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A Molecular Full-Adder and Full-Subtractor, an Additional Step toward a Moleculator

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Abstract: Over the past decade, there has been remarkable progress in the development of molecular logic and arithmetic systems, which has brought chemists closer to the realization of a molecular scale calculator (a Moleculator). This paper describes a significant step in this direction. By integrating past and new approaches for molecular logic reconfiguration, we were able to load advanced arithmetic calculations onto a single molecular species. Exchanging chemical inputs, monitoring at several wavelengths simultaneously, as well as using negative logic for the transmittance mode significantly increase the input and output information channels of the processing molecule. Changing the initial state of the processor is an additional approach used for altering the logical output of the device. Finally, introducing degeneracy to the chemical inputs or, alternatively, controlling their interactions to form identical chemical states minimizes the complexity of realizing three-bits addition and subtraction at the molecular scale. Consequently, using a commercially available fluorescein molecule, acid and base chemical inputs, and a simple UV−vis measurement setup, integration of a full-adder and, for the first time, a full-subtractor is now possible within individual molecules.

Introduction

Modern microprocessors have undergone amazing miniaturization during the past years, leading to remarkable improvements in computational competence and speed. On the verge of the 21st century, the ability to reduce the size of electronic devices is anticipated to reach its limits, and therefore, alternative molecular approaches that might replace present computation technology are being vigorously pursued.[1]

The remarkable progress that has been achieved in the development of molecular logic gates[2−6] and their integration into working automaton[7] and arithmetic systems[8−21] has brought chemists closer to the realization of a molecular scale calculator (a Moleculator). These devices, which process chemical or optical inputs and generate light output signals, operate in a wireless mode; thus, they have the potential for computation on a nanometer scale that silicon-based devices cannot address. The ability to run these processors inside well-defined nanospaces is another important step toward this goal.[22]

Initially, different molecular devices for the performance of AND,[23−25] OR,[23,26] XOR,[27,28] NOR, [29−31] NAND,[32,33] XNOR,[34,35] and INHIBIT[29,36] fundamental Boolean function were developed.

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10.1021/ja058564w CCC: $33.50 © 2006 American Chemical Society

Further, chemically triggered logic gates which can operate on solid supports have recently been reported.[37−39] The realization that it is also possible to load arrays of Boolean functions onto a single molecule or, alternatively, to expose a superposition of logic gates concealed within the simplest chemical indicators and reagents[40] has stimulated chemists to develop a new class of programmable logic gates, capable of executing a variety of logic functions.[41] Such reconfiguration is achieved with molecules that process different sets of chemical inputs[42−45] or generate simultaneously multiple light output signals.[33,40,46] The most recent processors[17,18,47−49] combine both approaches, and thus gain an enhancement in both the amount of information that can flow into the device and the data transmitted from it.

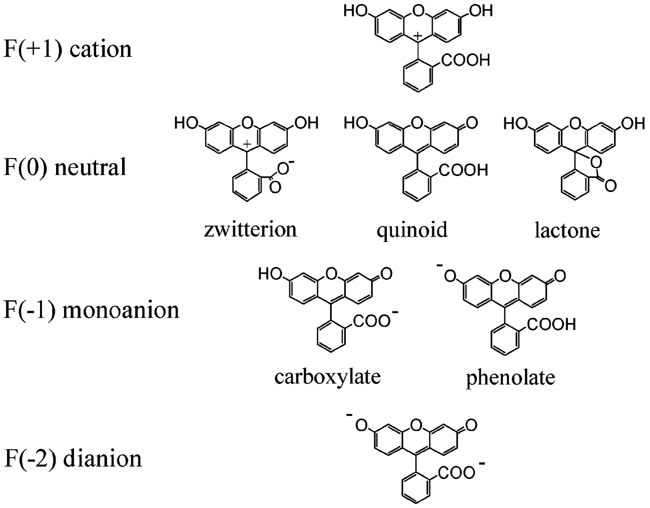
In this way, we have recently demonstrated the feasibility of individual molecules to perform distinct arithmetic operations between two bits[17,18] and also to be reset in a manner similar to a miniaturized calculator.[18] In these systems, the choice of chemical inputs controls over the algebraic operation, that is, addition or subtraction, while observing at several wavelengths simultaneously affords the arithmetic results.

As the ultimate challenge for molecular arithmetic systems is a complete mimicry of electronic calculators, our current efforts are aimed at the expansion of the processing power of a plain fluorescein molecule to add and subtract multiple bits. Unlike the electronic processors, which require integration of several arithmetic units, we circumvent the need for connectivity by combining additional approaches for molecular logic reconfiguration. Applying negative logic by monitoring opposite output signals at the transmittance and absorbance modes,[40] changing the initial state of the processing molecule,[25] and, more importantly, introducing degeneracy into the chemical inputs[18] or, alternatively, controlling their interactions to form identical chemical states, we have managed to load full addition and, for the first time, full subtraction arithmetic operation onto a single molecular species.

Experimental Section

Fluorescein was purchased from Fluka and was used without further purification. It was dissolved in water, and the solution was filtered. Acetic acid (0.015 M) was added to the clear solution, and the pH was adjusted to 3.3. Absorption spectra were measured on a Beckman DU-7500 diode array spectrophotometer. Spectra observed at pH values of 1.9, 3.3, 5.6, and 12 were in good agreement with previous determinations.[50−52] Fluorescein concentration was determined assuming a molar absorptivity of 76 900 M^{-1} cm^{-1} for the fluorescein dianion in 0.1 M NaOH.[50]

Scheme 1. Chemical Structures of Fluorescein



Results and Discussion

Tuning the Ionization State of Fluorescein. The popularity of fluorescein lies in its high extinction coefficient, large fluorescent quantum yield, and well-developed conjugation chemistry to biomolecules. Its spectral properties have been widely investigated,[50−57] indicating that it can exist in four ionization forms (cation, neutral, monoanion, and dianion), each possessing distinct spectral properties (Scheme 1). The cation F(+1) and the dianion F(−2) are expected to occur in only one chemical form. The neutral fluorescein F(0) can exist as three different protolytic species (zwitterion, lactone, and quinoid). The predominant neutral form in aqueous solution is subjected to different interpretations,[53] in which either the quinoid[51] or the lactone[53] is usually believed to be prevalent. For the monoanionic species F(−1), two chemical forms with the negative charge either on the carboxylate group or on a ring hydroxyl can be anticipated. Of these, the carboxylate form is expected to dominate owing to the generally more acidic character of this group (Scheme 1).

Recently, we have shown that switching between the four ionization states of fluorescein provides a molecular system with exceptional computational properties.[18] Clearly, it is difficult to find chemical inputs that can selectively target the carboxylate and phenolate groups of a single fluorescein molecule. However, calculated protolytic distribution for fluorescein through the entire pH spectrum has shown that at certain pH values characteristic absorption peaks corresponding to prevalent ionization species can be obtained.[51−53] Therefore, switching between these forms could be achieved choosing chemical inputs that selectively modify the pH of the solution (Figure 1).

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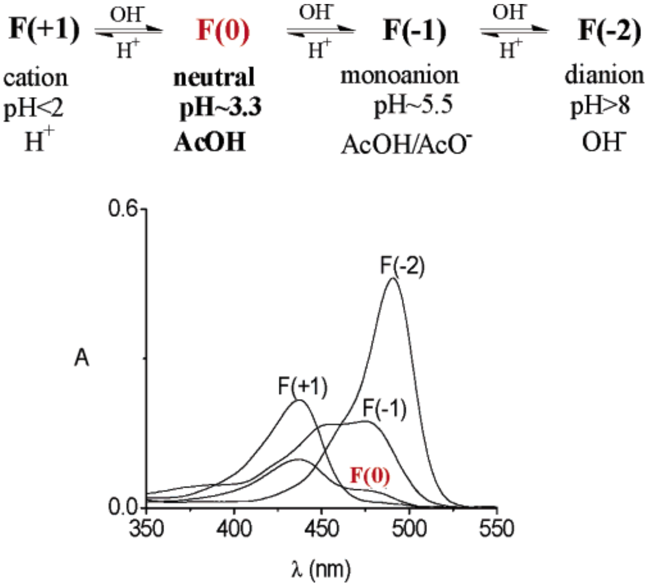

Figure 1. Switching between the ionization states of fluorescein, that is, cation F(+1), neutral F(0), monoanion F(−1), and dianion F(−2). Top: Dissolving fluorescein (6 μM) in aqueous acetic acid solution (0.015 M, pH = 3.3) induces the formation of the neutral form F(0). Selective ionization using HCl (0.013 M) or NaOH (0.013 M) results in a four-state molecular switch. In each of the states, a single ionization form is dominant. Bottom: The corresponding absorption spectra.

As a first step, a predominant neutral F(0) form was obtained in aqueous solution of acetic acid (pH = 3.3). Addition of an acid (HCl) input signal increased the solution acidity (pH = 1.9) followed by the appearance of the cationic species F(+1). Alternatively, insertion of a base (NaOH) to a solution containing the neutral species F(0) resulted in the formation of a buffer solution (pH = 5.6), where the monoanion F(−1) form is dominant. However, with an extra amount of base, the buffer limits were exceeded (pH = 12) and a characteristic dianion spectrum was observed. As each step can be reversed with the addition of a complementary input signal, a four-state molecular switch was obtained (Figure 1). We note that in a more acidic environment a complete conversion to a single cationic form is also possible.[51−53] However, milder conditions, where the cationic species is dominant,[51−53] are perfectly suitable for realizing Boolean computation, in particular, for obtaining a molecular processor capable of reconfiguring between a full-adder and, for the first time, a full-subtractor arithmetic device.

Arithmetic Operations. Although two-bits molecular scale arithmetic has been demonstrated with a number of molecular half-adders,[9−13] -subtractors,[14−16] or both,[17,18] realizing three-bits numerical processing at the molecular level is far more intricate. While the former[9−18] require molecules that process four combinations of two input signals, arithmetic operations between three bits should account for eight possible combinations of three inputs. This may explain why such molecular systems are rare and so far confined to full-adders arithmetic devices.[19−21]

It occurred to us that for fluorescein this complexity can be substantially minimized by introducing a degeneracy into the input signals or, alternatively, by controlling their interactions to form identical chemical environments. A careful analysis of the truth tables for the full-adder and -subtractor reveals that, out of the eight possible operations performed by each of the devices, only one algebraic function, namely, $1 + 1 + 1 = 3$ for the full-adder or $0 - 1 - 1 = -2$ for the full-subtractor, possesses a logical output (algebraic result) having no analogy in the half-adder or half-subtractor.[58] Therefore, extending the power of a fluorescein-based half-adder or -subtractor to process three bits can be simplified by introducing a third chemical input, identical to one of the inputs previously used, which in combination with the other two inputs, induces merely a single new chemical state on the processing molecule. To elucidate the operation principles of this approach, we first describe the operation of a "half"-arithmetic device, from which the full subtraction or addition is straightforwardly achieved.

A Molecular Full-Subtractor Based on Self-Subtracting Chemical Inputs. An electronic half-subtractor and its molecular analogue[18] are illustrated in Figure 2. In the electronic device, input signals are processed simultaneously by two parallel operating logic gates, XOR and INHIBIT, producing the difference (D) and borrow (B) bits, respectively. The molecular analogue, on the other hand, is based on a plain fluorescein molecule in its predominant neutral form F(0). Addition of acid (X = HCl) input signal causes the formation of a predominant cation F(+1), while insertion of base (Y = NaOH) chemical input results in characteristic monoanion F(−1) form. Both inputs together annihilate each other. Therefore, the protonation state of the molecule remains unchanged. The desired truth table for XOR and INHIBIT logic gates is obtained by monitoring at two wavelengths, 447 and 474 nm, respectively (Figure 2b).

Both systems, electronic and molecular, can be considered as basic devices performing $x-y$ operations, while the latter does it in a much smaller scale. However, the electronic system is far more powerful as the basic components can be further integrated into higher circuits with superior processing power. For example, connection of two half-subtractors and an additional OR gate results in a full-subtractor circuit that can perform subtraction between three digits (Figure 3). A full-subtractor[58] processes three inputs, x, y, and borrow in (B_{in}), in such a way that the difference (D) and borrow out (B_{out}) of $x - y - B_{in}$ are obtained. The truth table resulting from this arithmetic circuit (Figure 3, left) indicates that eight algebraic operations can be performed by this circuit. Note that in the case of a high borrow (B=1) the difference (D) output result takes into account an addition of 2 to x: (a) $0 - 0 - 0 = 0$, no borrow; (b) $0 - 1 - 0 = (-1)$ results in a high borrow, so the equation becomes $2 - 1 - 0 = 1$; (c) $1 - 0 - 0 = 1$, no borrow; (d) $1 - 1 - 0 = 0$, no borrow; (e) $0 - 0 - 1 = (-1)$, high borrow, so $2 - 0 - 1 = 1$; (f) $0 - 1 - 1 = (-2)$, high borrow, so $2 - 1 - 1 = 0$; (g) $1 - 0 - 1 = 0$, no borrow; and finally, (h) $1 - 1 - 1 = (-1)$, high borrow, so $3 - 1 - 1 = 1$.

Although, a few examples demonstrating the feasibility of communication between molecular processors[2,59−61] and even arithmetic units[19] have been reported, it is still a great challenge to connect molecular components. Circumventing the need for connectivity, we take advantage of a unique feature of this system, as well as many other photoionic logic gates, that is,

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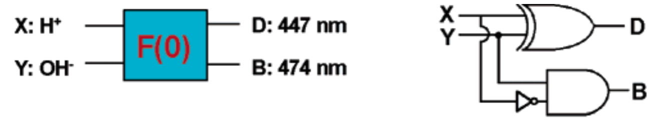
(a)



$$F(+1) \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} F(0) \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} F(-1)$$

(b)

Input		Output	
X_{H+}	Y_{OH-}	INH:B 474 nm	XOR:D 447 nm
0	0	0.076 (low)	0.139 (low)
0	1	0.296 (high)	0.273 (high)
1	0	0.036 (low)	0.260 (high)
1	1	0.084 (low)	0.140 (low)

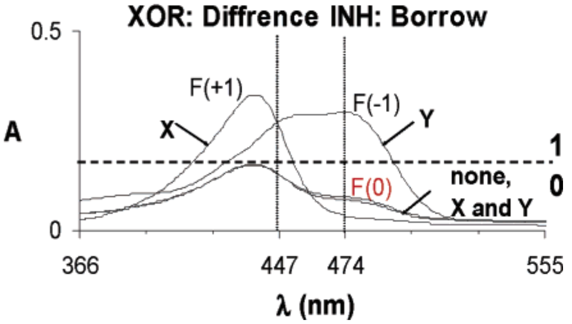


Figure 2. (a) Top: Schematic presentation of an electronic half-subtractor (right) and its molecular analogue (left). Bottom: In this device, fluorescein equilibrates between three ionization forms. (b) Introduction of acid (x) and base (y) chemical inputs to a solution of fluorescein (9.9 μM) in its neutral F(0) form results in spectroscopic changes (right) corresponding to a truth table of a half-subtractor logic circuit (left). Borrow (B) and difference (D) are monitored at 474 and 447 nm, respectively. Outputs: 1 (A > 0.165), 0 (A < 0.165).

	X	Y	B_{in}	B_{out}	D
a.	0	0	0	0	0
b.	0	1	0	1	1
c.	1	0	0	0	1
d.	1	1	0	0	0
e.	0	0	1	1	1
f.	0	1	1	1	0
g.	1	0	1	0	0
h.	1	1	1	1	1

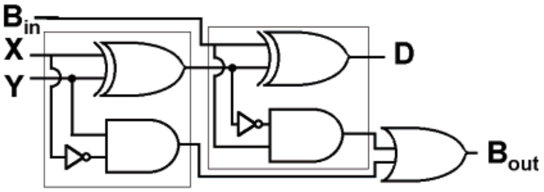


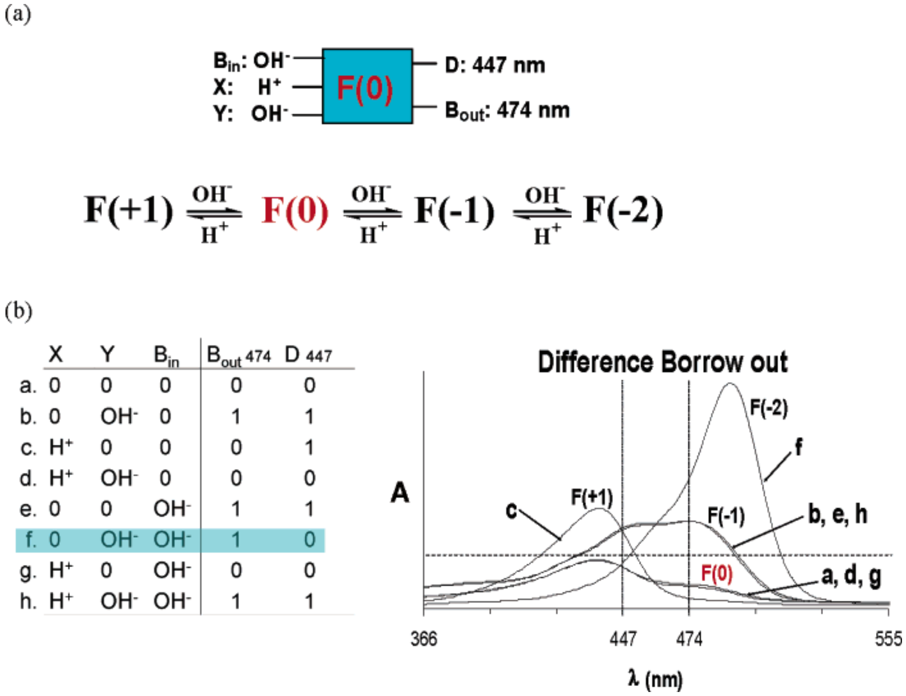
Figure 3. An electronic full-subtractor and its truth table: borrow out (B_{out}) and difference (D) correspond to $x - y - B_{in}$ algebraic operations. Note (i) in the absence of a third B_{in} signal, the equation becomes $x - y - 0$, hence, rows a−d possess the same output signals of a half-subtractor; (ii) the equations expressed in lines a, d, and g, as well as in rows b, e, and h share the same algebraic result, hence they provide identical output signals; (iii) only line f, corresponding to $0 - 1 - 1$, possesses logic outputs (1, 0) that have no analogy in a truth table of a half-subtractor.

chemical input interactions. In particular, we have recognized the well-established acid−base annihilation approach,[14,16−18,27] which has been originally applied for the operation of the first XOR logic gate,[27] as a powerful tool for subtracting multiple bits at the molecular level.

Perhaps the most noticeable distinction between the electronic and the chemical half-subtractor (Figure 2) is the way subtraction of $1 - 1 = 0$ is achieved. While in the electronic device both input digits ($x = 1$ and $y = 1$) are processed within the device itself, the chemical inputs (H^+ and OH^-) annihilate each other before reaching the molecular processor. It seems as if the binary numbers subtract themselves. This realization, namely, that chemical numerical processing can take place without the intervention of a molecular processor, enables the expansion of the molecular half-subtractor to a full-subtractor, simply by introducing a third chemical input (OH^-) coding for the additional borrow in (B_{in}) bit. The difference (D) and borrow out (B_{out}) bits are still obtained by monitoring at 447 and 474 nm, respectively (Figure 4a).

To understand how this reconfiguration works, we must emphasize several features within the truth table of a full-subtractor (Figure 3). First, when the third input (B_{in}) is zero (lines a−d), the equation becomes $x - y - 0$. Thus, the output signals are analogues to a half-subtractor circuit. Second, since lines a ($0 - 0 - 0$), d ($1 - 1 - 0$), and g ($1 - 0 - 1$) share the same algebraic result, they possess identical output values (0, 0). Similarly, rows b ($0 - 1 - 0$), e ($0 - 0 - 1$), and h ($1 - 1 - 1$) also possess the same output signals (1, 1). Consequently, there is a single combination of inputs f ($0 - 1 - 1$) with numerical outputs (1, 0) that have no correspondence in the half-subtractor.

In the same way, a molecular full-subtractor (Figure 4a) based on the half-subtractor depicted in Figure 2 will also perform two-bits subtraction in the absence of the additional B_{in} input. Therefore, lines a−d in the truth table of a molecular full-subtractor are inherently obtained (Figure 4b). In addition, the combination of chemical inputs expressed in lines d (H^+, OH^-, 0) and g (H^+, 0, OH^-) must give rise to the same output signals generated by a (0, 0, 0), due to annihilation of H^+ and OH^- (outputs: 0, 0). Similarly, input combinations expressed in e (0, 0, OH^-) and h (H^+, OH^-, OH^-) should also result in identical output signals (outputs: 1, 1) produced by b: (0, OH^-, 0).



	X	Y	B_{in}	B_{out} 474	D 447
a.	0	0	0	0	0
b.	0	OH^-	0	1	1
c.	H^+	0	0	0	1
d.	H^+	OH^-	0	0	0
e.	0	0	OH^-	1	1
f.	0	OH^-	OH^-	1	0
g.	H^+	0	OH^-	0	0
h.	H^+	OH^-	OH^-	1	1

Figure 4. (a) A molecular full-subtractor based on the previous half-subtractor F(0) (Figure 2) and an additional borrow in (B_{in} = NaOH) input signal (top). In this device, fluorescein equilibrates between four ionization forms (bottom). (b) Absorption spectra (right) and truth table (left), where the difference (*D*) and borrow out (B_{out}) are observed at 447 and 474 nm, respectively. Note (i) lines a−d correspond to the molecular half-subtractor (Figure 2); (ii) due to input annihilation, input combinations in rows a, d, g, as well as b, e, and h must provide identical output signals; (iii) therefore, only the combination of inputs expressed in line f (0, OH^-, OH^-) induces a new chemical state F(−2), which does not exist in the half-subtractor. This provides the required output signals (1, 0) for the completion of a full-subtractor.

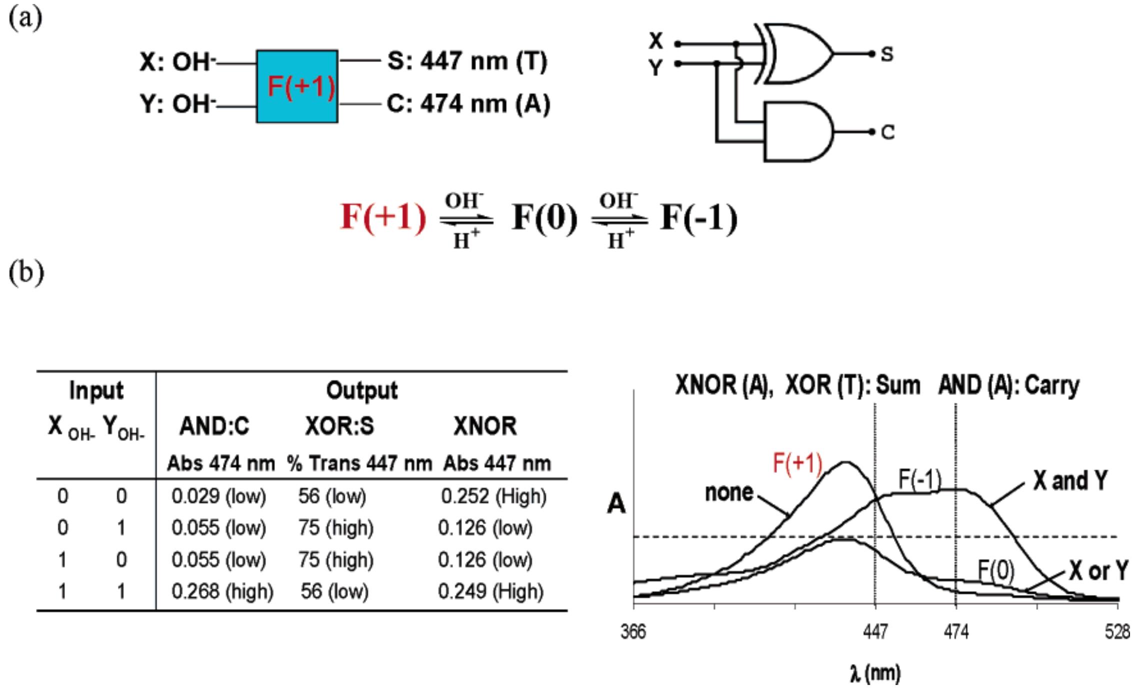
Only the combination of inputs expressed in f (0, OH^-, OH^-) induces a new chemical environment (pH = 12) that has no corresponding analogy in the molecular half-subtractor. In such basic conditions, a fluorescein dianion is formed (Figure 4a), providing the correct output algebraic result (outputs: 1, 0) for the equation 0 − 1 − 1. Figure 4b shows the effects of the chemical inputs on the absorption spectra of fluorescein, resulting in a complete molecular full-subtractor device.

A Molecular Full-Adder Based on Input Degeneracy and Simultaneous Observation at the Absorbance and Transmittance Modes. A common method for expanding the output channels for a given molecule is based on the simultaneous opposite, absorbance (*A*), and transmittance (*T*) output values, which can be observed even at the same wavelength.[40] For example, if a YES operation is demonstrated through an absorbance output, a NOT operation will result from a transmittance output. This approach of "negative logic" has recently been applied also for the fluorescent mode.[16] Considering the simplicity by which such an inverter is obtained, it is not surprising that transmittance output signals have been applied for the operation of the original half-adder[9] and half-subtractor[14] molecular devices. Previously, we have shown that a fluorescein molecule can function as a half-adder, operating solely in the absorption mode.[18] Here we demonstrate another half-adder within the same molecule, which operates in both transmittance and absorbance modes. This half-adder has the advantage that it can be expanded to function as a full-adder logic device.

A fluorescein cation F(+1) can add two bits by processing identical chemical inputs (NaOH) and generating output signals at 447 and 474 nm (Figure 5). We note that the power of input degeneracy for arithmetical processing was initially recognized for photons, as part of the first molecular full-adder device[19] (i.e., through a beam splitter), then demonstrated with chemical input signals.[18] Addition of merely one of the inputs (NaOH) to the solution containing the cationic species F(+1) causes formation of the neutral form F(0). Insertion of a second chemical signal further converts it to the monoanion F(−1). Consequently, monitoring the changes in absorption at 447 nm corresponds to a XNOR logic gate, generating a low output only in response to a single high input, while observing the absorption at 474 nm results in an AND gate, producing a high output merely in the presence of two high inputs.

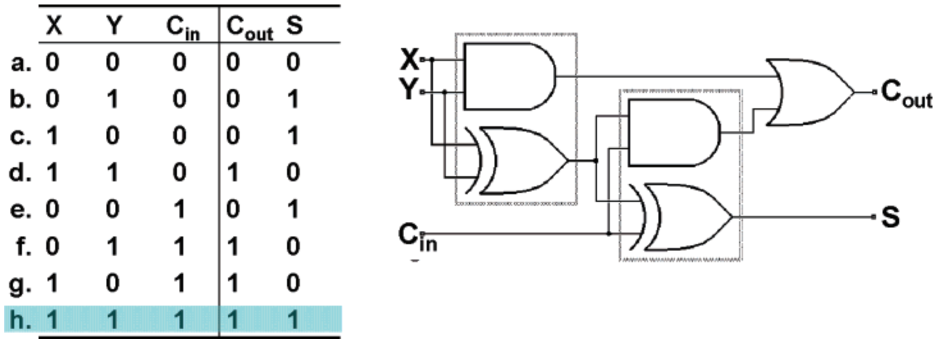
To acquire a half-adder with parallel operating AND and XOR logic gates, we take advantage of the inverting nature of the transmittance mode. Particularly, the XNOR gate at 447 nm in the absorbance mode (*A*) can be read as a XOR logic gate via transmittance (*T*). The truth table in Figure 5 shows that by monitoring % transmittance at 447 nm and absorbance at 474 nm, the sum and carry output bits for 0 + 0, 0 + 1, 1 + 0, and 1 + 1 are obtained. It should be noted that the relatively high threshold value in the transmittance mode can be significantly improved, for example, by using a longer optical path.[40] Yet, to acquire the simplest calculating machine, we have preferred to maintain the standard spectroscopic conditions and relatively low concentrations previously used for the full-subtractor.

Integration of two electronic half-adders and an additional OR logic gates results in a full-adder device (Figure 6). A full-adder processes three inputs, *x*, *y*, and carry in (C_{in}), in such a way that the sum (*S*) and carry out (C_{out}) of $x + y + C_{in}$ are obtained. The truth table resulting from this arithmetic circuit indicates that eight algebraic operations can be performed by this circuit: (a) 0 + 0 + 0 = 0 (00); (b) 0 + 1 + 0 = 1 (01); (c) 1 + 0 + 0 = 1 (01); (d) 1 + 1 + 0 = 2 (10); (e) 0 + 0 +



Input		Output		
X_{OH^-}	Y_{OH^-}	AND:C Abs 474 nm	XOR:S % Trans 447 nm	XNOR Abs 447 nm
0	0	0.029 (low)	56 (low)	0.252 (High)
0	1	0.055 (low)	75 (high)	0.126 (low)
1	0	0.055 (low)	75 (high)	0.126 (low)
1	1	0.268 (high)	56 (low)	0.249 (High)

Figure 5. (a) Top: Schematic presentation describing an electronic half-adder (right) and its molecular analogue (left). Bottom: In this device, fluorescein equilibrates between three ionization forms. (b) Introduction of identical chemical inputs (x, y = NaOH) to a solution of fluorescein in its predominant cationic form F(+1) results in spectroscopic changes (right) corresponding to a truth table of a half-adder logic circuit (left). Carry (C) and sum (S) are monitored at 474 nm (absorbance) and 447 nm (% transmittance), respectively. Outputs: absorption (A), transmittance (T), 1 ($A > 0.165$, $\%T > 60$), 0 ($A < 0.165$, $\%T < 60$).



	X	Y	C_{in}	C_{out}	S
a.	0	0	0	0	0
b.	0	1	0	0	1
c.	1	0	0	0	1
d.	1	1	0	1	0
e.	0	0	1	0	1
f.	0	1	1	1	0
g.	1	0	1	1	0
h.	1	1	1	1	1

Figure 6. An electronic full-adder: carry out (C_{out}) and sum (S) correspond to $x + y + C_{in}$ algebraic operations. Note (i) in the absence of a third C_{in} signal, the equation becomes $x + y + 0$, hence rows a−d possess the same output signals of a half-adder (Figure 5); (ii) the equations expressed in lines b, c, and e, as well as in rows d, f, and g, share the same algebraic result, hence provide identical output signals; (iii) only line h, corresponding to $1 + 1 + 1$, possesses logic outputs (1, 1) that have no analogy in a truth table of a half-adder.

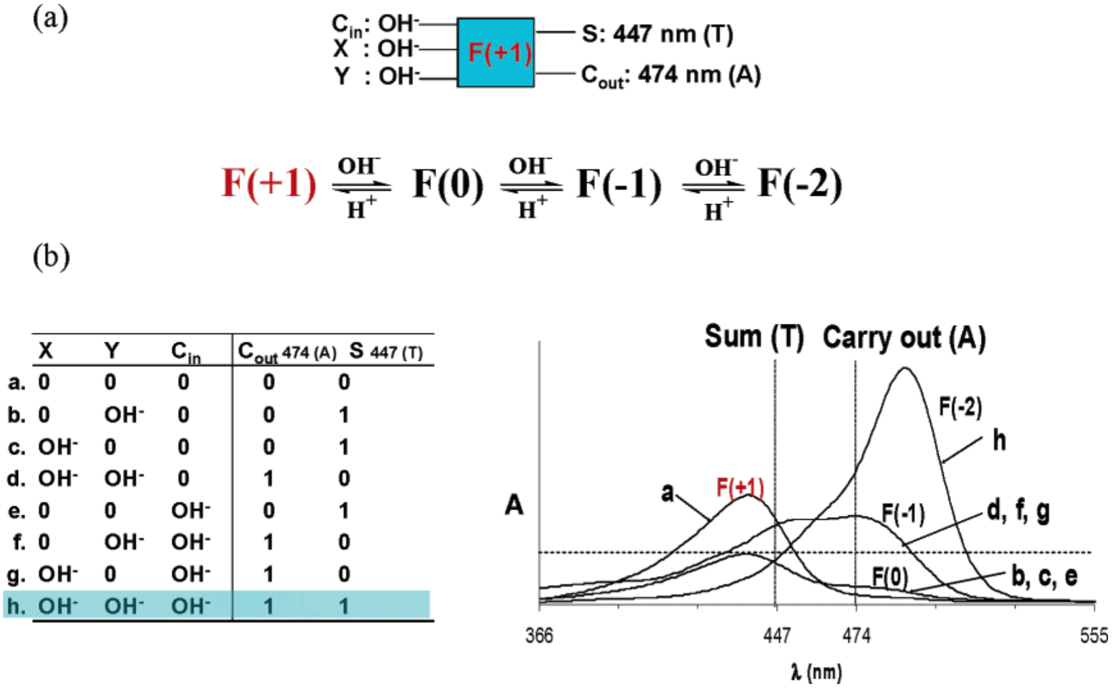
$1 = 1$ (01); (f) $0 + 1 + 1 = 2$ (10); (g) $1 + 0 + 1 = 2$ (10); and finally, (h) $1 + 1 + 1 = 3$ (11). Only the last equation possesses numerical outputs (1, 1) having no equivalence in the half-adder.

A molecular full-adder (Figure 7) is obtained from fluorescein by introducing a third, identical chemical input (NaOH) to the half-adder described in Figure 5. Due to the similarity of the input signals, the sum and carry out for the equation corresponding to a−g are generated by the half-adder. Only when a third input h (OH^-, OH^-, OH^-) is introduced, then the equation becomes $1 + 1 + 1$, and hence cannot be processed by the previous half-adder. However, under these conditions, a fluorescein dianion F(−2) is formed (Figure 7b) with high transmittance at 447 nm and high absorbance at 474 nm, corresponding to correct sum and carry out signals for $1 + 1 + 1 = 11$. The truth table for the complete molecular full-adder is described in Figure 7.

Conclusions

Figure 8 summarizes the way by which fluorescein in its neutral F(0) form can function as a complete three-bits moleculator performing addition and subtraction algebraic operations. A full-subtractor, with outputs at 447 and 474 nm, is achieved in the absorption mode, while setting the initial state to the cationic form F(+1) and observing transmittance at 447 nm provides a molecular full-adder. Simple combinations of acid and base are used to set the initial state, to code for the input numbers, and for resetting.[18] As the chemically encoded numbers are inserted sequentially, two solutions of acid and base chemical inputs are sufficient for the performance of all arithmetic operations.

Clearly, there is a long way to go before a practical molecular calculator could be implemented. Regardless of its attractive size, the processing power of fluorescein is still limited to a small number of bits, its operating speed is restricted to the



	X	Y	C_{in}	C_{out} 474 (A)	S 447 (T)
a.	0	0	0	0	0
b.	0	OH⁻	0	0	1
c.	OH⁻	0	0	0	1
d.	OH⁻	OH⁻	0	1	0
e.	0	0	OH⁻	0	1
f.	0	OH⁻	OH⁻	1	0
g.	OH⁻	0	OH⁻	1	0
h.	OH⁻	OH⁻	OH⁻	1	1

Figure 7. (a) A molecular full-adder is based on the previous half-adder F(+1) (Figure 5) and an additional carry in (C_{in} = NaOH) input signal (top). In this device, fluorescein equilibrates between four ionization forms (bottom). (b) Absorption spectra (right) and truth table (left), where the sum (*S*) and carry out (C_{out}) are observed at 447 nm (% transmittance) and 474 nm (absorbance), respectively. Note (i) lines a−d correspond to the molecular half-adder (Figure 5); (ii) due to input degeneracy, input combinations in rows b, c, e, as well as d, f, and g must provide identical output signals; (iii) only the combination of inputs expressed in line h (OH^-, OH^-, OH^-) induces a new chemical state F(−2), which does not exist in the half-adder. This provides the required output signals (1, 1) for the completion of a full-adder device.

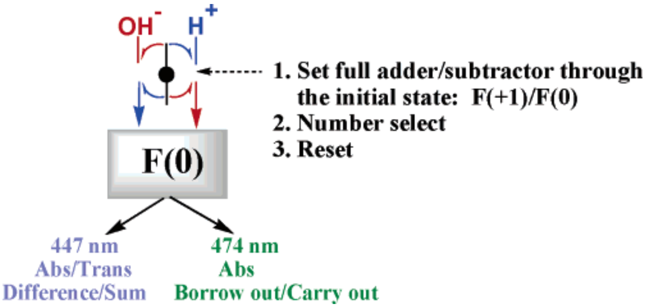


Figure 8. Fluorescein−Moleculator. A molecular device capable of adding and subtracting three bits and resetting. Addition is performed with identical input signals (OH^-), while subtraction takes advantage of acid (H^+) and base (OH^-) annihilation, which enables the inputs to "subtract" each other before reaching the molecular processor (Abs = absorption, Trans = transmittance).

diffusion rate of the chemical inputs, and although, it possesses reset capability,[18] an increase in the volume of the solution may be a concern for executing multiple arithmetic cycles. Moreover, the absorbance and transmittance modes are far less detectable than fluorescence mode, and since there are several equilibrating species involved in computing, this system cannot, so far, operate at the level of a single molecule.

On the other hand, this system validates the variety of approaches developed for molecular logic reconfiguration by demonstrating a three-bits molecular calculator with a commercially available molecule, acid/base chemical reagents, and simple UV−vis measurement setup. Exchanging chemical inputs,[42] monitoring at several wavelengths simultaneously,[33,40] as well as using negative logic for the transmittance mode[40] significantly increase the input and output information channels for the molecular processor. Moreover, the ability to change the initial state of a multi-state molecular switch[25] circumvents the need for an additional processor, thus providing an additional approach for molecular logic reconfiguration. Finally, introducing degeneracy to the chemical inputs[18] or, alternatively, controlling their interactions to form identical chemical states minimizes the complexity of realizing three-bits addition and subtraction at the molecular level. This degeneracy of chemical states for the input signals is of particular importance, as it demonstrates that future molecular calculators should not necessarily carry various receptors for multiple inputs recognition, but rather operate with a minimum amount of functional components (Figure 8).

To conclude, we have shown that the variety of languages by which different molecules comprehend Boolean logic[2−6] and basic arithmetic[8−21] could be integrated and, together with new approaches for molecular logic reconfiguration, provide advanced numerical processing at the molecular scale. Consequently, only a few years after two molecules have remarkably calculated that $1 + 1 = 2$,[9] a single molecular species apparently knows that $1 + 1 + 1 = 3$ as well as that $1 - 1 - 1 = -1$. This by itself indicates that the international school for molecules is heading in the right direction.

Acknowledgment. Support from the European Union (HPRN-CT-2000-00029), the G. M. J. Schmidt Minerva Center on Supramolecular Architecture and the Helen and Martin Kimmel Center for Molecular Design is greatly acknowledged. A.S. holds the Siegfried and Irma Ulmann professorial chair.

JA058564W