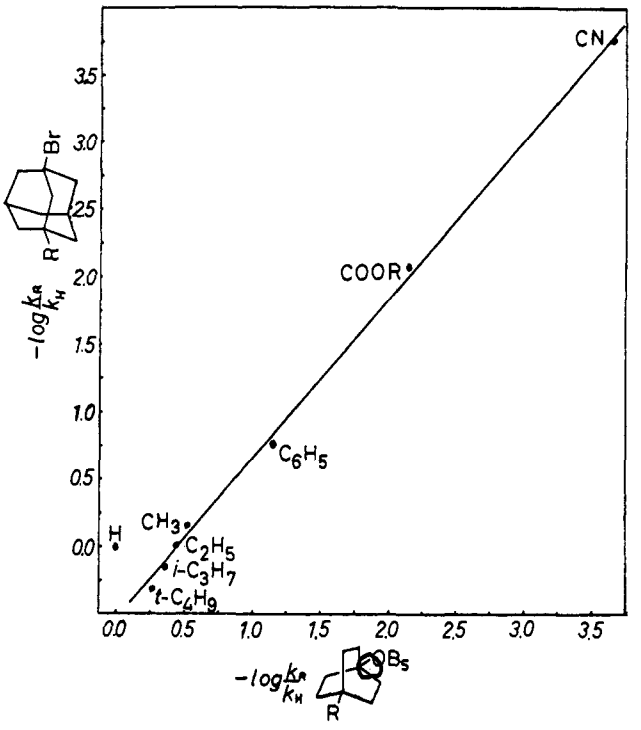

Figure 1. Log relative acetolysis rates of 4-substituted 1-bicyclo-[2.2.2]octyl brosylates at 75° plotted against the log relative 80% ethanolysis rates of 3-substituted 1-adamantyl bromides, also at 75°. Data from Table I.

The introduction of a 4-methyl group in the bicyclooctyl system produces an unexpectedly large threefold reduction in solvolysis rate. Although there is a regular rate increase along the series methyl, ethyl, isopropyl, *t*-butyl, all of these substituents produce a rate diminution relative to hydrogen. In this respect, the behavior of the bicyclo[2.2.2]octyl system differs from the adamantyl, where hydrogen occupies an intermediate position in relation to the alkyl series (Table I).

The anomalous position of hydrogen is emphasized in Figure 1, a linear free energy plot of the adamantyl and the bicyclooctyl data. Included are points for a number of electron-withdrawing substituents, which help define the correlation line (slope 1.19, correlation coefficient 0.999, point for H omitted).

Excellent results are also obtained when the data from each polycyclic system are plotted separately against $\sigma^*_{CH_2}$ constants.[3,4] Table II summarizes the results and provides a comparison with recent literature observations. As expected, the sensitivity toward substituents is much more pronounced for carbonium ion solvolysis (ρ −2.7) than for free radical (ρ −0.4), carboxylic acid dissociation (ρ +0.7), or SN2 displacement (ρ +0.25) processes.

The nonhydrogen substituents have similar effects on both adamantyl and bicyclooctyl solvolyses (Figure 1), effects very probably largely inductive in origin. This conclusion is reinforced by the excellent correlation with $\sigma^*_{CH_2}$ constants (Table II).

The failure of hydrogen to maintain a constant position in the rate order of the two systems (Table I and Figure 1) indicates that the difference between the nonhydrogen substituents and hydrogen cannot be entirely inductive in origin. We believe that steric effects are responsible for these deviations of hydrogen.

Deviations from strict tetrahedral geometry are the rule rather than the exception in organic compounds.[16] When hydrogen is replaced by a methyl group or other carbon-based substituent, a small but significant change in geometry is produced (*e.g.*, isobutane ∠CCC 111.15°[17] *vs.* neopentane ∠CCC 109.5°). Replacement of hydrogen by methyl in the system we have studied should also produce a change in structure which would be reflected in the solvolysis rates. In our compounds *both* the substituents and the leaving groups are attached directly to the rigid polycyclic ring systems and, hence, steric effects should be more pronounced than in cases (*e.g.*, those involving carboxylic acid pK_a's)[5] where the reaction sites are farther removed or where smaller structural changes during reaction would be anticipated.[2]

Although the adamantyl and the bicyclooctyl systems would be expected to respond similarly to substituent inductive effects, they should respond differently to substituent steric effects, because of variation in the intervening connective structures. The greatest steric effect should be observed when hydrogen is replaced by a carbon atom. For this reason, the position of hydrogen in a rate-order series may be variable, and may depend critically on the nature of systems involved (Table I and Figure 1).

We interpret our results to show that alkyl groups in saturated systems *do have* an inductive order of electron release increasing from methyl through *t*-butyl. The behavior of hydrogen as a substituent is variable, evidently due to differences in steric effects from system to system.[7] Until the magnitude of these steric effects can be evaluated accurately, or their absence ensured, conclusions regarding the direction of inductive effects of alkyl groups relative to hydrogens should be reserved. In particular, it probably is unwise to interpret the rate depressions produced by methyl substitution[7-11] as firm evidence for the "electron-withdrawing" nature of such groups in saturated systems.

Acknowledgment. This research was supported by grants from the National Science Foundation, the National Institutes of Health, and the Petroleum Research Fund, administered by the American Chemical Society.

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Causes for the Low Efficiency of Thymine and Uracil Photodimerization in Solution

Sir:

A vast amount of research[1] has implicated dimerization of pyrimidine bases as being responsible for photodeactivation of the nucleic acids. Such photodimerizations in DNA[2] or in frozen aqueous thymine solutions[3]

(1) R. B. Setlow and W. L. Carrier, *J. Mol. Biol.*, **17**, 237 (1966), and references cited therein.
(2) J. Eisinger and A. A. Lamola, *Biochem. Biophys. Res. Commun.*, **28**, 558 (1967).
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proceed from the excited singlet state *via* excimers. The major thymine dimer so obtained possesses the *cis-syn* head-to-head structure.[4] Sensitization and quenching studies have shown that thymine, either in DNA[5] or free in solution,[6] can also dimerize from its excited triplet state, although the major dimer in acetonitrile solution apparently possesses a different structure from that of the "ice dimer."[6] We have obtained results which illustrate important kinetic differences between singlet- and triplet-state photodimerizations of thymine and uracil.

Degassed acetonitrile solutions 2–10 × 10^{-4} *M* in pyrimidine and containing various concentrations of *cis*-1,3-pentadiene were irradiated at 2750–2900 Å.[7] Relative quantum yields of pyrimidine disappearance were then determined by uv analysis. Stern–Volmer plots were linear out to large percentages of quenching, indicating that at these concentrations the photodimerization of both bases is predominantly a triplet-state reaction.[8,9] Table I contains values of the slopes obtained at various base concentrations.

Table I. Quenching of Thymine and Uracil Photodimerizations by 1,3-Pentadiene in Acetonitrile

[Pyrimidine], 10^{-4} *M*[a]	$k_q\tau$, M^{-1} [b]	τ, 10^{-6} sec
	Thymine	
2.70	26,000	2.36
4.33	20,800	1.89
6.75	15,700	1.43
9.68	12,200	1.12
	Uracil	
1.89	21,300	1.94
1.96	19,600	1.78
2.70	18,600	1.69
3.19	12,900	1.17
4.08	11,500	1.04

[a] Average concentration; total conversions 10–15%. [b] Slopes of Stern–Volmer plots reproducible to ±5%.

Lamola has reported 2537-Å dimerization quantum yields in acetonitrile of 0.005 and 0.05 for thymine and uracil, respectively.[6] Some of the inefficiency is due to relatively low intersystem-crossing yields.[6] We have compared quantum yields of dimerization (assumed equal to one-half the quantum yield for disappearance of pyrimidine) with those of sensitized isomerization of 0.10 *M* *cis*-1,3-pentadiene[10] for 3.9 × 10^{-4} *M* uracil and for 6.2 × 10^{-4} *M* thymine, with the conclusion that only 3% of thymine triplets and 10% of uracil triplets actually dimerize. The results are in close agreement with Lamola's 2537-Å data[6] and confirm that quenching is by triplet-energy transfer.

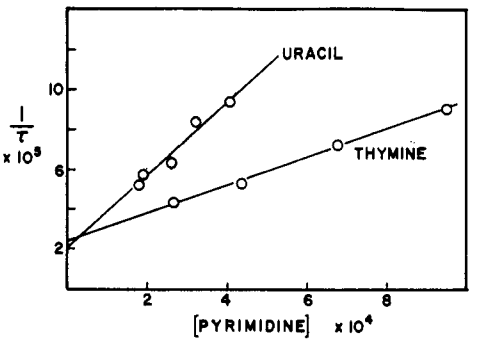

Figure 1. Dependence of triplet-state lifetimes of thymine and uracil on ground-state concentrations.

Low quantum yields generally are attributed to competition from physical radiationless decay of the triplet state. However, the following analysis demonstrates that such is not the case for thymine and uracil. The Stern–Volmer slopes equal $k_q\tau$, where k_q is the bimolecular rate constant for energy transfer and τ is the triplet lifetime of the pyrimidine. The τ values in Table I were calculated on the basis of k_q equaling 1.1 × 10^{10} M^{-1} sec^{-1} in acetonitrile at 25°.[11] Equation 1 describes the dependence of τ on k_d, k_a, and [Pyr], where k_d equals the rate of direct pseudounimolecular decay of the triplet, k_a is the bimolecular rate constant for reaction with a ground-state molecule, and [Pyr] is the pyrimidine concentration.

$$1/\tau = k_d + k_a[\text{Pyr}] \qquad (1)$$

Figure 1 presents plots of the data in Table I according to eq 1, and Table II contains values of the rate constants. At least three important conclusions can be drawn from the results.

Table II. Kinetic Data for Photodimerization of Thymine and Uracil

Quantity	Thymine	Uracil
k_d, 10^8 sec	2.3	2.0
k_a, 10^9 M^{-1} sec	0.70	1.82
Φ_{DIM}	0.005[b]	0.04[c]
Φ_{ISC}[a]	0.18	0.40
ϕ_P	0.04	0.13

[a] Values taken from ref 6. [b] 6.2 × 10^{-4} *M*. [c] 3.9 × 10^{-4} *M*.

(1) The rates of radiationless decay of the two triplet species are the same and are of the order of magnitude normally associated with simple carbonyl triplets in solution. A considerable amount of study has been devoted to the analogous photodimerizations of cycloalkenones;[12] the severe concentration dependence of quantum yields indicates values of 10^8 sec^{-1} and higher for k_d. The great difference between the pyrimidines and the ketones may reflect the greater flexibility of the rings in the latter

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(7) The 2753-, 2804-, and 2894-Å lines of a 450-W Hanovia medium-pressure mercury arc are transmitted to varying degrees through 1 mm of Pyrex and are absorbed to varying degrees by the bases. Neither pentadiene nor the pyrimidine dimers absorb significantly under these conditions.

(8) In saturated solutions, a few per cent unquenchable reaction occurred, probably by singlet-state dimerization of molecular aggregates.

(9) In 0.10 *M* dimethylthymine solutions photodimerization is mostly a singlet-state reaction: H. Morrison and R. Kleopfer, *J. Am. Chem. Soc.*, 90, 5037 (1968).

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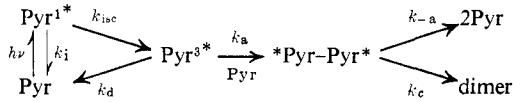
compounds compared to the rigidity of the pyrimidine rings.

(2) The values of k_a are quite large and resemble those one might estimate for the cyclic enones.[12] Triplet thymine adds to ground-state thymine only one-third as fast as triplet uracil adds to ground-state uracil. This effect is probably due to some steric hindrance by the methyl group of thymine.

(3) If k_d were the *only* pathway for radiationless decay, the rate constants in Table II and Lamola's Φ_{ISC} values would predict Φ_{DIM} values of 0.31 for 3.9×10^{-4} *M* uracil and 0.12 for 6.2×10^{-4} *M* thymine. There obviously is a further major source of inefficiency. The data demand that most of the original photoadduct of triplet base with ground-state base must be able to decay back to two ground-state molecules. The following mechanistic scheme yields eq 2 and 3, where ϕ_{AD} is the probablity that triplet base will react with ground-state base and ϕ_P is the probability that the intermediate will proceed on to stable dimer.



$$^1/_2\Phi_{PYR} = \Phi_{DIM} = \left(\frac{k_{isc}}{k_i + k_{isc}}\right)\left(\frac{k_a[Pyr]}{k_d + k_a[Pyr]}\right)\left(\frac{k_c}{k_{-a} + k_c}\right) \quad (2)$$

$$\Phi_{DIM} = \Phi_{ISC}\phi_{AD}\phi_P \quad (3)$$

There are two possibilities for the structure of the intermediate: (1) a triplet excimer, or (2) a ground-state σ-bonded biradical. A singlet excimer does intervene in singlet-state dimerizations, but it proceeds on to stable ground-state dimer with 100% efficiency ($\phi_P = 1$).[13] The low ϕ_P values for triplet uracil and thymine, as well as their relative values, are nicely consistent with a biradical intermediate. Cleavage of 1,-4 biradicals is always an important reaction;[14] coupling of the bistertiary or secondary, tertiary biradical from thymine should be slower than coupling of the necessarily bissecondary biradical from uracil. Since all four *cis*-fused dimers may be formed,[9] the k_a and ϕ_P values we report are probably composites of four sets of such values. Consequently, until the actual structures of the triplet-state photodimers are determined, further speculation about the nature of the intermediate would be meaningless.

Toki and Sakurai have proposed a very similar scheme, based on similar kinetic studies, to explain the low quantum efficiency for the photocycloaddition of benzophenone to furan.[15] No triplet-state photocycloaddition yet reported proceeds with unit quantum yield, even extrapolated to infinite substrate concentration. It is likely that reversible adduct formation occurs in all cases, especially if biradicals are involved.

Acknowledgment. We are grateful for financial support from The National Science Foundation and for helpful discussions with Dr. Angelo Lamola and Professor James Trosko.

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(17) National Institutes of Health Predoctoral Fellow, 1966 to present.

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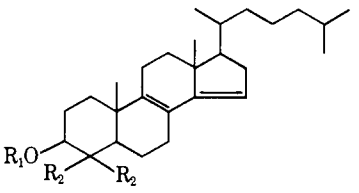
Evidence for the Biological Conversion of $\Delta^{8,14}$ Sterol Dienes into Cholesterol

Sir:

As previously reported,[1] the elimination of the 14α-methyl group of lanosterol during its biological conversion into cholesterol is accompanied by the stereospecific removal of one of the hydrogen atoms in position 15. Correct interpretation of stereochemical requirements in the formation of farnesyl pyrophosphate[2] from *dl*-(2*S*)-[2-^{3}H]mevalonic acid shows that the labeled hydrogen atoms are present in positions 1α, 7β, 15α, 22*S*, 26 or 27, and 30 or 31 of lanosterol.[3] Our previous results show that the hydrogen eliminated is the one at position 15α and not position 15β as erroneously stated.

Our results allowed us to hypothesize the existence of not yet recognized intermediates between lanosterol[4] and 4,4-dimethyl-5α-cholesta-8,24-dien-3β-ol[5] in the biosynthetic pathway to cholesterol. The saturation of the double bond in the side chain is known to occur at different stages.[6] A possible precursor appeared to be 4,4-dimethyl-5α-cholesta-8,14-dien-3β-ol (**1**), and this hypothesis has been verified by studying the transformation of the labeled compound into cholesterol in rat liver homogenates.



1, $R_1 = H$; $R_2 = CH_3$
2, $R_1 = COCH_3$; $R_2 = CH_3$
3, $R_1 = H$; $R_2 = H$
4, $R_1 = COCH_3$; $R_2 = H$

Radioactive **1**[5,7] (8.58 μCi/μmol) was prepared as described for 5α-cholesta-8,14-dien-3β-ol[8] by isomerization of 4,4-dimethyl-cholesta-5,7-dien-3β-ol[9] in the

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