(450 mg) in CH_2Cl_2 (50 mL) was treated with $I(s\text{-coll})_2ClO_4$[2a] (570 mg, 1.09 mmol) in the same manner as for (−)-**25** (vide supra) to give a mixture of isomeric coupling products (358 mg, 41%) containing >90% **44** (by ^1H NMR). **44**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.127 (s, 9 H), 0.135 (s, 9 H), 1.24–1.27 (d, J = 6.5 Hz, 3 H), 1.88–1.95 (dd, J = 3.5, 15 Hz, 1 H), 2.41 (s, 3 H), 2.41–2.46 (br d, J = 15 Hz, 1 H), 2.99–3.06 (d, J = 19 Hz, 1 H), 3.19–3.27 (dd, J = 0.9, 19 Hz, 1 H), 3.4–3.5 (m, 1 H), 3.66–3.69 (app t, J = 2.8 Hz, 1 H), 3.97–4.00 (app t, J = 3.6 Hz, 1 H), 4.08 (s, 3 H), 4.22–4.30 (m, 1 H), 4.55 (br s, 1 H), 5.51–5.53 (m, 1 H), 5.65–5.66 (br d, J = 2.9 Hz, 1 H), 7.37–7.40 (d, J = 8.5 Hz, 1 H), 7.74–7.81 (app t, J = 8 Hz, 1 H), 8.01–8.04 (dd, J = 0.9, 7 Hz, 1 H), 13.27 (s, 1 H), 14.08 (s, 1 H).

7-*O*-(2′,6′-Dideoxy-2′-iodo-α-D-talopyranosyl)daunomycinone (24). A solution of **44** (and isomeric coupling products) (298 mg, 0.373 mmol) in THF (34 mL) was desilylated with HF–pyridine (1.7 mL) as for **42** above (18 h total). Chromatography (1–4% MeOH/CH_2Cl_2) gave **24** (195 mg, 80%) as a red glass. A later fraction contained the corresponding α-D-galacto-pyranosyl (daunomycinone equatorial, iodine equatorial) isomer (~3 mg, 1%) [^1H NMR (250 MHz, $CDCl_3$) anomeric proton δ 5.02–5.06 (d, J = 8.6 Hz)]. **24**: $[\alpha]^{22}_D$ +301° (*c* 0.095, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.31–1.34 (d, J = 6.6 Hz, 3 H), 1.84–1.89 (d, J = 11 Hz, 1 H), 1.93–2.00 (dd, J = 3.6, 15 Hz, 1 H), 2.39 (s, 3 H), 2.39–2.45 (br d, 1 H), 2.73–2.77 (d, J = 10 Hz, 1 H), 2.98–3.06 (d, J = 19 Hz, 1 H), 3.21–3.29 (br d, J = 19 Hz, 1 H), 3.27–3.35 (m, 1 H), 3.73–3.78 (dd, J = 1.8, 11 Hz, 1 H), 4.09 (s, 3 H), 4.26 (s, 1 H), 4.27–4.29 (d, J = 4.9 Hz, 1 H), 4.48–4.58 (br q, J = 6.6 Hz, 1 H), 5.52–5.54 (m, 1 H), 5.74 (br s, 1 H), 7.38–7.42 (d, J = 8.5 Hz 1 H), 7.76–7.82 (app t, J = 8 Hz, 1 H), 8.02–8.06 (dd, J = 0.8, 7.4 Hz, 1 H), 13.27 (s, 1 H), 14.14 (s, 1 H); IR (KBr) 3150–3600 (br, OH), 2980, 2940, 1715, 1620, 1580, 1415, 1385, 1355, 1290, 1240, 1215, 1000 cm^{-1}; MS (FAB-NOBA/NaI) *m/z* 677 (4.8, MNa^+), 654 (3.8, M^+), 321 (40), 307 (100), 289 (49), 176 (58); HRMS (FAB-NOBA/NaI) *m/z* (MNa^+) calcd for $C_{27}H_{27}O_{11}INa$ 677.0496, obsd 677.0519. Anal. Calcd for $C_{27}H_{27}O_{11}I$: C, 49.56; H, 4.16. Found: C, 49.20; H, 4.17.

Acknowledgment. This research was supported by PHS Grant HL 25848. A Merck Postdoctoral Fellowship to D.B.B. is gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Registry No. (*E*,*E*)-**1**, 91861-09-5; (*Z*,*E*)-**1**, 91861-07-3; (*Z*,*Z*)-**1**, 91861-08-4; **2**, 138407-61-1; (±)-**2**, 138512-00-2; **3**, 138407-62-2; (±)-**3**, 138512-01-3; **4**, 104130-24-7; (±)-**4**, 138512-02-4; **5**, 138407-63-3; **6**, 138512-03-5; **7**, 138407-64-4; **8**, 138407-65-5; **9**, 138407-66-6; **10**, 138407-67-7; **11**, 138407-68-8; **12**, 138407-69-9; **13**, 138407-70-2; **14**, 138407-71-3; **15**, 138407-72-4; **16**, 138407-73-5; **17** (isomer 1), 138513-31-2; **17** (isomer 2), 138407-74-6; **18a**, 138407-75-7; **18b**, 138407-76-8; **19**, 138407-77-9; (−)-**21**, 75829-69-5; (+)-**21**, 54621-94-2; **22**, 138407-78-0; **23**, 138512-04-6; **24**, 138512-05-7; (−)-**25**, 138432-66-3; (+)-**25**, 138407-79-1; **26**, 138512-06-8; **27**, 138512-07-9; **28**, 138512-08-0; **29**, 104069-03-6; (±)-**29**, 138512-09-1; **30**, 95475-50-6; (±)-**30**, 138512-10-4; **31**, 76739-66-7; **32**, 138512-11-5; (±)-**32**, 138512-12-6; **33**, 109278-72-0; **34**, 138512-13-7; (±)-**34**, 138512-14-8; **35**, 106930-36-3; **36**, 138407-80-4; **37**, 138407-81-5; **38**, 138512-15-9; **39**, 138407-82-6; (−)-**40**, 138512-16-0; (+)-**40**, 138512-17-1; **41**, 134355-03-6; **42**, 138407-83-7; **43**, 138512-18-2; **44**, 138407-84-8; (±)-(2*R**,4*S**)-4-hydroxy-2-methyl-2,3-dihydro-4*H*-pyran, 80754-66-1.

Supplementary Material Available: Tables of fractional coordinates, bond distances, torsional angles, anisotropic temperature factors, and summaries of the X-ray crystallographic determinations for compounds **22** and **23** (38 pages). Ordering information is given on any current masthead page.

Synthetic Replicators and Extrabiotic Chemistry

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Abstract: Synthetic replicators can be generated by covalent attachment of two complementary structures to form a self-complementary molecule. The complementarity refers to sizes, shapes, and the weak, intermolecular forces that characterize molecular recognition phenomena. New self-complementary structures were obtained by coupling imides to synthetic receptors for imides, and their properties as replicators were explored. The new structures use hydrogen bonding of thymine derivatives to diaminotriazines as the recognition vehicle, and autocatalytic behavior is experimentally demonstrated during the covalent coupling step. Self-complementarity and molecular aggregation are discussed in terms of orientation of recognition surfaces with respect to one another. The development of other replicating systems based on alternative binding forces is discussed. The term *extrabiotic* is proposed for synthetic systems which exhibit lifelike behavior.

Synthetic replicators are at the interface of chemistry and biology, and they provide a means by which lifelike molecular behavior can be expressed in model systems. A recent example involves the coupling of adenine derivatives to suitably constructed imides.[1] Such systems can show sigmoidal growth,[2] reciprocity, and even mutation[3]—features characteristic of evolution at the molecular level. Here we present a new system based on thymine derivatives and propose that self-replicating molecules are a reasonable, perhaps inevitable, consequence of molecular recognition.

Self-complementarity represents the key feature of minimalist replicators,[4] and we have been much influenced by biological structures that show such properties. Most relevant are palindromic sequences of nucleic acids which can dimerize into double-stranded forms. However, the self-complementarity feature is so *economical* that a number of biological structures use it to advantage. For example, multisubunit enzymes, clathryn triskelions, and viral capsid proteins fit together in a 3-dimensional array; their subunits are self-complementary.[5]

Systems of manageable size for studies in solution that share this feature can be prepared by covalent coupling of two complementary fragments into a single unit. In this context, complementary refers to size, shape, and the weak intermolecular forces that characterize molecular recognition phenomena. The

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(2) Rotello, V.; Hong, J.-I.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 9422–9423.
(3) Hong, J.-I.; Feng, Q.; Rotello, V.; Rebek, J., Jr. *Science*, in press.
(4) Nowick, J. S.; Feng, Q.; Tjivikua, T.; Ballester, P.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 88315.
(5) Branden, C.; Tooze, J. *Introduction to Protein Structure* Garland: New York, 1991; Chapter 11. In the larger (and more trivial) sense, any substance that enjoys a crystalline state must enjoy enough self-complementarity to stabilize its lattice by intermolecular forces.
(6) Barr, R. G.; Pinnavaia, T. J. *J. Chem. Phys.* **1986**, *90*, 328. Three-dimensional arrays have also been described: Simard, M.; Su, D.; Wuest, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 4696.

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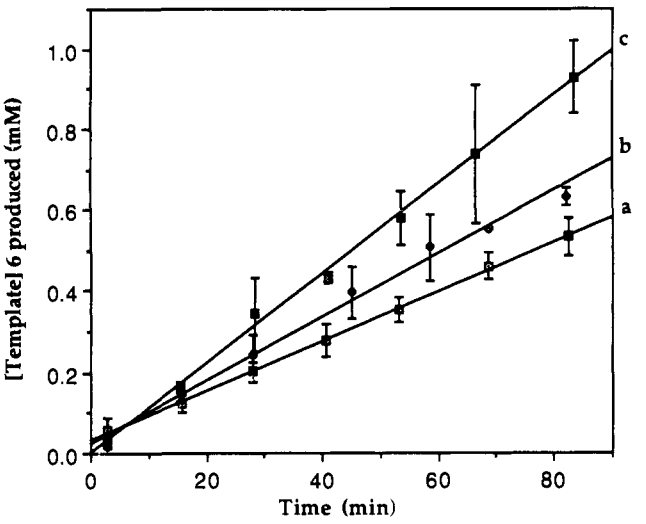
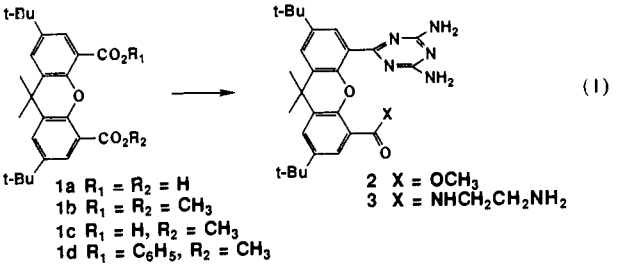


Figure 1. Appearance of **6** as a function of time: (a) no additive; (b) 25% **6** added; (c) 50% **6** added. Initial concentrations are [3] = [**5b**] = 8.0 mM in $CHCl_3$. Et_3N (18 equiv) was present in all reaction solutions. Error bars represent standard deviations of multiple independent runs.

use of hydrogen bonding with its modest directionality and easily recognized patterns has been quite successful in this regard.[7] A good deal is known about imide interactions with diaminopyridine derivatives,[8] and we have used this hydrogen-bonding motif in organic solvents to construct synthetic receptors for thymine and other imides.[9]

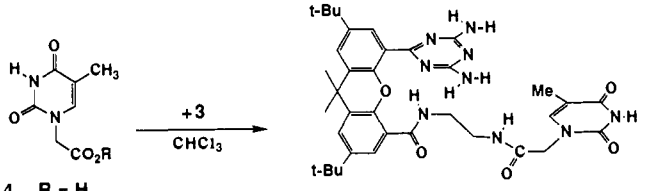
These are readily assembled from the xanthenedicarboxylic acid[4] **1a** through simple functional group manipulations (eq 1).



(1)

For example, the dimethyl ester **1b** can be monodeprotected by brief treatment with HBr. The resulting acid ester **1c** is coupled to phenol to produce the mixed ester **1d**, which is condensed with biguanide to give the diaminotriazine methyl ester **2**. Merely warming the triazine in neat ethylenediamine gave the nucleophilic amine component **3**.

For the thymine module, we elaborated thymineacetic acid **4** to its trichlorophenol ester **5a** and phenyl ester **5b**. Coupling of



(2)

(7) For reviews see: Hamilton, A. D.; Pant, N.; Muehldorf, A. *Pure Appl. Chem.* **1988**, *60*, 533–538. Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245–255.

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(10) Nowick, J. S.; Ballester, P.; Ebmeyer, F.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8902. Acid **1** is commercially available from Aldrich Chemical Co.

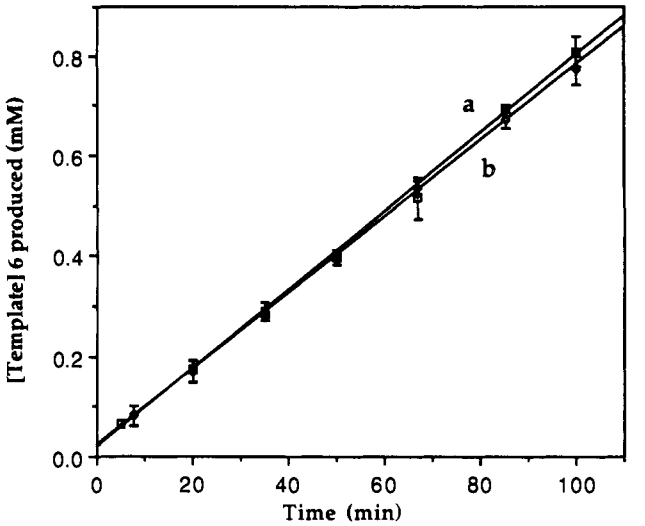

Figure 2. Apperance of **6** as a function of time: (a) no additive; (b) 25% **2** added. Initial concentrations are [3] = [**5b**] = 8.0 mM in $CHCl_3$. Et_3N (18 equiv) was present in all reaction solutions. Error bars represent standard deviations of multiple independent runs.

the amine **3** with the thymine ester **5a** gave the self-complementary structure **6** for use in replication studies. Fortunately, **6** was quite soluble in organic solvents such as $CDCl_3$, which permitted examination of its properties over a range of concentrations.

The autocatalytic behavior of the new species was demonstrated as previously described.[4] The appearance of product **6** with time during the coupling of amine **3** with the less reactive phenyl ester **5b** was followed by HPLC (the coupling rate with **5a** was too rapid to follow conveniently). In Figure 1, the initial rate for the coupling reaction (the background rate) is shown. When 0.25 equiv of product **6** is added to the coupling mixture, the initial rate increases. With 0.5 equiv of the product added, an even larger increase in the initial rate is observed.

We have already discussed, in considerable detail,[4] the shapes of these product growth curves as a function of the various coupling rates involved, and in parallel work with nucleic acid derivatives, von Kiedrowski[11] has formulated the "square root law". Because the product is self-complementary, it can form cyclic dimers, a process that reduces the amount of monomeric catalyst that can act as a template for its own formation. The coupling rate is therefore proportional to the square root of the concentration of the product. An additional feature of such systems is that the initial production formation of the reaction is quite linear with time, and the sigmoid behavior can be observed only in special circumstances.[12]

The possibility that the template was acting merely as a general-base catalyst was excluded with control experiments. Triazine methyl ester **2** was added to the coupling reaction, but no enhancement of the initial rate was observed (Figure 2). The autocatalytic effect appears to be due to the formation of a termolecular complex **7** (eq 3). In this reaction, both of the materials are gathered on the template surface in such a way that a relatively effortless transition state for amide bond formation can be reached. The initial product is the dimer **8**; dissociation of this dimer then exposes more template surfaces for the autocatalytic effect. Using dilution titration techniques, and the chemical shift of the imide proton as a measure of aggregation, we were able to obtain a dimerization constant for the dimer of 3×10^4 M^{-1} in $CDCl_3$.

This is only the second structural system in which self-complementarity has been parlayed into replication, and it is reasonable to ask how generalizable this feature may be. It is our premise that any recognition even involving weak intermolecular forces

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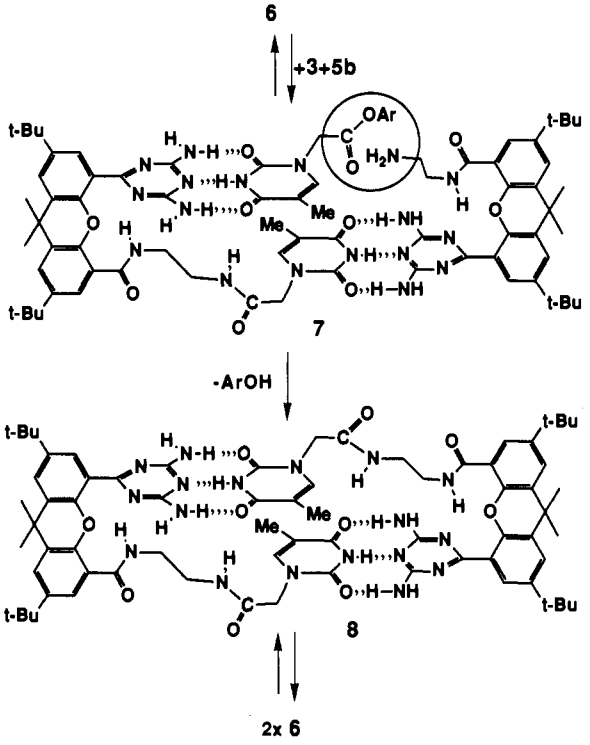
(12) von Kiedrowski, G.; Wlotzka, B.; Helbing, J.; Matzen, J. M.; Jordan, S. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 423.



(3)

can lead to self-replicating systems. All that is required is that the two complementary subunits become covalently attached to form a single self-complementary whole. Further, the recognition surfaces must be oriented in such a manner that permits dimerization into a cyclic complex. When these conditions are met, the molecule becomes a minimalist replicator, it can act as a template for productive termolecular complexes. When the recognition surfaces are fixed in divergent orientations, the units may assemble in a chain of polymers[13] or other repeating mosaics of significance to material science. The biological assemblies discussed previously also feature these divergent recognition surfaces.

The binding forces need not be limited to hydrogen bonds in organic solvents; for example, the interaction of a ligand with a metal can also be the basis of a self-replicating system,[14] and many situations can be envisioned in host–guest chemistry that could lead to self-complementary structures. A specific example that we are pursuing in collaboration with F. Diederich is the inclusion of aromatics in cyclophane complexes in aqueous solution.

In conclusion, the evolution of self-replicating systems can be considered a simple consequence of molecular recognition. The only accident needed for the generation of minimalist, self-complementary replicators is covalent bonding. These synthetic molecules and solvents are certainly not those of prebiotic or early biotic earth.[13] Even so, the phenomena they express, replication, reciprocity, and mutation, must also have been features of those molecules that were of the prebiotic world.

Apart from the replicators which have emerged in our laboratories, there are spectacular examples of synthetic molecules whose behavior (if molecules can be said to behave) is *lifelike*. For example, the helicates,[16] which self-assemble and resemble nucleic acid double helices turned inside out, "homo DNA", a ladderlike structure that shows all the earmarks of replicating systems,[17] and the autopoetic replication of micelles[18] are all systems that feature properties that have counterparts in biological chemistry. Parallel developments in computer science have also led to entities that show replication and evolution.[19] As these constructs are not easily absorbed into the realm of prebiotic or biotic chemistry, we propose the term *extrabiotic* to describe them. Our expectation is that extrabiotic chemistry will recruit themes, structures, and phenomena from the larger world of chemistry but will continue to be inspired by developments in molecular biology.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a 250-MHz Bruker instrument. Mass spectra were obtained on a VG instrument, an Se-20 mass spectrometer, or a Varian CH-5 instrument (high resolution). IR spectra were obtained on an IBM IR/32 FTIR spectrometer.

Xanthene Diacid Dimethyl Ester 1b. Xanthene diacid **1a** (13.28 g, 32.3 mmol) was refluxed in methanol (500 mL) and sulfuric acid (20 mL) for 4 h. After cooling, the precipitate was filtered off, washed with cold methanol, and dried to yield the dimethyl ester **1b** (14.56 g, 97%): mp 220 °C; IR (KBr) 2964, 2905, 2870, 1730, 1707, 1445, 1316, 1276, 1101, 1009, 894, 784 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.63 (d, J = 2.4 Hz, 2 H), 7.54 (d, J = 2.4 Hz, 2 H), 3.97 (s, 6 H), 1.64 (s, 6 H), 1.33 (s, 18 H).

Xanthene Diacid Monomethyl Ester 1c. Gaseous HBr was bubbled into CH_2Cl_2 at 0 °C for 25 min, and dimethyl ester **1b** (12.39 g, 28.25 mmol) was added at 0 °C. The intensely yellow solution was stirred for 2 h at 0 °C (TLC). The reaction mixture was poured into ice-cold water (500 mL). The aqueous layer was saturated with NaCl and extracted twice with CH_2Cl_2 (200 mL); the combined organic layers were dried ($MgSO_4$) and concentrated to give 11.89 g (99%) of pure monoacid **1c**: mp 178 °C; IR (KBr) 3317 (COOH, sharp), 2963, 2908, 2872, 1717, 1444, 1324, 1270, 1245, 1118, 998, 788 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 11.92 (s, 1 H), 8.25 (d, J = 2.5 Hz, 1 H), 7.98 (d, J = 2.4 Hz, 1 H), 7.70 (d, J = 2.4 Hz, 1 H), 7.67 (d, J = 2.6 Hz, 1 H), 4.01 (s, 3 H), 1.68 (s, 6 H), 1.37 (s, 9 H), 1.36 (s, 9 H).

Xanthene Phenyl Methyl Diester 1d. A solution of xanthene diacid monomethyl ester **1c** (1.00 g, 2.36 mmol), phenol (666 mg, 3.0 equiv), and DMAP (10 mg) in 20 mL of dry CH_2Cl_2 was treated with DCC (535 mg, 1.1 equiv). After 6 h, the reaction mixture was concentrated and chromatographed to give 1.112 g of impure product, which was contaminated with ~10% of DCC-derived impurities. This impure material was used directly for the next step: ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.82 (d, J = 2.4 Hz, 1 H), 7.63 (d, J = 2.4 Hz, 1 H), 7.58 (d, J 2.4 Hz, 1 H), 7.55 (d, J = 2.4 Hz, 1 H), 7.23–7.47 (m, 4 H), 3.63 (m, 3 H), 1.67 (s, 6 H), 1.37 (s, 9 H), 1.33 (s, 9 H).

Diaminotriazine Methyl Ester 2. A solution of the impure xanthene phenyl methyl diester **1d** (826 mg), biguanide (230 mg), and triethylamine (500 μL) in 15 mL of absolute EtOH under argon was heated to reflux for 90 min. While the mixture was hot, the white solid was filtered off; it was then washed with ~5 mL of ethanol to give 547 mg of pure triazine methyl ester **2**. An additional 47 mg was obtained from the filtrate by flash chromatography (5% MeOH in CH_2Cl_2). Total yield was 594 mg (69% from xanthene diacid monomethyl ester **1c**): mp 335–336 °C; IR (KBr) 3497, 3484, 3282, 3102, 2964, 2870, 1717, 1643, 1620, 1542, 1515, 1437, 1394, 1273, 1260, 828 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$); δ 7.48–7.55 (m, 4 H), 5.21 (br, 4 H), 3.76 (s, 3 H), 1.65 (s, 6 H), 1.34 (s, 9 H), 1.32 (s, 9 H).

Diaminotriazine Amine 3. Diaminotriazine methyl ester **2** (275 mg, 0.562 mmol) was suspended in anhydrous ethylenediamine (20 mL) under argon, and the suspension was heated to 46 °C for 13 h. The reaction mixture was heated for an additional 2 h at 67 °C. Removal of ethylenediamine under reduced pressure gave **3** as a white solid (quantitative): mp 275 °C dec; IR (KBr) 3350, 3195, 2962, 2869, 1653, 1617, 1539, 1437, 1394, 1266, 827 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.45 (t, J = 6.1 Hz, 1 H), 8.16 (d, J = 2.4 Hz, 1 H), 7.53–7.56 (m, 3 H), 5.88 (br, 4 H), 3.50 (q, J = 6.1 Hz, 2 H), 2.82 (t, J = 6.1 Hz, 2 H), 1.67 (s, 6 H), 1.58 (br, $NH_2 + H_2O$), 1.34 (s, 18 H); HRMS calcd for $C_{29}H_{39}N_7O_2$ 517.3165, found 517.3162.

Thymine-1-acetic Acid Active Ester. A solution of thymine-1-acetic acid **4** and the phenol derivative (2–3 equiv) in dry THF under argon at

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0 °C was treated with *N*-ethyl-*N'*-(3-(dimethylamino)propyl)carbodiimide methiodide (1.0 equiv) and stirred overnight while the solution was allowed to warm to room temperature. The supernatant solution was concentrated and flash-chromatographed with appropriate solvent. The product obtained was triturated in hexanes.

2,4,5-Trichlorophenyl Ester 5a: 23% yield; mp 177-178 °C; IR (KBr) 1775, 1696, 1457, 1350, 1234 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.30 (br, 1 H), 7.58 (s, 1 H), 7.37 (s, 1 H), 7.01 (m, 1 H), 4.73 (s, 2 H), 1.96 (d, J = 1.3 Hz, 3 H).

Phenyl Ester 5b: 41% yield; mp 193-194 °C; IR (KBr) 1756, 1696, 1652, 1457, 1203 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.35 (br, 1 H), 7.40 (t, J = 7.3 Hz, 2 H), 7.26 (t, J = 7.4 Hz, 1 H), 7.13 (d, J = 7.4 Hz, 2 H), 7.02 (m, 1 H), 4.69 (s, 2 H), 1.95 (d, J = 1.0 Hz, 3 H); HRMS calcd for $C_{13}H_{12}N_2O_4$ 260.0797, found 260.0795.

Diaminotriazine-Thymine Template 6. Diaminotriazine amine **3** (61 mg, 0.118 mmol) and the trichlorophenyl ester **5a** (43 mg, 1.0 equiv) were allowed to react for 20 min in 6 mL of dry CH_2Cl_2 and Et_3N (100 μL) under argon. Flash chromatography of the concentrated residue with 5-10% MeOH in CH_2Cl_2 gave 81 mg (100%) of **3** as a white powder: mp 200-205 °C; IR (KBr) 3340, 3217, 2960, 2850, 1684, 1652, 1538, 1535, 1432 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 12.9 (br, 1 H), 8.34 (t, 1 H), 8.08 (d, J = 2.2 Hz, 1 H), 7.75 (br, 2 H), 7.57 (d, J = 2.3 Hz, 1 H), 7.52 (d, J = 2.1 Hz, 1 H), 7.47 (d, J = 2.1 Hz, 1 H), 7.31 (br, 1 Hr), 7.07 (s, 1 H), 5.43 (br, 2 H), 4.31 (s, 2 H), 3.3-3.5 (m, 4 H), 1.90 (s, 3 H), 1.67 (s, 6 H), 1.34 (s, 18 H); HRMS calcd for $C_{36}H_{45}N_9O_5$ 683.3544, found 683.3543.

Kinetic Studies. The reaction of thymine ester **5b** with diaminotriazine amine **3** in the presence or absence of template **6** was performed in $CHCl_3$ solution containing 18 equiv of triethylamine (TEA). A Waters 600 HPLC (Multisolvent Delivery System) equipped with a UV detector (Waters, Lambda-Max, Model 481 LC spectrophotometer) set at 254 nm (AUFS = 1.0) was used for analysis of reaction mixtures. Analyses were performed using a reverse-phase column (Beckman C18 column, Ultrasphere ODS dp, 5 μ, 4.6 mm, i.d. × 25 cm, flow rate = 1.0 mL/min) and a mixture of water/methanol/TEA (16:84:0.6) as a mobile phase. The integration of peaks and calculation of concentrations were performed using an NEC computer and Waters 820 Baseline software. Chloroform was dried over molecular sieves. All experiments were performed at ambient temperature (21.5-23.0 °C). Each run was performed two or three times to obtain average values for data.

Typical Reaction Procedures. A Wheaton reaction vial (0.3 mL) equipped with a Microflex Miniert valve and Microflex stir vane was charged with 40 μL of diaminotriazine amine **3** stock solution (2.0×10^{-2} M), 20 μL of $CHCl_3$, 2 μL of TEA, and finally 40 μL of thymine ester **5b** stock solution (2.0×10^{-2} M). Aliquots (2.0 μL) were withdrawn periodically and analyzed by HPLC. The retention times of product (template) **6**, diaminotriazine amine **3**, and thymine active ester **5b** were 7.4, >12, and 2.4 min, respectively.

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Registry No. 1a, 130525-39-2; **1b**, 140663-26-9; **1c**, 140663-27-0; **1d**, 140663-28-1; **2**, 140663-23-6; **3**, 140663-24-7; **4**, 20924-05-4; **5a**, 140676-57-9; **5b**, 140663-29-2; **6**, 140663-25-8; biguanide, 56-03-1; ethylenediamine, 107-15-3.

Ab Initio Study of Vibrationally Preferred Deuteration Sites in the Cyclopropane-d_2 Radical Cation

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Abstract: The relative stabilities of various positional isomers of partially deuterated cyclopropane cations have been studied theoretically, using ab initio UHF/6-31G** calculations, and compared with the results of low-temperature matrix-isolation ESR (electron spin resonance) experiments. Deuteration at the top carbon is, from differences in zero-point vibrational energies (ZPE), calculated to be more favorable than in any of the basal positions, in agreement with experiments on the cyclopropane-*1,1*-d_2 cation (the ground state of the cation being an obtuse, equilateral triangle). The relative abundance of the isomers, observed at 4 K in the absence of annealing, is found to correspond to the calculated Boltzmann distribution at 100 K, indicating that thermal equilibration is hindered at temperatures below this. This agrees with experimental studies of the dynamic Jahn-Teller effect, as well as experiments involving annealing at 20-77 K. Somewhat unexpectedly, the preferred deuteration sites are in the longer C-H bonds, in contrast to, e.g., the methane or *n*-butane cations, where the opposite is true. It is shown that this is caused by strong interactions in the low-frequency (bending) part of the vibrational spectrum.

1. Introduction

Partial deuteration has been applied very successfully during recent years in connection with electron spin resonance (ESR) studies of hydrocarbon radical cations.[1] As an example, it was possible by this technique, in combination with accurate quantum-chemical calculations, to resolve the long-standing discussion about the ground-state conformation of the methane radical cation.[2-4] By studying the doubly deuterated species, $CH_2D_2^+$, it was shown that the methane cation has a C_{2v} distorted ground state and that the deuterium atoms preferentially occupy the two shorter bonds, whereas the protons occupy the two longer bonds. In certain cases, however, it has been impossible to associate the observed ESR spectra with any unique nuclear arrangement even at low temperatures, and thus a mixture of conformations has had to be assumed in order to obtain satisfactory simulations of the spectra.[5-9]

We have, in a recent paper,[10] analyzed one such case in detail, namely, the *n*-butane cation (more precisely, the *n*-butane-*1,1,4,4*-d_4 and *n*-butane-*1,4*-d_2 radical cations), and shown that

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