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A Molecular Keypad Lock: A Photochemical Device Capable of Authorizing Password Entries

David Margulies, Clifford E. Felder, Galina Melman, and Abraham Shanzer*

Contribution from the Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

Received July 25, 2006; E-mail: abraham.shanzer@weizmann.ac.il

Abstract: This paper describes a new concept in the way information can be protected at the molecular scale. By harnessing the principles of molecular Boolean logic, we have designed a molecular device that mimics the operation of an electronic keypad lock, e.g., a common security circuit used for numerous applications, in which access to an object or data is to be restricted to a limited number of persons. What distinguishes this lock from a simple molecular logic gate is the fact that its output signals are dependent not only on the proper combination of the inputs but also on the correct order by which these inputs are introduced. In other words, one needs to know the exact passwords that open this lock. The different password entries are coded by a combination of two chemical and one optical input signals, which can activate, separately, blue or green fluorescence output channels from pyrene or fluorescein fluorophores. The information in each channel is a single-bit light output signal that can be used to authorize a user, to verify authentication of a product, or to initiate a higher process. This development not only opens the way for a new class of molecular decision-making devices but also adds a new dimension of protection to existing defense technologies, such as cryptography and steganography, previously achieved with molecules.

Introduction

The increasing role electronic devices play in our daily lives, as well as our constant need to pursue superior technologies, have raised a wide interest in the development of molecular systems mimicking the operation of electronic logic gates and circuits.[1−31] Besides their integration in the heart of digital computers, electronic logic circuits control the operation of a variety of devices around us,[32] from calculators and store automation to video games and music equipment. In the past few years, the feasibility of molecular logic gates to be integrated into practical decision-making devices has also been demonstrated. Although these devices so far include merely an interactive game,[33] a few moleculators[34] (see also refs 35−50), and a comparator,[50] such progress raises an unavoidable thought

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regarding our ability to create a molecular analogue for every electronic product.

An important electronic logic device, which has not yet been mimicked at the molecular level, is a keypad lock.[32] This device is used for numerous applications in which access to an object or data is to be restricted to a limited number of persons. What complicates an electronic keypad circuit over a simple logic gate is the fact that its output signals are dependent not only on the proper combination of the inputs but also on the correct order by which these inputs are introduced. In other words, one needs to know the exact password that opens this lock.

The development of a molecular-scale keypad lock is a particularly attractive goal as it represents a new approach for protecting information at the molecular scale. Molecular security is currently achieved by steganography or cryptography methods,[51] used to hide or to encrypt a message, respectively. Invisible inks are a classic example of chemical steganography. These materials provide hidden images that cannot be photocopied, thus securing the authentication of a variety of products. Enhanced security can be achieved using erasable materials[52] and their compression into high-density storage devices.[53] Molecular cryptography has also been accomplished through various methods for encrypting messages on DNA strands.[54−56]

In this paper, we propose a password entry, considered as the front line of defense against intruders, as a third approach for securing information at the molecular scale. A password entry is used neither to hide nor to encrypt information but rather to prevent access from an unauthorized user.[51] We prove the feasibility of this approach by demonstrating a reconfigurable molecular keypad lock whose fluorescence is revealed only in response to correct sequences of three input signals. We first describe the design and function of a programmable molecular device, capable of executing a range of Boolean functions. Then, we depict the way these functions could be integrated into a more complex circuitry at the molecular scale. Specifically, we have developed a kinetically controlled, priority-AND molecular logic gate, capable of authorizing different photoionic passwords.

Results and Discussion

An Electronic Keypad Lock. An electronic keypad lock is a common security device, comprised of several interconnected logic gates, that can control an opening of a door or a safe, an alarm system, and more. Figure 1 describes a 3-input AND logic gate (left) and a particular example of a simple electronic lock (right), which also processes three input signals. Both devices generate a high output in response to three high inputs, namely, A and B and C; however, the electronic keypad lock is more selective, as it produces an electrical signal to only one (ABC) out of six possible combinations of ABC, ACB, BAC, BCA, CAB, and CBA. Specifically, in the electronic lock, which integrates three 2-input AND logic gates, LED D1 will switch ON only when buttons S1, S2, S3 are pushed in the right order.

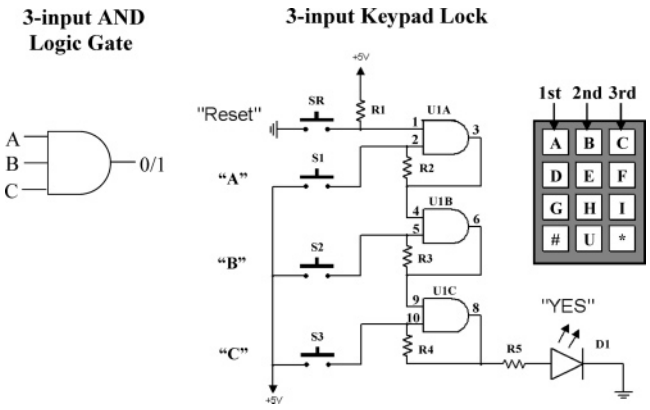

Figure 1. (Left) Three-input molecular AND logic gate and (right) three-input electronic keypad circuit. What complicates an electronic keypad circuit over a simple logic gate is the fact that its output signal is dependent not only on the proper combination of the inputs but also on the correct order by which these inputs are introduced. The lock, obtained from the integration of several AND logic gates, generates an electronic output only when the relevant password keys (ABC) are pushed in this exact order.

Pin 1 is held HIGH by R1. This enables gate U1A, and when button S1 is pressed, the output at pin 3 will go HIGH. It locks itself ON through R2 and enables gate U1B, by taking pin 4 HIGH. Now, if S2 is pressed, the output of gate U1B will lock itself ON through R3, and by taking pin 9 HIGH, enable gate U1C. Pressing S3 will cause gate U1C to do the same thing, only this time its output at pin 8 through R5 turns LED D1 ON. Each of the other buttons in the keypad can be connected to a RESET button SR, so if pressed the circuit will reset and the password entry will fail. During this moment, pin 1 goes LOW, hence the output at pin 3 will go LOW. It locks itself OFF through R2 and disables gate U1B, by taking pin 4 LOW. In a similar way, the output at pin 6 will go LOW and the output at pin 8 will go LOW. This will switch LED D1 OFF.

Design. To realize a molecular logic device capable of distinguishing between different input sequences, we exploit our experience in the design and synthesis of fluorescent biosensors mimicking the function of siderophores;[57−71] these are the

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natural microbial iron chelators secreted by bacteria to bind extra-cellular iron and mobilize it into their cells. Harnessing this ingenious bacterial machinery to control over iron−ligand binding state, we were able to demonstrate a range of devices, including molecular carriers,[63−71] a molecular switch based on iron translocation,[72] and more recently a reconfigurable molecular logic gate endowed with calculating skills.[39] The latter device has been further developed to a complete Boolean network of seven logic gates. Remarkably, this array has shown a preferential response to particular sequences of input signals, which can encode photoionic passwords.

A molecule assembled as Fluorescein−Linker−Pyrene (FLIP) is a reconfigurable logic gate that can operate as a molecular keypad lock (Figure 2a). The binding site of FLIP resembles the natural coprogen siderophore having three hydroxamic acids capable of selectively binding iron in great efficiency and a proline group, which facilitates its folding around the metal ion. Two fluorophores, pyrene (donor) and fluorescein (acceptor), are attached at both terminus of the receptor chain, enabling the molecule to fluoresce at two distinct regions, blue and green, respectively. To force the fluorophores to approach in close proximity to the ferric ion, two of the hydroxamate binding sites were directly attached to the fluorophores in a way that dictates an oriented position upon binding. Empirical force field (EFF) calculations[70] have shown that in the presence of iron(III), the hydroxamate binding groups wrap around the metal ion in a roughly octahedral arrangement that constrains the molecular backbone into a highly ordered helical twist. In the most stable conformation, the two fluorescent groups are situated parallel to each other, with their centroids 7 Å apart and with a projection angle close to 30° (Figure 2b).

Although a reversible binding of iron can induce merely two states on the molecule, i.e., bound or nonbound (Figure 2a,b), the effect of acid and base input signals on FLIP is somewhat more complex, as fluorescein can equilibrate between several ionization states, consisting of no less than seven protolytic forms.[73−80] As each of the states possesses a characteristic absorption spectrum, it is possible to follow the changes that occur upon protonation.

Figure 2c depicts a few examples. In ethanol, two peaks are observed with maximums at 344 and 500 nm, corresponding to the pyrene and fluorescein units, respectively. Under these conditions, fluorescein seems to exist mainly in its monoanion form F(−1). Although, a protolytic equilibrium between the mono- and dianion species might provide a more accurate description for FLIP in ethanol, for simplicity we will refer to this state as monoanion F(−1) predominant form. This interpretation is in good agreement with previous studies, which regard the monoanion as the predominant species in ethanol.[78]

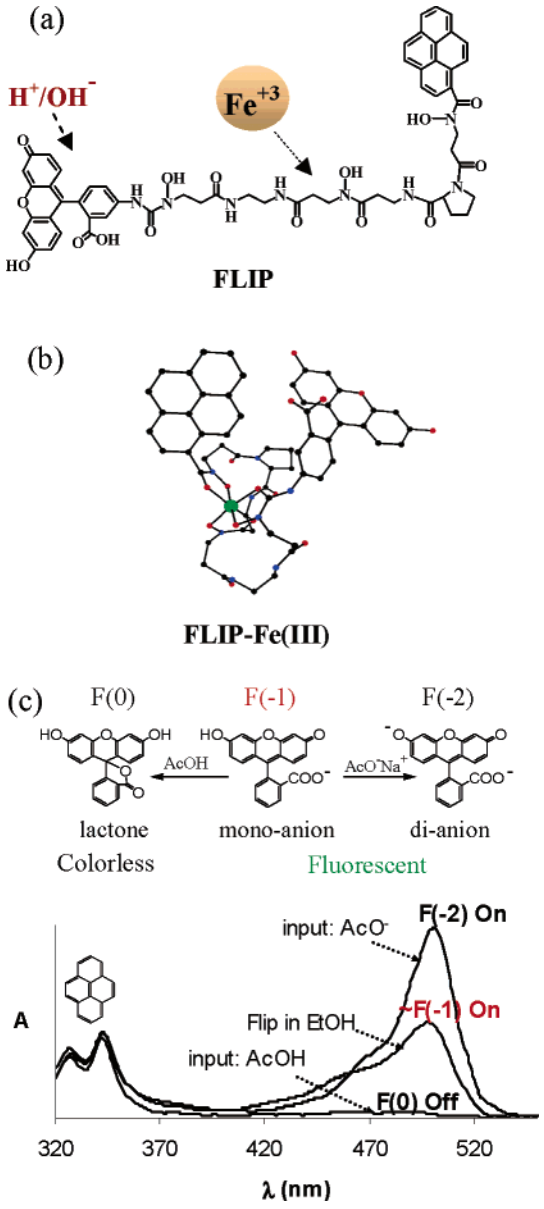

Figure 2. Reconfigurable molecular logic gate capable of performing as a molecular keypad lock. (a) Processing molecule is composed as Fluorescein−Linker−Pyrene (FLIP). The functional linker mimics the structure of a natural bacterial iron(III) carrier (siderophore), whereas the two fluorophores, pyrene and protonable fluorescein, function as blue and green emission channels, respectively. (b) Calculated structure of the iron complex performed by EFF force field program.[70] (c) Changes that occur on the absorption spectra of FLIP in response to acid and base input signals. Changes are observed at 500 nm, where the protonable fluorescein absorbs, whereas the spectrum of the chemically inert pyrene unit (344 nm) remains unchanged. In ethanol solution, the monoanion fluorescein F(−1) is prevalent. Addition of sodium acetate results in a characteristic peak of the highly fluorescent dianionic form F(−2), whereas insertion of acetic acid provides the colorless non emissive lactonic species, F(0). Conditions: 8.7 μM FLIP in ethanol, inputs: 2% aqueous solutions of AcOH or AcO^-Na^+, 0.01N.

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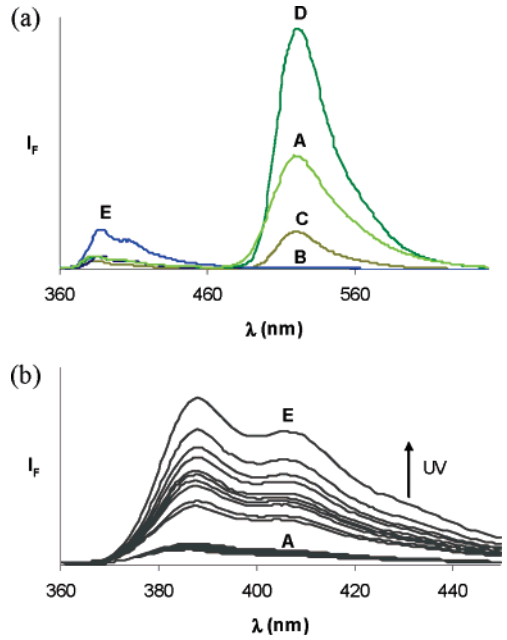
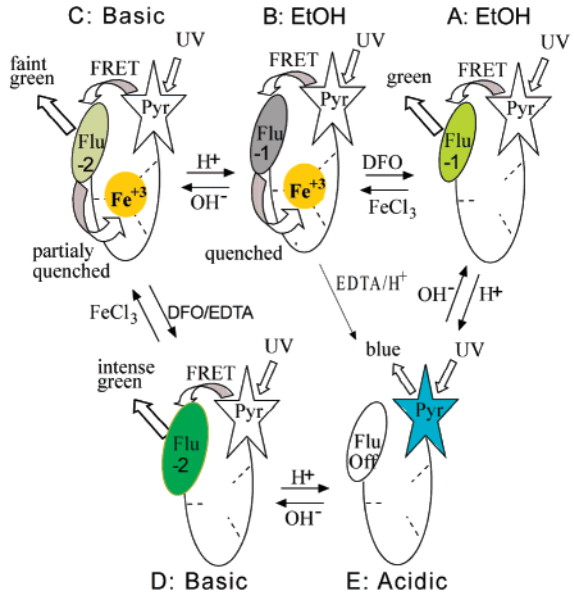


Figure 3. (a) Fluorescence spectra for states A−E excited at 344 nm, corresponding to Scheme 1: (A) 1 mL FLIP 0.5 μM in ethanol, (B) A + 1 eq $FeCl_3$, (C) B + 10 μL $AcO^-Na^+_{(aq)}$ 2 M, (D) A + 10 μL $AcO^-Na^+_{(aq)}$ 2 M, (E) A + 10 μL $HCl_{(aq)}$ 1 M or 20 μL $AcOH_{(aq)}$ 1 M. (b) Repeated scans under continuous excitation at 344 nm revealed light induced fluorescence enhancement of the blue channel in state E. Whereas in ethanol (A) a minor enhancement of pyrene emission intensity was observed,[81] in acidic environment (E) this transformation is far more significant. Each scan corresponds to 18 s of irradiation of E in AcOH.

Scheme 1. Fluorescence Outputs of FLIP Can Interchange in Such a Way That a Boolean Network Is Established[a]



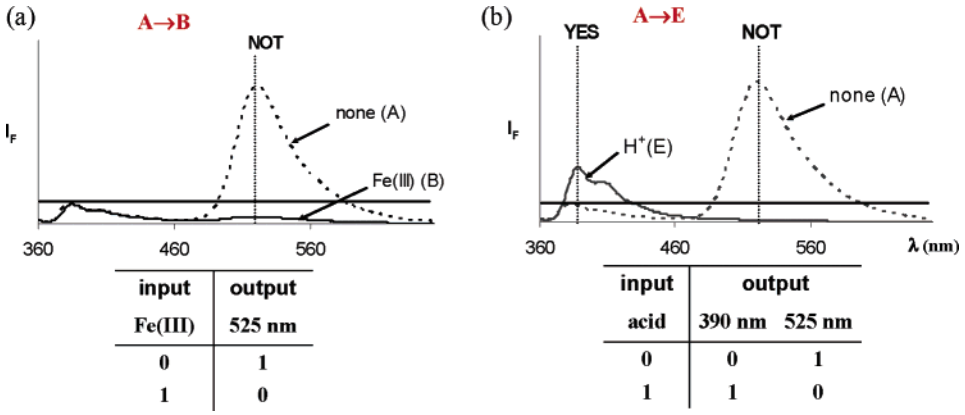
[a] A green fluorescence emission is achieved in ethanol when the ferric ion is not bound and the fluorescein (Flu) is in its monoanion F(−1) fluorescent forms (A). Addition of iron(III) to the ethanol solution of FLIP results in a fluorescence quenching by the metal ion (B) and almost a total elimination of fluorescein emission. When a base is added to B, the monoanion fluorescein F(−1) deprotonates to its more fluorescent dianion F(−2) form, resulting in a faint green luminescence from the iron complex (C). Extraction of iron from state C or, alternatively, addition of a base to state A generates state D, in which the metal quencher is not bound and fluorescein is in its highly emissive dianion F(−2) state (D). A blue fluorescence (E) is generated in acidic media when the fluorescein is not emitting (Off) and iron(III) is not bound. Consequently, the FRET process does not take place and the green emission of the fluorescein unit is replaced with a blue pyrene luminescence.

Upon addition of acetic acid to FLIP in ethanol, a total elimination of fluorescein absorption is observed, indicating that the neutral fluorescein F(0) is obtained in its colorless, non conjugated, lactonic form. The fact that the acidification of the solution takes place in an organic solvent rather than in a polar aqueous solution is the reason for a preferential formation of the lactonic species over the quinoid or zwitterion neutral forms.[75] Alternatively, when a base is added to FLIP in ethanol, an enhancement of the absorption spectrum of fluorescein at 500 nm is observed, and a typical absorption peak of the dianion F(−2) is formed. In opposed to pH-dependent transformations of fluorescein absorption, the absorbance of the pyrene aromatic unit (344 nm), having no protonable functional groups, remained unchanged. The relevant emissions bands, corresponding to each of the states in Figure 2c, are presented in Figure 3.

Five Fluorescent States. Through a reversible binding of iron and/or protonation of the fluorescein unit, several chemical states can be obtained from FLIP. Scheme 1 describes the conditions by which the fluorescence outputs of FLIP can be controlled, in a way that a Boolean network is established. A key principle for understanding this scheme is the fact that mainly the dianion F(−2) and monoanion F(−1) forms contribute to the fluorescein emission at 525 nm. In addition, the first is known to possess higher quantum yield.[73] The corresponding fluorescence spectra for states A−E are shown in Figure 3a.

Five different fluorescence states can be obtained from FLIP, namely, a green luminescence at 525 nm (A), no emission (B), faint green emission (C), intense green fluorescence (D), and blue emission at 390 nm (E). State A describes a green fluorescence emission achieved in ethanol when the ferric ion is not bound and the fluorescein is in its monoanion F(−1) fluorescent form (Figure 2c). In this case, fluorescence resonance energy transfer (FRET) takes place between the donor (pyrene) and acceptor (fluorescein) leading a predominant emission from the fluorescein unit. Addition of iron(III) to the ethanol solution of FLIP results in a fluorescence quenching by the metal ion (B) and almost a total elimination of fluorescein emission is obtained from FLIP−Fe(III), as expected from a fluorescent siderophore analogue upon iron binding.[63−71]

State C describes the change that occurs when a base is added to the ferric complex in ethanol. As depicted in Figure 2c, under such conditions the monoanion fluorescein unit F(−1) deprotonates to its more fluorescent dianion F(−2) form,[73] resulting in an increased emission from the complex, in such a way that a faint green luminescence is observed even from the bound fluorescein. Extraction of iron(III) from state C or, alternatively, addition of a base to state A generates state D, in which the metal quencher is not bound and fluorescein is in its highly emissive state F(−2). This results in the strongest emission at 525 nm (D). A blue fluorescence (E) is generated in acidic media when the fluorescein is not emitting (Off) and iron(III) is not bound. Acidification of the solution results in protonation of the fluorescein unit to its transparent, non-emissive lactonic form (Figure 2c). Consequently, the FRET process does not take place, and the green emission of the fluorescein unit is replaced with a blue pyrene luminescence. The same transformation occurs in higher acidity (e.g., HCl as an input) when a fluorescein cation F(+1) starts to appear;[34] therefore, for the



input	output
Fe(III)	525 nm
0	1
1	0

input	output	
acid	390 nm	525 nm
0	0	1
1	1	0

Figure 4. (a) Molecular NOT logic gate. (b) Simultaneous YES/NOT molecular logic gates. Conditions: as in Figure 3.

general case of acidic environment (E), the green channel is described as "Off" luminescence.

Interestingly, the blue emission intensity in state E was enhanced with increasing irradiation time (Figure 3b). This indicates that in addition to FRET exclusion, a rapid photochemical process further contributes to the blue-channel enhancement in acidic environment. In an in-depth article, Sun et al. have suggested that unstable pyrene photoproducts might be responsible for the enhanced emission.[81] Figure 3b shows the changes in the blue-channel intensity obtained under repeated scans in ethanol (A) and in acidic environment (E). Both processes lead to an enhancement in the blue channel, which clearly supports the observation of Sun et al.;[81] however, in acidic environment, this transformation is far more significant. The tendency of pyrene to form a radical in an acidic environment[82] and the capacity of a siderophore cavity to scavenge it[83,84] might be the reason that this phenomenon is so profoundly observed in state E. As far as Boolean logic is concerned, this photoreaction leads to an improved sensitivity of the blue channel, which does not change the overall outcome of the processor. Irreversibility might be a concern, but this is already an inherent problem of many chemical-based logic systems, which has been addressed elsewhere.[43]

Quenching of pyrene[85] or fluorescein[65] in siderophore analogues or other hydroxamate-based ligands has been addressed before and is considered to occur by energy transfer[85] or electron transfer[65] processes. Heavy-atom-assisted intersystem crossing is usually ruled out because the emission is generally not quenched by gallium, being heavier than iron. For FLIP, the situation is somewhat more complex, as not only two distinct fluorophores are involved in the emission process, but also FRET comes as an additional parameter whose influence on the quenching mechanism deserves further investigation. In this respect, it is noteworthy that Scheme 1 depicts a simplified model corresponding to the processes we consider most crucial for the generation of the different optical states. Other processes,[5] such as spatial separation between donor and acceptor, quenching of fluorescence induced by unprotonated hydroxamates or by the chemical input themselves, iron interfering in the FRET process, as well as change in the polarity of the solvent[85] might also play a role. That is to say that the chemical inputs might have some additional effects on FLIP. For example, it should be expected that the emission intensities of state D, obtained by adding a base to A (route A→D), would not be identical to those obtained by extraction of iron from C (route C→D), due to the different chemical reagents and starting conditions involved. Nevertheless, in this experimental setup, these differences are minor; hence, the overall picture depicted in Scheme 1 is perfectly suitable for the design of various Boolean functions at the molecular scale.

Elementary Logic Operations. Fundamental logic gates are the basic building blocks for the construction of superior logic devices. This is true for automaton[33] and moleculators[34−50] as well as for a keypad lock (Figure 1). Switching between states A−E (Scheme 1), a Boolean network of various fundamental logic gates can be established (Figures 4 and 5). The underline principle we use is based on chemical input multiplicity,[39] that is, a combinatorial recognition approach that enables FLIP to process a variety of the chemical inputs with a minimum amount of receptors. Although molecular logic gates can be comprised of several receptors, each recognizes a specific chemical input,[3,6] in our design: (i) a single chemical input can target a specific receptor, (ii) distinct inputs can be recognized by the same receptor, and finally (iii) a single chemical species can target several receptors simultaneously. Similar principles enable the olfactory system to recognize about 10 000 different volatile chemicals with only 1000 types of receptors.[86]

Targeting the siderophoric receptor with iron(III) as input, route A→B results in green emission quenching and a NOT logic gates in the green channel (Figure 4a). Alternatively, using an acidic input that target the fluorescein unit, route A→E provides, parallel YES/NOT outputs in the blue and green channels, respectively (Figure 4b). Combination of the inputs above, route B←A→E corresponds to a NOR gate at 525 nm (Figure 5a). In this case, each of the inputs targets a different receptor, in a way that either iron (III), acid, or both eliminate of the emission at 525 nm.

It is also possible to realize logic function with different inputs that target the same receptor. Starting from the metal complex

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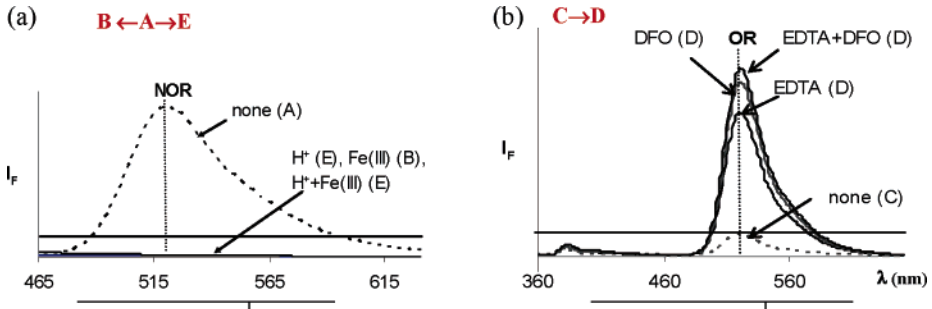

input		output
Fe(III)	acid	525 nm
0	0	1
1	0	0
0	1	0
1	1	0

input		output
EDTA	DFO	525 nm
0	0	0
1	0	1
0	1	1
1	1	1

Figure 5. (a) Molecular NOR logic gate. Conditions: as in Figure 3. (b) Molecular OR logic gate. Inputs: 20 μL saturated $EDTA_{(aq)}$, 20 μL $DFO_{(aq)}$ 5 mM.

in basic environment (C), the ferric ion can be selectively removed by two different chelators, i.e., by ethylenediamine tetraacetic acid (EDTA) or by the natural desferrioxamine (DFO) siderophore (C→D). A basic solution (C) is required to maintain the ionization state of fluorescein upon addition of EDTA, which is also an acid. Because the ferric ion is removed by each of the chelators or both, an OR logic gate at 525 nm is obtained (Figure 5b).

When the ferric complex is present in ethanol (B), an acidic chemical input can simultaneously affect the fluorescein unit and the iron-binding domain in a way that XOR/INHIBIT (C←B→E) and AND/INHIBIT (B→E→D) operations are obtained.[39] The latter routes (D←C←B→E→D), previously described as part of a molecular arithmetic system,[39] not only complete the operation of FLIP to seven fundamental logic operations of YES, NOT, NOR, OR, AND, XOR, and INHIBIT but also provide the basis for realizing a keypad lock at the molecular scale.

A Molecular Keypad Lock. To acquire a molecular keypad lock, the next step must be the development of a mechanism by which a molecule could distinguish between different input sequences. Electronic locks are built by connecting several elementary logic gates (Figure 1); however, it has already been demonstrated that molecular logic systems should not necessarily follow circuitry, but can rather make use of a variety of approaches for molecular logic reconfiguration.[34] For route B→D (Scheme 1), this could be achieved by controlling the kinetics of iron extraction, in a way that reconfigures a simple AND gate into a 3-input priority-AND molecular logic device.

Starting from the iron complex in ethanol (state B in Scheme 1) and using an acidic iron chelator (EDTA) and a base (AcO^-Na^+) as inputs, an AND[39] logic gate is obtained at 525 nm. EDTA alone extracts the iron, but also protonates the fluorescein to in its inactive form (state E). Insertion of acetate to B provides a basic environment, yet, the iron is still bound (state C). Only when both inputs are present, the solution is basic and the iron is removed, which leads to an intense fluorescence at 525 nm (D).

Now it is possible to operate this AND gate through two possible pathways (Figure 6). In the first route (B→C→D), a base is first added, followed by addition of the EDTA, whereas in the second route (B→E→D), the order of insertion is switched. Because both pathways lead to an identical chemical state, both will ultimately result in a high output at 525 nm. However, as the extraction of a ferric ion from a siderophore by EDTA is inhibited in basic environment,[87] a vast difference in the reaction rate between the two paths is observed.

When base is added before EDTA (3 min interval time), only a faint green emission is detected from the bound fluorescein unit. Monitoring the emission intensity over time reveals that only after several hours a full recovery of fluorescence is achieved (Figure 6a). On the other hand, when EDTA is first added to the solution, followed by insertion of base, an intense emission at 525 nm from the nonbound fluorescein is immediately observed (Figure 6b). These observations are consistent with previous studies, revealing a mechanistically interpreted kinetic scheme that involves two parallel pathways for siderophores-EDTA iron exchange.[87] One involves a direct attack of the EDTA on the ferric ion, whereas in the other the hydroxamate binding groups are first protonated[87,88] followed by a rapid attack of the competing ligand. Therefore, when EDTA is first added, the solution becomes acidic, leading to partial protonation of the hydroxamate residues in FLIP-Fe(III) and a rapid iron extraction. On the contrary, when base is initially added, the ferric ion becomes tightly bound, which causes an inhibition of the metal exchange process. Consequently, by limiting the gate to operate solely for a few minutes, this gate becomes a 2-input priority-AND molecular logic gates that process EDTA (*E*) and base (*B*) as inputs and generates a high output only in response to sequence *EB*.

To realize a molecular keypad lock, it is essential to increase the number of inputs, as two bits (*E* and *B*) provide only limited numbers of password combinations, namely, *EB* or *BE*. Steps toward molecular AND gates endowed with multiple bits processing have recently been reported.[6,16] For FLIP this has been achieved simply by introducing the excitation beam (344 nm) as an additional input signal.[10,36] In opposed to chemical inputs, a light input signal has the advantage that it does not accumulate in solution, hence its operation is restricted solely to the period of activation.

Figure 7a describes a molecular keypad lock that "opens" by inserting the right sequences of three keys: EDTA (*E*), base

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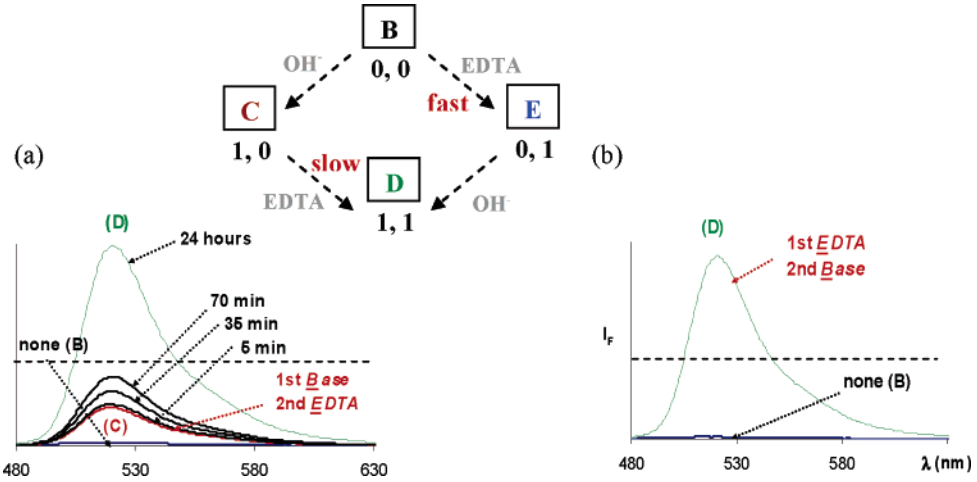

Figure 6. Two-input priority-AND molecular logic gate that processes EDTA (*E*) and base (*B*) as inputs and generates a high output only in response to sequence *EB*. The exchange reaction between the siderophore analogue and EDTA is inhibited in basic environment,[87] therefore a vast difference in the reaction rate between the two paths is observed. (a) When base is added before EDTA (route B→C→D), only a faint green emission is observed due to ionization of the bound fluorescein unit. Monitoring the emission intensity over time revealed that only after several hours a full recovery of fluorescence is achieved. (b) When EDTA is first added to the solution (route B→E→D), followed by insertion of base, an intense emission at 525 nm from the nonbound fluorescein is immediately observed. Conditions: 1 mL of 0.5 μM of FLIP−Fe(III) in ethanol. Inputs: 10 μL of aqueous NaOAC (2 M), 20 μL of saturated EDTA.

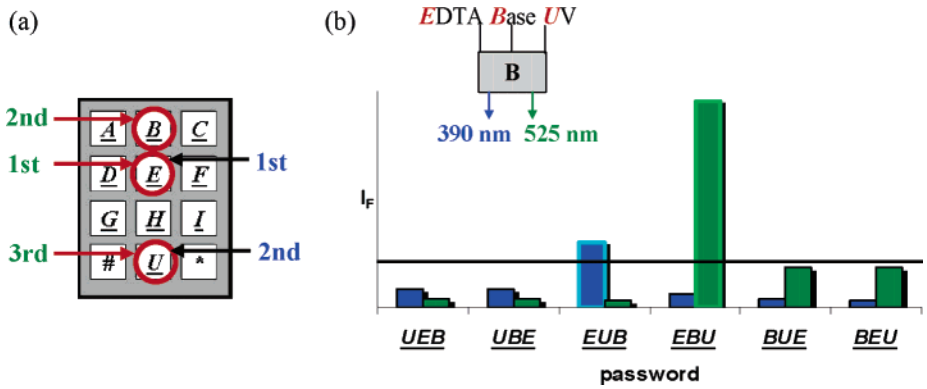

Figure 7. Molecular keypad lock. (a) Keys *B*, *E*, and *U* hold the relevant inputs (Base, EDTA, and UV, respectively) applicable for generating a strong green emission at 525 nm, only when a correct password (*EBU*) is entered. In addition, only sequence *EU* will generate a high output at 390 nm. The other keys can hold a high concentration of fluorescence quenchers, so if pressed the password entry will fail. (b) Outputs in the blue and green fluorescence channels, corresponding to the six possible input sequences, inserted with an interval time of 3 min.

(*B*), and UV light (*U*). Only keys *E*, *B*, and *U* hold the correct inputs that can initiate a strong fluorescence at 525 nm, whereas keys *E* and *U* are enough for generating high emission at 390 nm. The other keys can hold a high concentration of fluorescence quenchers, so if pressed, the password entry will fail. What makes this device possible is the fact that its operation time is restricted to 9 min, during which, each input operates for 3 min before insertion of the next. In this way, there is a sufficient time for EDTA to extract the iron in acidic environment, but not enough for removing the iron under basic conditions. At any point during this period, if a high output is detected in the blue or green channel, it authorizes a valid password.

Figure 7b shows the outputs in the blue and green fluorescence channels, obtained for the six possible input combinations, i.e., *UEB*, *UBE*, *EUB*, *EBU*, *BUE*, and *BEU*. When light input signal is applied first (*UEB* or *UBE*), then the fluorescence output is generated by the iron complex in ethanol (state B in Scheme 1) having low output in both green and blue emission channels. In codes *BUE* and *BEU*, the complex in basic solution is excited (state C), which results in a faint green luminescence output below the threshold line. Only sequence *EBU* provides the right password entry for the generation of an intense green fluorescence, as only then is the iron quencher rapidly removed and the fluorescein in its dianion F(−2) fluorescent state; hence, the excitation beam will find an emitting species at 525 nm (state D). In addition, only sequence *EU* can generate a high output at 390 nm (state E). Consequently, this molecular device is now applicable for authorizing two different users, in a manner similar to a simple ATM banking machine (Figure 7a). One holds the exact combination keys for activating the green channel, whereas the other can activate the blue channel using a different password entry.

Conclusions

This paper describes a new concept in the way information can be protected at the molecular scale. By harnessing the principles of molecular Boolean logic,[1] we have designed a reconfigurable molecular lock that has the power to authorize two different code entries, *EBU* that activates the green channel, and *EU* that triggers the blue channel.

The information in each channel is a single-bit light output signal that can be used to authorize a user, to verify authentication of a product, or to initiate a higher process. Additional security comes from the fact that this device operates in the

fluorescence mode; hence, it has the potential be concealed down to the level of a single molecule.[89] In addition, the accumulation of chemical inputs that prevent this lock, as well as many other molecular logic systems from resetting,[43] might be advantageous in some cases, as it limits the code entry to be inserted only once.

To the best of our knowledge, this is the first example of a molecular system capable of processing password entries; hence, it can add a new dimension of protection to other defense technologies, such as cryptography and steganography, previously achieved with molecules. A few years ago, Bancroft et al. have shown the way a message could be encrypted on a DNA strand (cryptography) and be hidden inside a tiny microdot (steganography).[54] The concept proposed in this paper refers to the possibility of preventing access to such information, in a manner similar to a password entry requested for accessing electronic computers.[51] In this way, even when both the location of the information and the decryption keys are known, it is kept secure.

There is an additional merit to this work. The keypad lock presented here might just be a particular example for the general case of molecular systems, capable of distinguishing between different times of events. It is generally believed that the power of Boolean computing would find application in molecular agents capable of diagnosing biological disorders and produce the right signaling or even therapeutic outputs.[1,90] Considering that, the level of chemical agents in the blood stream is constantly changing, in a way that a disease can be pronounced in a particular order of different biochemical signals, biomolecular devices capable of distinguishing between different chemical sequences, might have considerable advantages over simple molecular logic gates.

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To conclude, we hope to have drawn attention to the potential use of molecular logic gates for security purposes, by demonstrating a new class of decision-making device at the molecular scale. Although the molecular lock presented here can so far process a limited number of password entries comprised merely of two and three input bits, it inspires the imagination toward the next generation of confidential identification technologies based on molecules. In fact, common security inks already function as simple YES logic gates that produce a fluorescence output, only in response to black light (UV) as an input. Future programmable molecular locks might have the capacity to process multiple password entries that provide theoretically unbreakable protection against forgery. Although this goal would probably require more powerful processors that might run on solid supports, it can be reasonably envisioned that, similar to the rapid evolution of molecular logic gates, improved security logic systems, based on molecules, would also be developed.

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Supporting Information Available: Synthesis of FLIP, chemical structures of EDTA and DFO, and fluorescence spectra of the molecular keypad lock. This material is available free of charge via the Internet at http://pubs.acs.org.

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