secondary structure, as evidenced by the single minimum at approximately 200 nm, indicative of a random coil (Figure 2, spectrum A). Reduction of the sample temperature to 4 °C did not change the spectrum.

We also employed a two-dimensional (2D) ROESY experiment[12a] to address the question of structure in GCN4(107-125). Under conditions similar to those employed for the CD studies, interresidue ROEs were not observed. If a significant fraction of the population was α-helical, strong ROEs should have been observed between the α and β protons of the i and $i+3$ residues.[12b] In addition, the optical spectrum of GCN4(107-125)[13] was identical under native and denaturing conditions (data not shown), indicating that the native conformation does not place the aromatic residues in a solvent-restricted environment. Thus, CD, UV, and NMR experiments all demonstrate that GCN4(107-125) does not adopt a stable secondary structure in aqueous solution at neutral pH.

Can secondary structure be induced in GCN4(107-125)? Figure 2 shows the results of adding increasing amounts of trifluoroethanol (TFE).[14] Although changes in the CD spectrum are apparent, they are not consistent with a large increase in α-helicity. The spectrum recorded in 75% TFE (C in Figure 2) suggests at most 20% α-helix content.[15] Other additives were also tested: monovalent salts (100 mM KCl), divalent salts (100 mM $MgCl_2$), and poly-L-lysine (a crude model for the putative positively charged protein GCN4 contacts in vivo). All failed to induce significant secondary structure as judged by CD (data not shown).

In summary, GCN4(107-125) does not adopt a stable secondary structure in solution nor does it have much helix-forming potential. However, our findings do not preclude the possibility that this peptide adopts a specific conformation in the presence of its in vivo target protein. Many peptides of this size or smaller exhibit significant secondary structure,[16] so the lack of structure in GCN4(107-125) is not simply due to its modest size. We believe these results are biologically relevant since a fusion protein containing GCN4(107-125) and no other GCN4 residues does activate transcription.[9] Nonetheless, it is important to note that GCN4(107-125) is a weak activator compared to the intact GCN4 protein and represents only a fragment of the true activation domain.[3b] This modest activation potential is typical of a variety of short acidic peptides that have been examined in vivo.[8a,b,17] It may be that they are weak activators precisely because they lack structural elements found in potent AADs. This view is supported by our preliminary studies with GCN4(107-144), a peptide that corresponds more closely to the full activation domain and is a much more potent activator in vivo. The CD spectrum of GCN4(107-144) suggests a significant amount of structure, but mostly β-sheet rather than α-helix (M.V.H. and T.K., unpublished results). Detailed structural studies of GCN4(107-144) are underway.

Acknowledgment. This work was supported by a grant from the Welch Foundation. T.K. is a recipient of an American Cancer Society Junior Faculty Research Award, M.V.H. is supported by an NIH Biophysics Training Grant.

(11) Each sample contained 0.8 mM GCN4(107-125) and 20 mM $NaPO_4$ (pH 7.6). Samples were scanned 10 times in a J600 spectropolarimeter using a 0.01 cm path length cell at 23 °C. Each spectrum was corrected for background by subtraction of an identical sample lacking peptide.

(12) (a) GCN4(107-125) (2 mM), 5 mM $NaPO_4$ (pD 7.6). All of the protons were assigned by a standard strategy[12b] involving a double-quantum phase-sensitive COSY experiment in D_2O in conjunction with ROESY and double-quantum phase-sensitive COSY experiments in DMSO-d_6. A ROESY experiment was employed because the 2D NOESY spectrum did not reveal any cross peaks. (b) Wüthrich, K. *NMR of Proteins and Nucleic Acids*; Wiley: New York, 1986.

(13) The sample contained 0.042 mM GCN4(107-125) and 24 mM $NaPO_4$ (pH 7.6) for the native study and was scanned from 400 nm to 240 nm in a 1.0 cm path length cell at 23 °C. Samples for denaturing studies were identical to that for the native study except that they contained up to 8.0 M urea, 5.7 M guanidinium hydrochloride, or 0.75 M sodium dodecyl sulfate.

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A New Photochemical Reaction and Its Mechanism: Rearrangement of Acyl and Imino Cyclopropenes[1]

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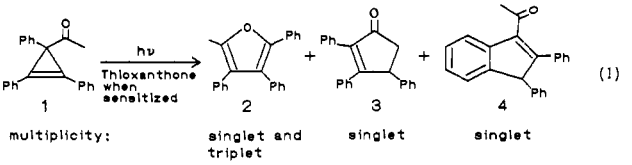
Received July 29, 1991

The search for fundamentally new photochemical reactions is arduous and only occasionally successful. However, this has remained one of our main goals. Our previous studies of the photochemistry of vinylcyclopropenes[2] led us to explore the chemistry of acyl- and imino-substituted cyclopropenes, both of which have been postulated[4] to be intermediates in the photochemical isomerizations of furans and pyrroles. We now report (1) a remarkable dependence of the photochemistry of acylcyclopropenes on multiplicity wherein the triplets rearrange smoothly to furans, (2) evidence for a reaction mechanism of the triplet rearrangement of the acylcyclopropenes different from that of the corresponding vinylcyclopropenes, (3) a striking dependence of the photochemistry on the substituent at C-3, (4) the first synthesis of an iminocyclopropene and the general stability of the acyl compounds, and (5) the triplet rearrangement of the iminocyclopropenes to pyrroles.

In our studies[2,3] of the photochemical rearrangements of vinylcyclopropenes to cyclopentadienes, we determined that four mechanisms were possible for the rearrangement and that the triplet excited state utilized an unusual mechanism quite different from the singlet. Hence we were interested in the behavior of the isoconjugate acyl- and imino-substituted cyclopropenes. One example is illustrated in eq 1 for acylcyclopropene **1**.



(1)

In contrast to the direct irradiation which affords a multiplicity of products,[4] thioxanthone (or (*N*,*N*-dimethylamino)benzophenone) sensitization led exclusively to 2,3,4-triphenyl-5-methylfuran (**2**); cf, eq 1. This initial success with the triplet photochemistry of an acylcyclopropene prompted us to attempt a synthesis of the hitherto unknown iminocyclopropene counterparts. The (benzoylimino)cyclopropene **5** was obtained by phenyllithium addition to 3-cyano-1,2,3-triphenylcyclopropene

(1) (a) This is publication No. 162 of our photochemical series. (b) For paper 161 see: Zimmerman, H. E.; Heydinger, J. A. *J. Org. Chem.* **1991**, *56*, 1747-1758.

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(3) (a) Note also the simultaneous discovery of the singlet rearrangement by Padwa and co-workers.[3b] (b) Padwa, A.; Blacklock, T. J.; Getman, D.; Hatanaka, N. *J. Am. Chem. Soc.* **1977**, *99*, 2344-2345. (c) Under our conditions we have not encountered reactivity with oxygen of acylcyclopropenes observed in ref 4a.

(4) (a) Padwa, A.; Akiba, M.; Chou, C. S.; Cohen, L. *J. Org. Chem.* **1982**, *47*, 183-191. (b) We have confirmed this singlet behavior.

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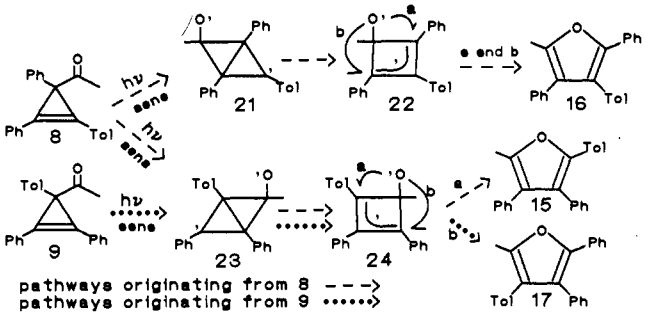
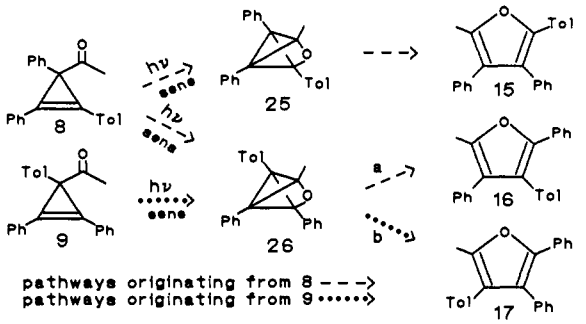
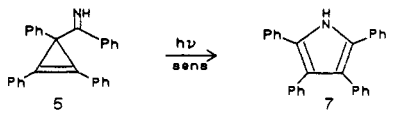
Scheme I. Mechanism C



Scheme II. Mechanism D



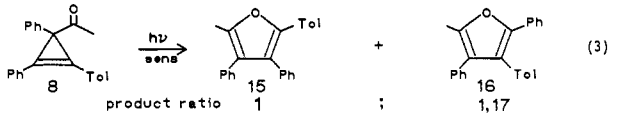
(**6**).[5,6] Thioxanthone sensitization of **5** led to 2,3,4,5-tetraphenylpyrrole (**7**) as the primary product. This transformation is outlined in eq 2.



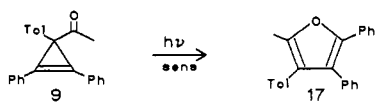
(2)

These results contrast with the behavior of acylcyclopropenes bearing hydrogen at C-3; thus we have confirmed literature reports[7] that 3-acetyl-1,2-diphenylcyclopropene (**10**) and 3-benzoyl-1,2-diphenylcyclopropene (**11**) lead only to syn $2_\pi + 2_\pi$ cycloaddition products.

With these exploratory experiments in hand, we proceeded to investigate the reaction mechanism of the triplet acylcyclopropene rearrangement. For this purpose we investigated 3-acetyl-2,3-diphenyl-1-*p*-tolylcyclopropene (**8**) and 3-acetyl-1,2-diphenyl-3-*p*-tolylcyclopropene (**9**). These rearranged analogously under sensitized conditions as described below in eqs 3 and 4. In the case of the triplet vinylcyclopropene rearrangement, there were four potential mechanisms. Their acyl counterparts are illustrated in Schemes I–IV. Comparison of the photoproducts with the



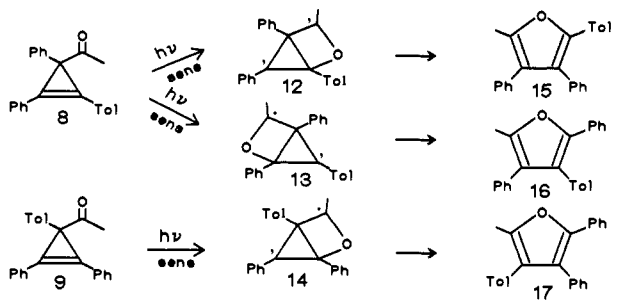
(3)



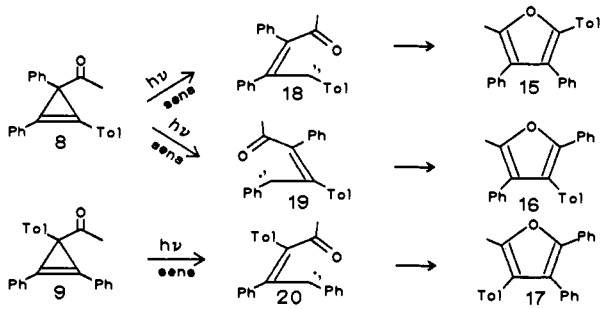
(4)

mechanistic Schemes I–IV shows that all four mechanisms (i.e. A–D) could account for the observed products. Mechanism C seemed particularly attractive, since it begins with the first step of the oxa-di-π-methane rearrangement and is the mechanism used by the vinylcyclopropene counterparts.

Scheme III. Mechanism A



Scheme IV. Mechanism B



However, reference to Scheme I reveals an inconsistency of Mechanism C. In this scheme we utilize dashed arrows for pathways originating with the 1-tolylcyclopropene **8** and dotted arrows for pathways originating with the 3-tolylcyclopropene **9**. In Mechanism C, diradical **22** correctly leads from 1-tolylcyclopropene **8** to one experimentally observed photoproduct, namely the 3-tolylfuran **16**. The counterpart diradical **24** accounts for the second photoproduct, the 2-tolylfuran **15**, obtained from the starting triplet (i.e. from ^{3}**8***). Also, in the reaction of the triplet of the 3-tolylcyclopropene **9** the same diradical **24** is utilized to provide a route to the 4-tolylfuran **17**.

The inconsistency is that diradical **24** is thus postulated as giving the 4-tolylfuran **17** when starting with reactant **9** (note the dotted arrow) while giving the 2-tolylfuran **15** when derived from reactant **8** (note the dashed arrow). Since partition of the intermediate needs to be independent of its source, Mechanism C cannot be operating.

Mechanism D, outlined in Scheme II, has precedent in the well-known oxetane formation by Paterno–Büchi cycloaddition of ketones to alkenes.[8] However, again there is an inconsistency in tricyclic intermediate **26** giving rise to 3-tolylfuran **16** when generated from triplet 1-tolylcyclopropene **8** and leading to the 4-tolylfuran **17** when formed from the triplet of 3-tolylcyclopropene **9**. Thus we can exclude this mechanism as well.

The remaining two mechanisms, A and B, are outlined in Schemes III and IV. These are structurally equivalent in the sense of having the same bonds formed and broken; however, they differ in chronology. In Mechanism A, there is initial C–O bonding followed by fission of a three-ring bond, while in Mechanism B, the three-ring bond is broken first followed by formation of the C–O bond. While Mechanism A involves an oxahousane diradical and Mechanism B involves a triplet carbene, the two are really just extremes in a mechanistic continuum. Nevertheless, we note that there is strong evidence from previous studies by Padwa, Pincock, and our own group[9] that, in contrast to the singlet counterparts, triplet cyclopropenes do not undergo ring fission. This leaves Mechanism A for the rearrangement. A remarkable feature is that the mechanism (i.e. A) utilized by the acylcyclopropenes differs from that (i.e. C) used by the vinylcyclopropenes of our earlier studies.[2d]

(5) (a) This differs from the observation of Breslow,[5b] who reported the reaction to give rise to 2,3,4,5-tetraphenylpyrrole under somewhat different conditions. The postulated mechanism of formation of the pyrrole proceeded via the conjugate base of the imine. (b) Breslow, R.; Boikess, R.; Battiste, M. *Tetrahedron Lett.* **1960**, 42–44.

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Acknowledgment. Support of this research by the National Science Foundation is gratefully acknowledged as is support of early stages by NIH Grant GM07487.

Registry No. **5**, 137570-31-1; **6**, 79919-09-8; **7**, 3263-79-4; **8**, 137570-32-2; **9**, 137570-33-3; **10**, 4400-53-7; **11**, 2892-41-3; **15**, 137570-34-4; **16**, 137570-35-5; **17**, 137570-36-6.

Supplementary Material Available: Details of the general photolysis conditions and preparative information as well as quantum yield determinations and runs and a table of thioxanthone sensitized quantum yields (3 pages). Ordering information is given on any current masthead page.

Molecular Recognition: Bis-Acylguanidiniums Provide a Simple Family of Receptors for Phosphodiesters

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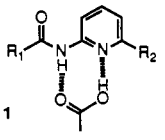
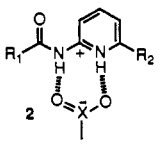
Received August 14, 1991

Recent reports from this[1] and other laboratories[2] have shown that molecules containing several hydrogen-bonding groups directed into a cleft or cavity can effectively recognize neutral substrates. For example, 2-(acylamino)pyridine derivatives form strong complexes with carboxylic acids[1a] via a neutral bidentate hydrogen-bonding interaction (**1**). We were interested in extending this directed hydrogen-bonding approach to anionic substrates such as phosphate and carboxylate. A straightforward strategy would involve protonating the pyridine to form the bidentate ion pair **2**. However, crystals grown from a 1:1 mixture of 2,6-dibutyramidopyridine (**3**) and diphenylphosphoric acid[3] show, in the solid state (Figure 1), that while proton transfer occurs the cyclic bidentate complex does not. Instead, the N-pyridine bonds rotate 180° to form two intramolecular hydrogen bonds between the pyridinium H and amide CO and two intermolecular hydrogen bonds between the amide NHs and two phosphate units,[4]

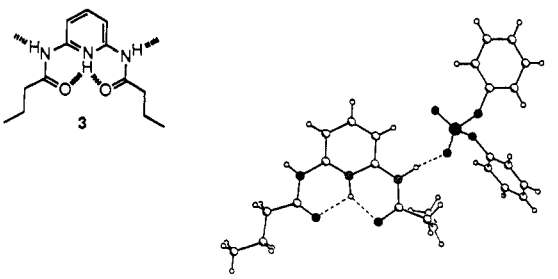


1



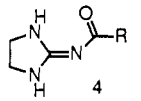
2

An intramolecular hydrogen bond of this type might be exploited as a rigidifying element in receptor design if an additional binding group were positioned at a site corresponding to the pyridine 3-carbon in **3**. This arrangement exists in 2-(acylamino)imidazolines, **4**, and a crystal structure of 2-(benzoylamino)imidazoline (Figure 2) showed that an intramolecular hydrogen bond between one ring NH and the benzoyl CO was present. In addition, the other NH and the acyl N were positioned to form a cyclic bidentate interaction with a second molecule. On the basis of our earlier studies of phosphorodiamidate recognition,[5] we reasoned that linking two protonated aminoimidazolines through an isophthalic acid spacer should lead to a simple receptor for phosphate ester anions.



3

Figure 1.



4

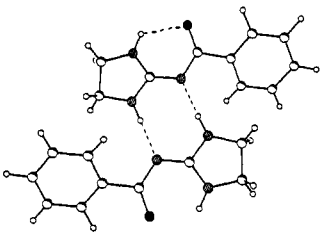
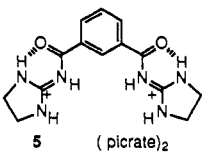
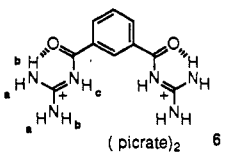


Figure 2.

Reaction of dimethyl isophthalate with 2-aminoimidazolinium *p*-toluenesulfonate in MeOH and NaOMe[6] followed by alumina chromatography (CH_2Cl_2–MeOH, 50:1 eluent) gave the corresponding bis-2-(acylamino)imidazoline in 16% yield. The basicity of (acylamino)imidazolines (pK_a = 7.09) is reduced relative to aminoimidazolines (pK_a = 13.58);[7] however, they can be readily protonated, and treatment with picric acid gave the dicationic receptor **5**. An even simpler receptor, **6**,[8] containing two acylguanidinium groups can be formed from the reaction of guanidinium hydrochloride and dimethyl isophthalate.[9] Both **5** and **6** could be converted into their tetraphenylborate (TBP) salts by treating the corresponding bis-hydrochloride with sodium tetraphenylborate. The ^1H NMR spectrum of **6** in CD_3CN shows three broad signals due to guanidinium hydrogens a, b, and c at 7.4, 8.2, and 11.2 ppm, respectively.[10] The large downfield shift of the b protons is consistent with the formation of an intramolecular hydrogen bond to each of the isophthaloyl carbonyl groups, as depicted in **6**.[10] These provide additional rigidity to the molecule,



5 (picrate)$_2$



(picrate)$_2$ 6

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(8) ^1H NMR of **6** (CD_3CN): δ 11.16 (br s, 2 H, CONH), 8.73 (s, 4 H, picrate), 8.49 (s, 1 H, 2-isophth), 8.26 (br s, 4 H, endo NH), 8.17 (dd, *J* = 8, 2 Hz, 2 H, 4,6-isophth), 7.69 (t, *J* = 8 Hz, 5-isophth), 7.40 (br s, 4 H, exo NH).

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