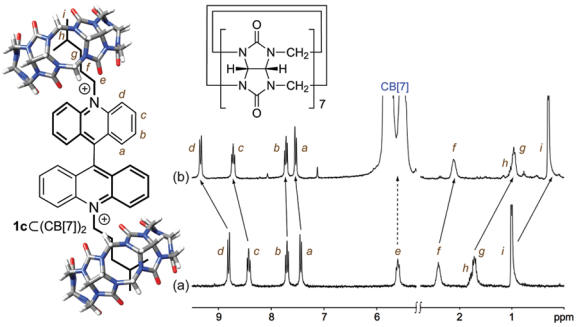

Figure 1. Structure of CB[7]. ^{1}H NMR spectra of (a) lucigenin derivative **1c** and (b) [3]pseudorotaxane **1c**⊂(CB[7])$_2$.

CB[*n*]/guest interactions can be readily monitored by nuclear magnetic resonance spectroscopy (NMR), and in some cases, these interactions are accompanied by changes in absorption and fluorescence properties.[5] However, to the best of our knowledge, they have never been monitored by chemiluminescence, a visually appealing phenomenon widely applied to analytical chemistry[6] in immunoassays, in the detection of proteins, drugs, and pollutants, as well as in the assessment of oxidative stress. This prompted us to test whether a CB[*n*]-controlled light-on/light-off switch could be developed, by perturbing the complex equilibria between the various partners of a chemiluminescent process. Lucigenin and their derivatives (*N*,*N*′-disubstituted-9,9′-biacridiniums; **1a**−**1d**) happen to be ideal structures for such a project, since they are expected to interact with CB[*n*]s via their *N*-substituents, the positively charged acridinium surroundings interacting with the carbonylated portal of CB[*n*], and the *N*-substituent sitting within the cavity of the macrocycle. Cyan light is emitted upon addition of hydrogen peroxide under basic conditions.[7]

Lucigenin derivatives **1b**−**1d** were prepared by *N*-alkylation of acridone, followed by zinc-promoted reductive coupling, and oxidation of the resulting biacridylidenes with aqueous nitric acid.[8] Substituents were chosen to span a significant range of binding affinities toward CB[7] (1.0×10^5, 1.3×10^6, and 1.7×10^9 M^{-1} in the case of guests **1b**−**1d**, respectively, as determined by competitive ^{1}H NMR titration in a 50 mM acetate buffer (pD 4.74) with guests[4b] having a known affinity toward CB[7]).[9] The characteristic[10] upfield shift of hydrogen nuclei located within the cavity of CB[7] was observed (Figure 1), and hydrogens located close to the CB[7] rim underwent a moderate downfield shift.[10]

To envisage how CB[7] may perturb the chemiluminescence of lucigenin derivatives **1** in the presence of alkaline hydrogen peroxide, one should first address the degradation pathways of acridinium units, which have been investigated over the past four decades (Figure 2). Lucigenin derivatives **1** undergo rapid reversible hydroxide and hydroperoxide anion additions to their 9- and 9′-positions, affording species such as biacridans **2a**−**2c**, acrylidene oxide **2d**, and 1,2-dioxetane **2e**.[7] While those intermediates undergo various complex nonchemiluminescent degradation processes,[7] a very minor pathway is the conversion of 1,2-dioxetane **2e** to biradical **3**, upon electron transfer from the nitrogen lone pair to the four-membered ring, and concomitant O−O bond cleavage.[11] Subsequent C−C bond cleavage leads to the formation of acridone **5** and diradical zwitterion **4**; intermediate **4** then relaxes to $S_1(\pi,\pi^*)$ acridone **5*** via back electron transfer and finally to $S_0(\pi,\pi^*)$ acridone **5** with emission of a photon.[11] According to previous studies,[7] both the rate of consumption of lucigenin and the light emission decay should follow pseudo-first-order kinetics, with very similar rate constants. Since the dynamic equilibria between lucigenin derivatives **1** and intermediates **2** are much faster than the formation of biradical **3** from dioxetane **2e** (a pre-equilibrium situation),[11] we expected that the rate of formation of acridone **5** could be greatly reduced, and the light emission dimmed or even interrupted, if lucigenin derivatives **1** were stabilized to the expense of biacridans **2** upon interaction with CB[7]. It has been reported on several occasions, in particular by Nau[12a−c] and Macartney,[12d] that ammonium cations undergo a significant pK_a shift upon encapsulation by CB[*n*]s (usually 1.2−4.5 pK_a units), since the cation displays a greater affinity than the neutral amine toward CB[*n*]s (corresponding to a 1.6−6.1 kcal/mol extra stabilization by CB[*n*]s). A similar trend is expected between positively charged biacridiniums **1** and neutral biacridans **2**, especially since the latter can probably accommodate only one CB[7] unit, according to semiempirical PM6-D optimization (Figure 3h).

As expected, upon addition of an excess amount of sodium peroxide (total concentration 0.10 M) to a solution of lucigenin derivatives **1a**−**1d** (1.0 mM), cyan light was emitted (λ_{max} = 485 nm; chemiluminescence quantum yields $(0.4-2.7) \times 10^{-3}$ einstein/mol, in accordance with

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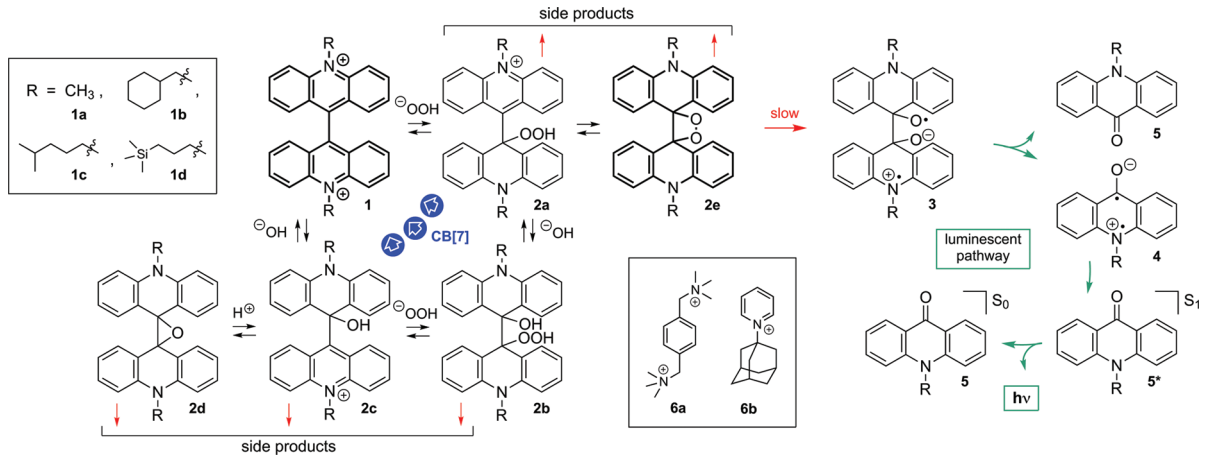

Figure 2. Plausible chemiluminescent pathway for the decomposition of biacridiniums **1a**−**1d**, and their stabilization by CB[7]. Structure of competitive guests **6a** and **6b** (trifluoromethanesulfonate as the counteranion).

previous characterizations of similar structures).[13] The emission intensity was monitored at 510 nm, at which wavelength acridiniums **1** barely absorb the emission of acridone **5*** (Figure 3a), and an exponential intensity decay was observed as a function of time, at least in the case of biacridiniums **1a**−**1c**; the decomposition of lucigenin derivative **1d** is clearly more complex (see Figure 3b for a logarithmic plot of the emission intensity vs time and the corresponding linear regressions; rates of light emission decays are 1.8×10^{-3}, 2.0×10^{-3}, and 5.8×10^{-3} s^{-1} in the case of acridiniums **1a**−**1c**, respectively). As mentioned on several occasions,[7b,13] reaction quantum yields of acridones **5** are very low (4−38%).

After 2 min, CB[7] (2.0 equiv) was added to the reaction cuvette, and light emission was immediately interrupted in the case of lucigenin derivatives **1c** and **1d** and dimmed approximately 10-fold when using biacridinium **1b**, which displays the weakest affinity toward CB[7] (Figure 3d−3g). Yet a series of complications prevent us from providing a quantitative relationship between the intensity attenuation and the binding affinity of precursors **1** and intermediates **2** toward CB[7]: (1) binding affinities of biacridiniums **1** cannot be measured under the conditions leading to their chemiluminescence and will differ, at least partly, from those determined in the reference acetate buffer; (2) while lucigenin derivatives **1c** and **1d** are both expected to be doubly encapsulated by CB[7], biacridinium **1b** probably coexists as a time-dependent mixture of free, [2]-, and [3]pseudorotaxane **1b**, **1b**⊂CB[7], and **1b**⊂$(CB[7])_2$; (3) biacridans **2** are likely to be present as time-dependent mixtures of free and monoencapsulated structures; (4) CB[7] may also complex acridones **5** as well as various intermediates and side products along the reaction pathway, albeit weakly. Overall, the rate retardation of the chemiluminescent reaction is caused by a preferential stabilization of lucigenin derivatives **1** by CB[7] over the transition state of the slow electron transfer from dioxetane **2e** to diradical **3**; since the geometry of the transition state is expected to resemble dioxetane **2e**, we consider that the stabilization of the latter by CB[7] likely mimics the stabilization of the transition state; in other terms, rates of electron transfers from dioxetane **2e**, **2e**⊂CB[7], and **2e**⊂$(CB[7])_2$ to the corresponding biradicals **3** are considered to be similar.

Addition of CB[7] to lucigenin (**1a**), which lacks the host binding site, does not interrupt the chemiluminescent reaction. To the contrary, CB[7] enhances its rate by a factor of 1.3 (Figure 3c); unfortunately, the complexity of the process prevents us from offering any justification for this phenomenon.

After an additional 6 min period, a competitive guest with a very high affinity toward CB[7] was added to release lucigenin derivatives **1b**−**1d** (xylylene **6a**, binding affinity 1.5×10^{10} M^{-1}; adamantylpyridinium (**6b**), binding affinity[4b] 2.0×10^{12} M^{-1}). The rate of the dissociation−association guest exchange process is expected to depend on the overall free Gibbs energy difference between CB[7]-encapsulated biacridinium **1** and the transition state of the dissociation or the association step, whichever is at higher energy. Consequently, (1) CB[7] was immediately ejected from pseudorotaxanes **1b**⊂CB[7] and **1b**⊂$(CB[7])_2$, and light emission was fully restored with no intensity loss (Figure 3d); (2) the same process was slightly slower with [3]pseudorotaxane **1c**⊂$(CB[7])_2$ (Figure 3e and the rounded section of the intensity profile between 480 and 500 s); (3) guest exchange with assembly **1d**⊂$(CB[7])_2$ was significantly slower, due to the stronger affinity of CB[7] toward the trimethylsilyl substituent. The effect is particularly pronounced when the competitive bulky adamantyl unit slips through the portal of CB[7], and this association is likely the rate-determining step. One should stress that this on−off−on switch, which shows no intensity loss after the 6-min long "off" period (at least in the case of

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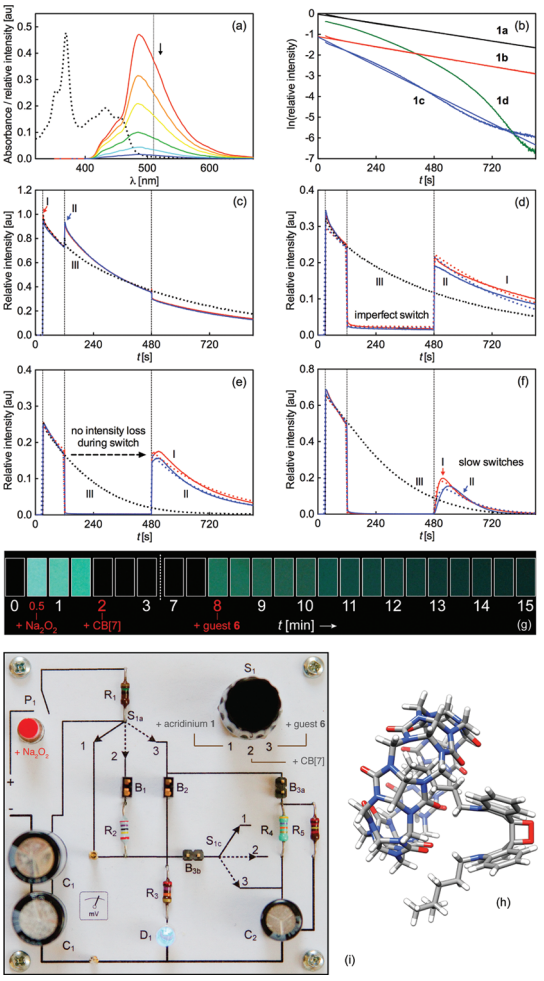

Figure 3. (a) Absorption (50 μM; dashed) and chemiluminescence spectra of biacridinium **1c** (0.25, 2, 3, 5, 7, and 10 min after peroxide injection). (b) Logarithmic plot of the light intensity decay vs time, with linear regressions indicating pseudo-first-order kinetics. Light emission decays of lucigenin derivatives (c) **1a**, (d) **1b**, (e) **1c**, and (f) **1d**. CB[7] is added at t = 120 s and competitive guests **6a** (red profiles, noted 'I') or **6b** (blue profiles, noted 'II') at t = 480 s. Reference profiles (dashed, and noted "III") are recorded in the absence of CB[7] and competitive guest. (g) Photographs of the on/off/on switch obtained with lucigenin derivative **1c** and competitive guest **6a**. (h) PM6-D optimized structure of dioxetane **2e**⊂CB[7] (obtained from biacridinium **1c**). (i) Resistor-capacitor circuit mimicking the luminescence profiles of biacridiniums **1b**–**1d**.

biacridiniums **1b** and **1c**; Figure 3d and 3e), is operational only because the various nonchemiluminescent degradation pathways do not target encapsulated (i.e., thermodynamically stabilized) lucigenin derivatives **1** as long as pseudobases **2** are depleted from the reaction mixture.[7] Some moderate intensity loss is observed in the case of biacridinium **1d** (Figure 3f), thereby indicating that the latter may undergo side reactions even while encapsulated.

Finally, like many supramolecular chemists who enjoy linking nanoscopic phenomena to macroscopic devices (molecular "plugs and sockets", "shuttles", "elevators", and "muscles" being just a few examples),[14] we found it didactically appealing to design the simplest electronic circuit possible, which would mimic our light-emitting chemical system (Figure 3i), with one general rule: one chemical action (addition of a reagent, for example) must correspond to one user action on the circuit: (1) adding sodium peroxide to a solution of biacridiniums **1** is mimicked by activating switch P_1 and charging capacitor C_1 (the small resistor R_1 prevents the shortcircuit of capacitor C_1 upon charging and can mimic the duration of the sodium peroxide injection that is nonzero). When switch S_1 is in position "1", capacitor C_1 discharges through resistor R_3 and diode D_1; the exponential voltage decay at capacitor C_1 is equivalent to the pseudo-first-order intensity decay of our chemiluminescent system. (2) Adding CB[7] is mimicked by switching S_1 to position "2". In the case of a perfect switch (biacridiniums **1c** and **1d**), bus B_1 is open and the circuit is interrupted; to mimic the imperfect switch with acridinium **1b**, bus B_1 is closed and capacitor C_1 is discharged over a large resistor R_2 in addition to R_3 and the diode. (3) Switching S_1 to position "3" corresponds to the injection of competitive guest **6a** or **6b** to the reaction cuvette; if the guest exchange is fast (lucigenin derivatives **1b** and **1c**), bus B_2 is set as closed, and capacitor C_1 discharges through resistor R_3 and diode D_1 again; if the exchange is relatively slow (acridinium **1d**), the progressive increase in light intensity (Figure 3f) can be mimicked by the charge of a smaller capacitor C_2 through resistor R_4 (buses B_{3a} and B_{3b} are closed and bus B_2 is open; resistor R_5 is added to counterbalance the added capacity and also mimics the intensity loss observed with this switch). As long as diode D_1 is replaced by a light source with a voltage-independent resistance, red and blue dashed lines in Figure 3d–3f represent the voltage profiles best fit to our chemiluminescence intensity measurements, and the overlap is pleasantly satisfactory.

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Supporting Information Available. Preparation and characterization of lucigenin derivatives **1b**–**1d**, their precursors **5b**–**5d**, and their interlocked assemblies with CB[7]; kinetic procedures, binding affinity measurements, and circuit diagram. This material is available free of charge via the Internet at http://pubs.acs.org.

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