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Trichocyanines: a Red-Hair-Inspired Modular Platform for Dye-Based One-Time-Pad Molecular Cryptography

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Current molecular cryptography (MoCryp) systems are almost exclusively based on DNA chemistry and reports of cryptography technologies based on other less complex chemical systems are lacking. We describe herein, as proof of concept, the prototype of the first asymmetric MoCryp system, based on an 8-compound set of a novel bioinspired class of cyanine-type dyes called trichocyanines. These novel acidichromic cyanine-type dyes inspired by red hair pigments were synthesized and characterized with the aid of density functional theory (DFT) calculations. Trichocyanines consist of a modular scaffold easily accessible via an expedient condensation of 3-phenyl- or 3-methyl-2*H*-1,4-benzothiazines with *N*-dimethyl- or *o*-methoxy-hydroxy-substituted benzaldehyde or cinnamaldehyde derivatives. The eight representative members synthesized herein can be classified as belonging to two three-state systems tunable through four different control points. This versatile dye platform can generate an expandable palette of colors and appears to be specifically suited to implement an unprecedented single-use asymmetric molecular cryptography system. With this system, we intend to pioneer the translation of digital public-key cryptography into a chemical-coding one-time-pad-like system.

Introduction

Translating typical electronic device technologies into chemical logic platforms is an attractive step toward the goal of implementing robust methodologies for the safe transfer of restricted access data, that is, cryptography.[1–3] Current molecular cryptography (MoCryp) systems, however, are almost exclusively based on DNA chemistry,[4–8] and to the best of our knowledge, reports of cryptography technologies based on other less complex chemical systems are lacking. To this aim, pH-sensitive organic dyes with a modular and tunable structure appear to be suitable candidates to meet the requirements of a robust chemical cryptography system. We describe herein, as proof of concept, the prototype of the first asymmetric MoCryp system, based on an eight-compound set of a novel bioinspired class of cyanine-type dyes. With this system, we intend to pioneer the translation of digital public-key cryptography into a chemical-coding one-time-pad-like system.[9–11]

To ensure efficiency, requisites that need to be met and optimized include: 1) information security, 2) asymmetry, 3) strength, entailing a prohibitive experimental/computational violation cost, and 4) a lack of ambiguity with no margins for human error. In this framework, safe encryption would be ensured by single use, as in one-time-pad methods. The main requirement for the proposed MoCryp system to meet the specific requisites of the private key was a set of structurally related, chemically stable organic dyes with high extinction coefficients and distinct trends in the pH-dependent response.

Cyanine dyes[12] exhibit a characteristic dipolar push-pull D–π–A architecture in which D is an enamine-type donor moiety, π is a conjugating spacer, and A is an imine-type acceptor group. Dyes of this family are in great demand for various applications including fluorescent labeling of biomolecules, imaging, sensing,[13–16] rewritable optical recording,[17–18] and use as thermochromic[19] and security[20] inks, and thus exhibit desirable features for the purposes of this study.

An attractive source of inspiration for innovative cyanine-type systems suitable for MoCryp applications came from the peculiar photochromic and acidichromic properties of $\Delta^{2,2'}$-bi-(benzothiazine)-based chromophores[21–23] modeled after pheomelanin pigments in red human hair and in feathers (Figure 1).[24–26] The most characteristic feature of these compounds is their doubly cross-conjugated yellow-to-red chromophore which undergoes a marked bathochromic shift to an intense blue coloration after exposure to acids.[22,23]

In this paper, we report the rational exploitation of the pH-tunable red hair chromophore 2*H*-1,4-benzothiazine to engineer a new class of bioinspired cyanine-type functional dyes with chemically tunable and pH-switchable absorption–emis-

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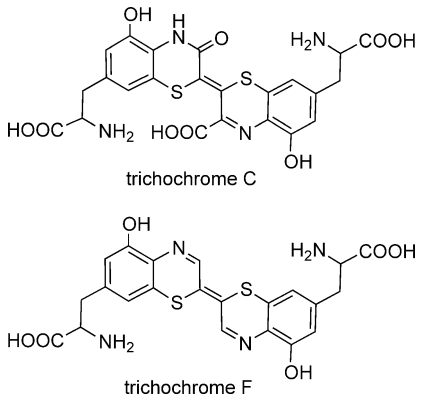


Figure 1. Structures of trichochromes isolated from red human hair and avian feathers.

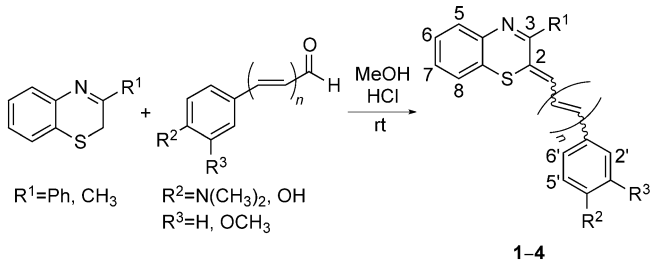
sion properties.[27,28] Based on these peculiar features, an original and innovative prototype of a molecular cryptography system is presented as a proof of concept.

Results and Discussion

Synthesis and characterization of trichocyanines

The novel cyanine-type dyes with D–π–A architecture—designated trichocyanines—were built on the 2*H*-1,4-benzothiazine ring as the imine-containing A component, a substituted phenyl ring as the electron-donating D component, and an exocyclic double bond with a further conjugation option as the π-bridge. The synthetic scheme, highlighting structural relationships of trichocyanines with red hair pigments, is shown in Figure 2.

An expedient working nomenclature for the tripartite scaffold of trichocyanines can be proposed, which is based on the distinguishing substituents of the D–π–A architecture, that is, the O/N group on the phenyl ring (D), the number of extra double bonds (0/1) and the Me/Ph substituent on the benzothiazine ring (A). For example, compound **1a** is trichocyanine TC(N/0/Ph), and **4b** is TC(O/1/Me). All compounds could be easily prepared in good yields by a facile condensation between a benzothiazine precursor and a benzaldehyde or cinnamaldehyde derivative and were obtained in pure form after chromatographic fractionation. The assignment of the proton and carbon resonances for the cyanines **1**–**4** as deduced by 2D NMR analysis is reported in the Experimental Section.



1a: R^1=Ph, R^2=$N(CH_3)_2$, R^3=H, *n*=0 **1b**: R^1=CH_3, R^2=$N(CH_3)_2$, R^3=H, *n*=0
2a: R^1=Ph, R^2=$N(CH_3)_2$, R^3=H, *n*=1 **2b**: R^1=CH_3, R^2=$N(CH_3)_2$, R^3=H, *n*=1
3a: R^1=Ph, R^2=OH, R^3=OCH_3, *n*=0 **3b**: R^1=CH_3, R^2=OH, R^3=OCH_3, *n*=0
4a: R^1=Ph, R^2=OH, R^3=OCH_3, *n*=1 **4b**: R^1=CH_3, R^2=OH, R^3=OCH_3, *n*=1

Figure 2. The dye platform for the red-hair-inspired trichocyanines.

In the case of cyanines **2a,b** and **4a,b**, analysis of the proton-proton coupling constants led to the assignment of E configuration to the C–C=C–C double bond, whereas assignment of the S–C=C–C double bond was integrated by density functional theory (DFT) calculations. Table 1 shows the relative free energies of several possible isomers/conformers of **2a** and **2b**, as representative trichocyanines. Based on these data, both **2a** and **2b** were assigned the Z, antipleriplanar, E structure.

Table 1. Computed relative free energies of selected isomers of **2a** and **2b**.[a]

S–C=C-C configuration	C=C–C=C conformation	ΔG_{PCM} [kcal mol^{-1}][b]	$\Delta G_{PCM,RRHO}$ [kcal mol^{-1}][c]
	2a		
E	antiperiplanar	2.7	2.9
E	synperiplanar	7.8	7.7
Z	antiperiplanar	0.0	0.0
Z	synperiplanar	4.0	3.8
	2b		
E	antiperiplanar	4.4	4.8
E	+synclinal	9.3	9.8
E	−synclinal	12.4	13.0
Z	antiperiplanar	0.0	0.0
Z	synperiplanar	3.8	4.3

[a] For all table entries the C–C=C–C double bond is in E configuration. A more complete computational exploration is reported in the Supporting Information. [b] Computed at the PBE0[29]/6-31+G(d,p) level. Solvation contributions obtained by the polarizable continuum model (PCM)[30–32] in MeOH are included. [c] Rotational/vibrational contributions to the free energy are computed at the rigid rotor/harmonic oscillator (RRHO) level.

Absorption properties of trichocyanines

The pH-dependent absorption properties of **1**–**4** are reported in Figures S10–S17 while the extinction coefficients are listed in Table S1, all in the Supporting Information. The behavior of **2a** and **4a** as representative members of the N and O series is shown in Figure 3.

With all compounds, a significant bathochromic shift (>100 nm) was observed upon protonation, which modified and intensified the visible color remarkably. Whereas the dimethylamino-substituted derivatives display a marked ipsochromic shift accompanied by discoloration at pH<3, suggesting a doubly cationic state resulting from protonation of the dimethylamino group, the hydroxy derivatives display an opposite bathochromic shift upon increasing pH from 7 to 11, which can be accounted for by the onset of a deprotonated anion state. A list of the spectrophotometrically measured pK_a values for all compounds is given in Table S2 in the Supporting Information. Based on this, it was verified that an addition sequence of ammonia–acetic acid–hydrochloric acid to compounds **1**–**4** implements two different series of three-state sys-

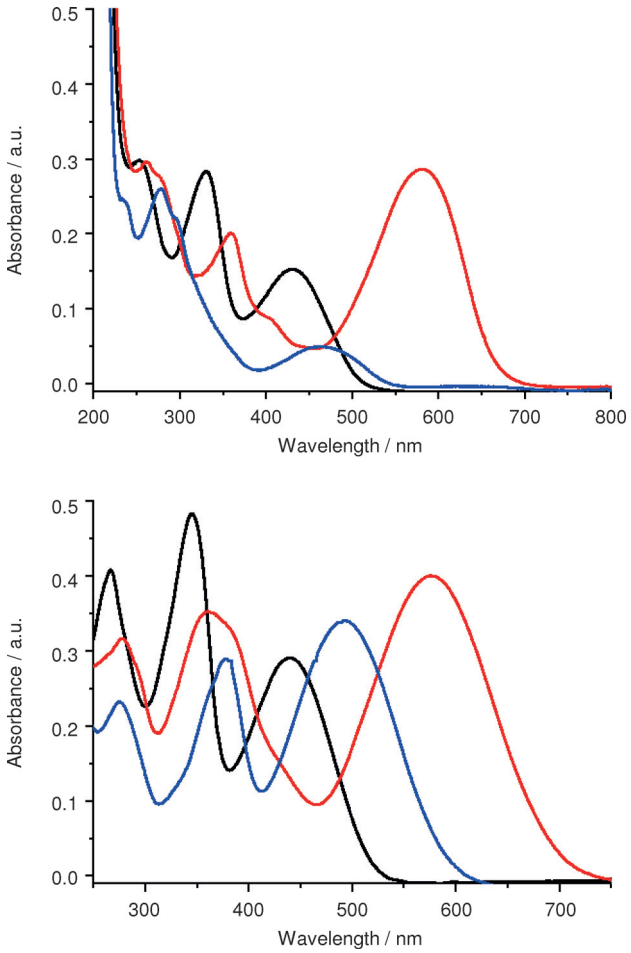


Figure 3. pH-Dependent absorption changes of compounds **2a** (top) and **4a** (bottom) in 3:1 MeOH/H_2O (*v*/*v*). Red trace: pH 3; black trace: pH 7; blue trace: pH 0 (top) and pH 11 (bottom).

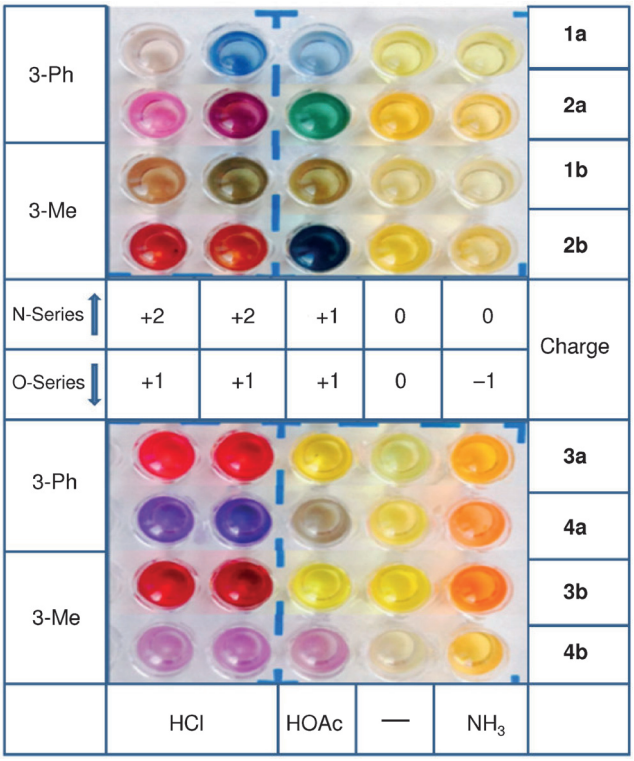


Figure 4. Color changes and charge states of trichocyanines **1–4** under different pH conditions.

tems in the pH range of 0–11, corresponding to a (+2)–(+1)–(0) charge pattern for **1–2** (featuring the dimethylamino group—N-series) and to (+1)–(0)–(−1) for **3–4** (bearing the 3-OMe-4-OH substitution pattern—O series) (Figure 4).

Time-dependent DFT[33–37] calculations of electronic transitions (carried out both with the hybrid PBE0[29] and with the hybrid *meta*-GGA M06-2X functional,[38] and the 6-311++G(2d,2p) basis set) reproduced the experimental trends well, and corroborated the interpretation of pH-dependent absorption properties of **1–4**.

Analysis of the computed electronic spectra of TC(N/0/Ph) and TC(N/1/Ph) confirmed that in all three relevant protonation states, the highest wavelength transition is HOMO–LUMO in character. Upon protonation of the benzothiazine nitrogen, the energy of the HOMO is lowered, and even more so that of the LUMO, thus justifying the observed bathochromic shift (Figure 5).

Some of the cyanine-type compounds displayed pH-dependent fluorescence in the range of 500–610 nm, though with relatively low quantum yields with respect to rhodamine B. (Figures S18–25 in the Supporting Information). Fluorescence was associated to benzothiazine derivatives bearing a 3-methyl group (Figure 6), suggesting that the phenyl group prevents or quenches emission. Moreover, with all compounds, emission was switched off at pH 3, and vinylogy decreased its intensity.

All compounds exhibited good resistance to fatigue over several cycles of pH switching (Figure 6). From the above data, we can conclude that the new cyanine-type scaffold displays four distinct control points for property tailoring and tuning: 1) the proton sensitive benzothiazine imine center, allowing for absorption shift and/or for complementary color/emission switch, 2) the 3-substituent on the benzothiazine ring, controlling emission, 3) the length of the π bridge, which finely tunes electronic communication between the push-pull structural elements, and 4) the electron-donating substituent(s) on the phenyl ring (Figure 7).

Since the dimethylamino group in the N-series provides a second switch point at strongly acidic pH, while the 3-methoxy-4-hydroxy (vanilloid) substitution pattern in the O-series allows alkali-induced tuning, this latter control point is critical for the nature of the three-state system (Figure 4).

The molecular cryptography system

The molecular cryptography (MoCryp) system is a first step toward an expedient chemical message system (CMS) implemented on the 8-compound set of the trichocyanine series. The proposed MoCryp system intends to implement the translation of public-key cryptography into a chemical coding system. (Figure 8).

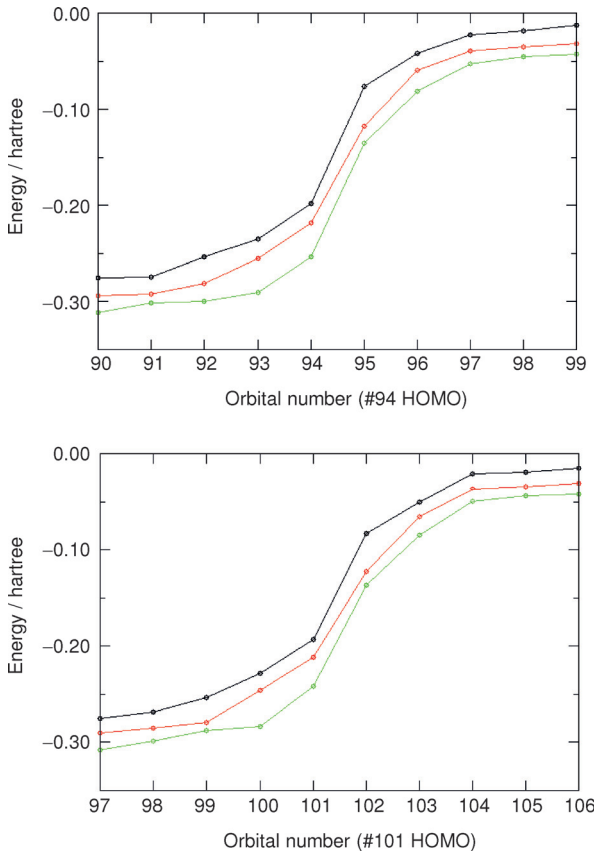


Figure 5. Energies (PBE0/6-311++G(2d,2p)//PBE0/6-31+G(d,p)) of selected orbitals of TC(N/0/Ph) (top) and TC(N/1/Ph) (bottom) in different protonation states. Black line: neutral form; red line: monoprotonated (iminium) form; green line: diprotonated form.

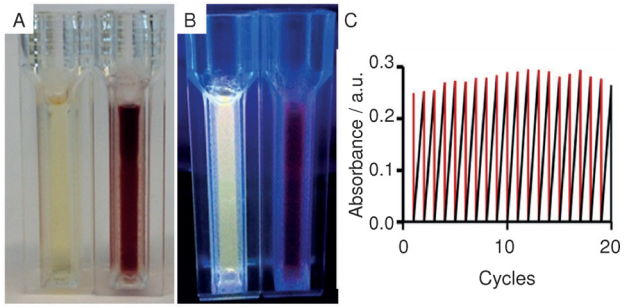


Figure 6. pH-Dependent visible absorption (A) and emission (B) behavior of compound **3b**. Shown are 3:1 MeOH/water (*v*/*v*) solutions at pH 7 (A and B, left cuvette) and at pH 0 (A and B, right cuvette). Multiple pH switch cycles of **3b** (C): absorbance at 548 nm upon alternating exposure to pH 0 (black) and pH 7 (red).

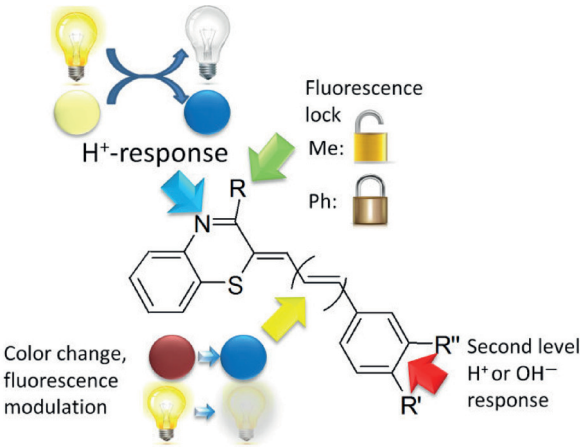


Figure 7. Summary of the main control points for the new red-hair-inspired dye platform.

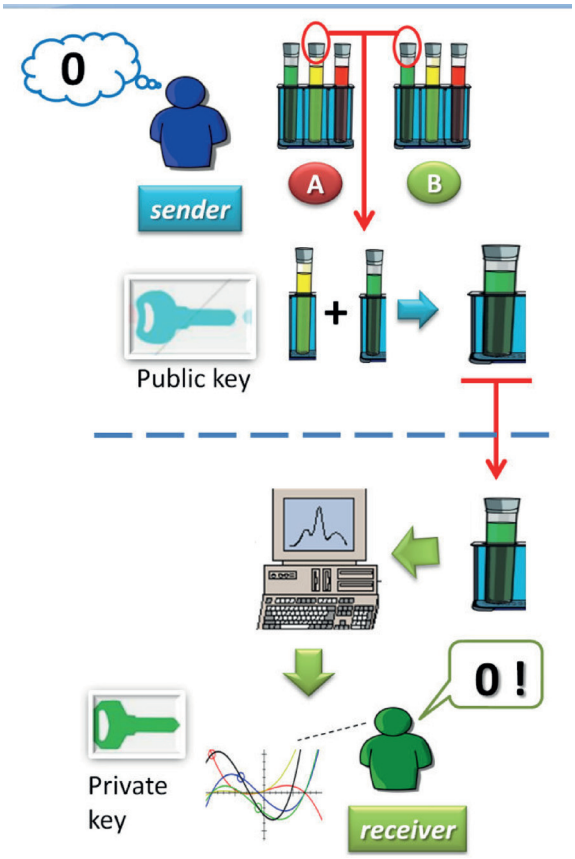


Figure 8. The molecular cryptography (MoCryp) code: A+A=1, B+B=1, A+B=0.

In the scheme shown in Figure 8, the sender elaborates the cipher text by properly mixing two solutions taken from two main code-generating sets, labeled A and B. The two sets, A and B, contain the same number of chemical solutions, each consisting of a well-defined mixture of the eight compounds in a variable relative concentration. The chemically encrypted message can be generated by knowing that mixing two solutions from the same set (A+A or B+B) generates "1", while mixing two solutions, one from each set (A+B) generates "0". This is the public key. The sequence of solutions forming the code string prepared by the sender on the basis of the public key is then physically transmitted or shipped to the receiver. Decryption of the chemical message by the receiver can be carried out using a UV/Vis spectrophotometer equipped with a computer to execute a highly secure cipher text generation process (detailed in the Supporting Information). Application of a suitable decryption function then assigns the digit (0/1) to

each element of the chemical text to form the cipher text. The following sequence of steps would then allow decryption of the chemical text:

1) The receiver records UV/Vis traces in the 300–700 nm range for each mixture of the string, first at alkaline pH and then at acidic pH.
2) The computer elaborates a secondary spectrum for each element of the string by determining the absorbance ratios at the selected pH values for each wavelength (for examples see the Supporting Information).
3) Application of a suitable decryption function then assigns the digit (0/1) to each element of the chemical text to form the cipher text. Selection of the decryption function is one of the strengths of the proposed code, since there is virtually an infinite range of security elements determined for example by the type of function (the simplest solution may be a definite integral), the two wavelength ranges, the number and levels of the thresholds that can be used to apply the function, and finally the possibility to use very specific intersecting functions.

The MoCryp system appears to be superior to most digital systems in all of the main requisites listed previously.

Use of a CMS instead of a conventional digital writing system imparts robustness against breaches, because it requires shipment of very complex strings of chemical compounds. Efficient intrusion detection is based on the simple fact that information decryption requires access to the objects (the chemical mixtures), and any intrusion would be immediately apparent by the failure to receive the chemical code. Notably, the fast and efficient acid-promoted condensation chemistry used for trichocyanine synthesis may be suitable for chemical coding via inkjet printing. In addition, it is possible to generate trichocyanines directly on a solid support such as paper (Figure 9). This would allow the use of two collections of single-use cartridges as the generating sets, making both direct duplication of the mixtures and chemical analysis of printed strings a virtually impossible event to any expert chemist who wishes to crack the code.

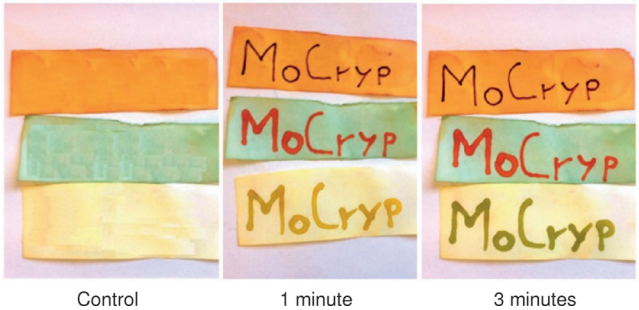


Figure 9. Writing with trichocyanines generated in situ. Left: the control shows filter paper strips dipped into three different aldehyde solutions in methanolic *p*-toluenesulfonic acid (top: 4-dimethylaminocinnamaldehyde, middle: ferulic aldehyde, bottom: 4-dimethylaminobenzaldehyde). Middle: image taken immediately after writing on the stripes with a methanol solution of 3-phenyl-2*H*-1,4-benzothiazine. Right: image 3 min after writing.

Furthermore, in the digital writing system, decryption consists in the conversion of the cipher text to the plain text, while in the proposed CMS, the decryption step is conversion of the chemical text into the cipher text by the private key. This feature endows the cryptographic system with a double security level: a primary level connecting the chemical mixtures to the cipher text and a secondary level relating the cipher text to the plain text. If the secondary encryption level is inessential, a conventional 8-digit barcoding system can be used.

Asymmetry depends on the private key, which is completely different from the public key. Asymmetry would be ensured by the fact that the sender knows how to generate 0 or 1 (public key) but does not know how the receiver will decrypt the string of mixed chemical solutions to obtain a binary code string (private key). Even an expert chemist, who may gain information as to what kind of structures are used in the code generating sets, will be unable to understand what criteria determine inclusion of a single mixture within the A or B sets, simply because the cipher text is generated by combinations of two similar mixtures from the sets. Because of the specific requirements of the private key, the MoCryp system can only be built upon specific sets of structurally related compounds exhibiting, besides chemical stability and high extinction coefficients, distinct trends in the pH-dependent response, allowing for selection of the code-generating mixtures. To this aim, the new class of bioinspired cyanine-type dyes disclosed uniquely suits the scope. Its basic features are:

1) A modular chemical scaffold that can be used to synthesize a broad range of chemically diverse dyes sharing suitable characteristics and chemical and spectral similarity to ensure the inviolability of the proposed cryptographic system.
2) A collection of pH-sensitive chromophores with differential pH-dependent behavior in two different wavelength ranges (see Supporting Information), a peculiar requisite of the newly developed series of cyanine dyes.
3) Availability of two three-state series allowing for facile realization of the code-generating sets A and B.

Inviolability stems from the theoretically infinite levels of complexity of the elements upon which the private key is built. These include: variable quantitative and qualitative compositions of the mixtures, lack of easily distinguishable characteristics of the generating sets A and B, use of two different pH values within a broad range, use of elaborate rather than plain absorbance data (ratios), selection of decryption functions, and criteria for interpreting decrypted data as 0 or 1.

Added to the above characteristics, the versatile MoCryp System developed herein is highly protected against human errors connected with solution mixing, variable compound concentrations, and so on, due to the use of absorbance ratios rather than absolute values. The system can be upgraded at different levels to expand the amount of information that can be exchanged and the level of security/protection. For example, it can be easily endowed with a robust security check and

control system based on the preparation of two strings of complementary code sequences (see Supporting Information).

Conclusions

We have developed a peculiar class of bioinspired and pH-switchable modular cyanine-type dyes we call trichocyanines, which display suitable characteristics to implement a molecular cryptography system (MoCryp) based on organic dyes. Strengths of the proposed system include a robust and versatile chemistry due to modular scaffolds allowing a high number of structural combinations, and the redundancy of the coding mixtures for binary coding. Because the modular scaffold allows access to a broad and tunable palette of colors and multiple wavelength readout, trichocyanines may also be a valuable molecular tool for diverse applications, especially pH-sensing.[39,40]

Experimental Section

Reagents and dry solvents were obtained from commercial sources and were used as received. UV spectra were recorded with a V-560 UV/Vis spectrophotometer (Jasco, Easton, USA). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively using a Bruker DRX-400 MHz spectrometer (Bruker, Billerica, USA). ^{1}H,^{1}H correlation spectroscopy (^{1}H,^{1}H COSY), ^{1}H,^{13}C heteronuclear single quantum coherence (^{1}H,^{13}C HSQC) spectroscopy, and ^{1}H,^{13}C heteronuclear multiple-bond correlation (^{1}H,^{13}C HMBC) spectroscopy were run at 400 MHz using Bruker standard pulse programs. Chemical shifts are reported in δ values downfield from tetramethylsilane (TMS). For positional assignment of compounds **1–4 a,b** refer to numbering as shown in Figure 2. Electrospray ionization mass spectrometry (ESI-MS) was conducted on a Agilent 1100 Series MSD HPLC (Agilent, Santa Clara, USA) instrument equipped with a UV-Vis detector and an electrospray ionization source in positive mode (ESI).

Synthesis of 3-methyl-2*H*-1,4-benzothiazine: A solution of *o*-aminothiophenol (0.34 mL) in anhydrous ethyl ether (1.5 mL) was treated at rt with chloracetone (0.26 mL) in anhydrous ethyl ether (8.0 mL) under vigorous stirring. After 24 h, the reaction mixture was centrifuged, and the solid separated, washed with $CHCl_3$ (20× 3 mL), and discarded. The supernatant was dried to give the pure compound as a light brown oil (120 mg, 48%): R_f = 0.62 (petroleum ether/EtOAc 7:3); ^{1}H NMR ($CDCl_3$): δ = 3.04 (s, 3H, CH_3), 3.71 (s, 2H, CH_2), 7.36 (m, 3H, H6, H7, H8), 8.14 ppm (d, J = 7,2 Hz, 1H, H5); ^{13}C NMR ($CDCl_3$) δ = 24.19 (CH_3), 28.95 (C2), 124.28 (C5), 124.4 (C8a), 127.58 (C8), 128.11 (C6), 131.06 (C7), 132.95 (C4a), 172.2 ppm (C3); UV/Vis (CH_3OH): λ_{max} (log ε) = 375 nm (3.07); MS (ESI): *m/z*: 164 $[M+H]^+$.

Synthesis of trichocyanines 1 a/b–4 a/b: general procedure

3-Phenyl-2*H*-1,4-benzothiazine (0.22 mmol) or 3-methyl-2*H*-1,4-benzothiazine (0.31 mmol) dissolved in MeOH/12 M HCl, (4:1, *v/v*) (5 mL) were treated with the appropriate aldehyde at equimolar ratios. The mixture was stirred at rt overnight, then diluted with H_2O (50 mL) and extracted with $CHCl_3$ (3×50 mL). The residues obtained from the combined organic layers were separated by column chromatography using a silica gel column. Solvent systems (*v/v*) and retention factors are listed below.

(*Z*)-*N*,*N*-Dimethyl-4-((3-phenyl-2*H*-benzo[*b*][1,4]thiazin-2-ylidene)-methyl)aniline [TC(*N*/0/Ph); 1 a]: yellow glassy oil (35 mg, 44%): R_f = 0.65 (cyclohexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ = 3.01 (s, 6H, $N(CH_3)_2$), 6.73 (d, J = 8.8 Hz, 2H, H3′, H5′), 6.90 (s, 1H, SC=CH), 7.10 (d, J = 7.2 Hz, 1H, H8), 7.14 (m, 1H, H6), 7.17 (m,1H, H7), 7.45 (m, 6H, H2′, H6′, H5, Ph_{meta}, Ph_{para}), 7.85 ppm (d, J = 7.6 Hz, 2H, Ph_{ortho}); ^{13}C NMR ($CDCl_3$): δ = 40.15 ($N(CH_3)_2$), 111.39 (C3′, C5′), 117.19 (C2), 122.8 (C1′), 123.37 (C8a), 125.06 (C6), 126.50 (C7), 127.15 (C8), 128.37 (Ph_{meta}), 129.22 (Ph_{para}), 129.51 (Ph_{ortho}), 129.74 (C5), 131.4 (C2′, C6′), 134.89 (SC=CH), 140.2 (Ph_{ipso}), 140.92 (C4a), 150.15 ($CNMe_2$), 162.48 ppm (C3); UV/Vis (CH_3OH): λ_{max} (log ε) = 440 nm (3.96); MS (ESI): *m/z*: 357 $[M+H]^+$.

***N*,*N*-Dimethyl-4-((1*E*,3*Z*)-3-(3-phenyl-2*H*-benzo[*b*][1,4]thiazin-2-ylidene)prop-1-enyl)aniline [TC(*N*/1/Ph); 2 a]**: orange glassy oil (28 mg, 33%): R_f = 0.55 (CH_2Cl_2/hexane 8:2); ^{1}H NMR ($CDCl_3$): δ = 3.00 (s, 6H, $N(CH_3)_2$), 6.59 (d, J = 16 Hz, 1H, SC=CHCH=*CH*), 6.61 (d, J = 12 Hz, 1H, SC=*CH*CH=CH), 6.66 (d, J = 8 Hz, 2H. H3′, H5′), 7.02 (dd., J = 12/16 Hz, 1H, SC=CHC*H*=CH), 7.13 (d, J = 8 Hz, 1H, H8), 7.18 (m, 2H, H6, H7), 7.36 (d, J = 8 Hz, 2H, H2′, H6′), 7.46 (m, 3H, Ph_{meta}, Ph_{para}), 7.77 (m, 2H, Ph_{ortho}); ^{13}C NMR ($CDCl_3$): δ = 39.92 ($N(CH_3)_2$), 111.78 (C3′, C5′), 118.91 (SC=CHCH=CH), 119.17 (C2), 124.01 (C8a), 124.65 (C1′), 124.84 (C6), 126.25 (C7), 127.03 (C8), 128.95 (Ph_{ortho}), 128.04 (C2′, C6′), 128.14 (Ph_{meta}), 129.36 (Ph_{para}), 129.46 (C5), 133.79 (SC=CHCH=CH), 138.56 (SC=CHCH=CH), 139.31 (Ph_{ipso}), 141.19 (C4a), 150.77 ($CN(CH_3)_2$), 161.54 ppm (C3); UV/Vis (CH_3OH): λ_{max} (log ε) = 464 nm (4.26); MS (ESI): *m/z*: 383 $[M+H]^+$.

(*Z*)-2-Methoxy-4-((3-phenyl-2*H*-benzo[*b*][1,4]thiazin-2-ylidene)-methyl)phenol [TC(*O*/0/Ph); 3 a]: yellow glassy oil (32 mg, 40%): R_f = 0.45 (CH_2Cl_2/hexane 8:2); ^{1}H NMR ($CDCl_3$): δ = 3.86 (s, 3H, OCH_3), 6.86 (s, 1H, SC=CH), 6.90 (d, J = 8 Hz, 1H, H5′), 6.99 (s, 1H, H2′), 7.01 (m, 1H, H6′), 7.10–7.13 (m, 3H, H6, H7, H8), 7.41 (m, 3H, Ph_{meta}, Ph_{para}), 7.45 (d, J = 8 Hz, 1H, H5), 7.78 ppm (m, 2H, Ph $_{ortho}$); ^{13}C NMR ($CDCl_3$): δ = 55.98 (OCH_3), 112.04 (C2′), 114.2 (C5′),122.29 (C2), 123.00 (C8a), 124.08 (C6′), 125.07 (C6), 126.72 (C7), 127.50 (C8), 128.46 (Ph_{meta}), 129.36 (Ph_{para}), 129.49 (Ph $_{ortho}$),129.73 (C1′), 130.00 (C5), 134.55 (SC=CH), 138.6 (C4a), 140.20 (Ph_{ipso}), 145.9 (C4′), 146.18 (C3′), 163.30 ppm (C3); UV/Vis (CH_3OH): λ_{max} (log ε) = 413 nm (3.94); MS (ESI): *m/z*: 360 $[M+H]^+$.

2-Methoxy-4-((1*E*,3*Z*)-3-(3-phenyl-2*H*-benzo[*b*][1,4]thiazin-2-ylidene)prop-1-enyl)phenol [TC(*O*/1/Ph); 4 a]: orange glassy oil (51 mg, 60%): R_f = 0.70 (hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ = 3.95 (s, 3H, OCH_3), 6.59 (d, J = 16 Hz, 1H, SC=CHCH=*CH*), 6.62 (d, J = 12 Hz, 1H, SC=*CH*CH=CH), 7.06 (dd, J = 12/16 Hz, 1H, SC=CHC*H*=CH), 7.15–7.20 (3H, H6, H7, H8), 6.97 (1H, H2′), 6.89 (d, J = 8 Hz, H5′), 7.46 (m, 4H, H5, Ph_{meta}, Ph_{para}), 7.77 ppm (m, 2H, Ph_{ortho}); ^{13}C NMR ($CDCl_3$): δ = 55.93 (OCH_3),108.38 (C2′), 114.64(C5′), 121.37 (C6′, SC=CHCH=CH), 124.05 (C2),124.23 (C8a), 125.09 (C8), 126.68 (C7), 127.47 (C6), 128.52 (Ph_{meta}), 129.27 (Ph_{ortho}), 129.49 (C1′), 129.85 (C5, Ph_{para}),133.15 (SC=CHCH=CH), 138.17 (SC=CHCH=CH), 139.14 (C4a), 139.31 (C, Ph_{ipso}), 146.52 (C4′),146.76 (C3′), 161.36 ppm (C3); UV/Vis (CH_3OH): λ_{max} (log ε) = 436 nm (4.01); MS (ESI): *m/z*: 386 $[M+H]^+$.

(*Z*)-*N*,*N*-Dimethyl-4-((3-methyl-2*H*-benzo[*b*][1,4]thiazin-2-ylidene)-methyl)aniline [TC(*N*/0/Me); 1 b]: yellow glassy oil (55 mg, 60%): R_f = 0.45 (hexane/EtOAc 8:2); ^{1}H NMR ($CDCl_3$): δ = 2.54 (s, 3H, CH_3), 3.02 (s, 6H, $N(CH_3)_2$), 6.75 (d, J = *8* Hz, 2H, H3′,H5′), 6.97 (s,1H, SC=CH), 7.09 (m, 1H, H6), 7.10 (m, 1H, H8), 7.15 (m, 1H, H7), 7.33 (d, J = *8* Hz,1H, H5), 7.54 ppm (d, J = *8* Hz, 2H, H2′, H6′); ^{13}C NMR ($CDCl_3$): δ = 26.07 (CH_3), 40.17 ($N(CH_3)_2$), 111.58 (C3′, C5′), 118.73 (C2), 122.33 (C8a), 123.42 (C1′), 124.80 (C6), 126.36 (C7), 127.12 (C8), 129.01 (C5), 131.04 (C2′, C6′), 134.57 (SC=CH), 139.28 (C4a),

141.9 (C4′), 159.56 ppm (C3); UV/Vis (CH_3OH): λ_{max} ($\log\varepsilon$) = 429 nm (3.85); MS (ESI): *m/z*: 295 $[M+H]^+$.

***N,N*-Dimethyl-4-((1*E*,3*Z*)-3-(3-methyl-2*H*-benzo[*b*][1,4]thiazin-2-ylidene)prop-1-enyl)aniline [TC(*N*/1/Me); 2b]**: orange glassy oil (32 mg, 32%): R_f = 0.40 (hexane/ethyl ether 8:2); ^{1}H NMR ($CDCl_3$): δ = 2.43 (s, 3H, CH_3), 3.00 (s, 6H, $N(CH_3)_2$), 6.68 (d, *J* = 8 Hz, 2H, H3′, H5′), 6.70 (d, *J* = 16 Hz, 1H, SC=CHCH=*CH*), 6.73 (d, *J* = 12 Hz, 1H, SC=*CH*CH=CH), 6.91 (dd, *J* = 12/16 Hz, 1H, SC=CHC*H*=CH), 7.10 (m, 1H, H7), 7.13 (m, 1H, H8), 7.15 (m, 1H, H6), 7.33 (d, *J* = 8 Hz, 1H, H5), 7.39 ppm (d, *J* = 8 Hz, 2H, H2′, H6′); ^{13}C NMR ($CDCl_3$): δ = 24.92 (CH_3), 40.55 ($N(CH_3)_2$), 112.19 (C5′, C3′), 119.38 (SC=*C*HCH=CH), 120.61 (C2), 123.27 (C8a), 124.81 (C6), 125.16 (C1′), 126.41 (C7), 127.2 (C8), 127.62 (SC=CH*C*H=CH), 128.28 (C2′, C6′), 129.41 (C5), 137.85 (SC=CHCH=*C*H), 140.01 (C4a), 150.59 (C4′), 158.88 ppm (C3); UV/Vis (CH_3OH): λ_{max} ($\log\varepsilon$) = 458 nm (3.65); MS (ESI): *m/z*: 321 $[M+H]^+$.

(*Z*)-2-Methoxy-4-((3-methyl-2*H*-benzo[*b*][1,4]thiazin-2-ylidene)-methyl)phenol [TC(*O*/0/Me); 3b]: yellow glassy oil (41 mg, 44%): R_f = 0.40 (hexane/EtOAc 8:2); ^{1}H NMR ($CDCl_3$): δ = 2.55 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.99 (s,1H, H2′), 7.09 (m, 1H, H6′), 7.11–7.14 (m, 4H, H5′, SC=*CH*, H6, H7), 7.16 (m, 1H, H8), 7.37 ppm (m, *J* = *8 Hz*,1H, H5); ^{13}C NMR ($CDCl_3$): δ = 25.87 (CH_3), 55.95 (OCH_3), 111.70 (C2′), 114.41 (C5′), 121.39 (C2), 121.78 (C8a), 123.55 (C6), 124.80 (C6′), 126.58 (C7), 127.42 (C8), 127.70 (C1′, SC=*C*H), 129.18 (C5), 138.84 (C4a), 145.84 (C4′), 146.25 (C3′), 158.90 ppm (C3); UV/Vis (CH_3OH): λ_{max} ($\log\varepsilon$) = 401 nm (3.41); MS (ESI): *m/z*: 298 $[M+H]^+$.

2-Methoxy-4-((1*E*,3*Z*)-3-(3-methyl-2*H*-benzo[*b*][1,4]thiazin-2-ylidene)prop-1-enyl)phenol [TC(*O*/1/Me); 4b]: orange glassy oil (42 mg mg, 42%): R_f = 0.35 (petroleum ether/EtOAc 7:3); ^{1}H NMR ($CDCl_3$): δ = 2.48 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 6.69 (d *J* = 16 Hz, 1H, SC=CHCH=*CH*), 6.72 (d, *J* = 12 Hz, 1H, SC=*CH*CH=CH), 6.91 (s,1H, H2′), 6.95 (dd, *J* = 12/16 Hz,1H, SC=CHC*H*=CH), 6.99 (m, 2H, H6′), 7.09 (d, 1H, *J* = 8 Hz, H5′), 7.10–7.15 (3H, H6, H7, H8), 7.35 ppm (d, *J* = 8 Hz, 1H, H5); ^{13}C NMR ($CDCl_3$): δ = 24.97 (CH_3), 55.98 (OCH_3), 108.32 (C2′), 114.71 (C6′), 121.46 (SC=CHCH=CH), 122.41 (C2), 121.35 (C5′), 124.79 (C8), 124.23 (C8a), 126.78 (C7), 127.42 (C6), 129.56 (C1′), 129.58 (C5), 133.15 (SC=*C*HCH=CH), 137.20 (SC=CHCH=*C*H), 139.76 (C4a), 146.44 (C4′), 146.79 (C3′), 158.53 (C3); UV/Vis (CH_3OH): λ_{max} ($\log\varepsilon$) = 434 nm (3.65); MS (ESI): *m/z*: 323 $[M+H]^+$.

Computational analysis: All calculations were performed with the Gaussian package of programs.[41] All structures were geometry optimized at the DFT level, with a hybrid functional (PBE0)[29] and a reasonably large basis set.[6–31 + G(d,p)] For each species, different tautomers/conformers, as well as different protonation states were explored. In those cases where conformational enantiomers exist, a single enantiomeric series was explored. Computations were performed either in vacuo, or by adoption of a polarizable continuum medium (PCM)[30–32] to account for the influence of the solution environment. In view of the faster convergence, a scaled van der Waals cavity based on universal force field (UFF) radii[42] was used, and polarization charges were modeled by spherical Gaussian functions.[43] Vibrational-rotational contributions to the free energy were also computed. UV/Vis spectra of the main species were computed in vacuo or in solution using the time-dependent density functional theory (TD-DFT) approach,[33–37] with the PBE0 functional and the 6–311 + + G(2d,2p) basis set. For comparison, TD-DFT calculations also were carried out with the M06–2X functional,[38] a hybrid *meta*-GGA which has proved satisfactory in reproducing the results of reference high-level post Hartree–Fock calculations of a series of cyanines.[44] To produce graphs, transitions below 5.6 eV were selected, and an arbitrary Gaussian line width of 0.15 eV was imposed; the spectra were finally converted to a wavelength scale.

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