$$\text{rel } k_R = \frac{\left(\frac{\text{rearranged}}{\text{unrearranged}}\right)_X}{\left(\frac{\text{rearranged}}{\text{unrearranged}}\right)_H} = \frac{(k_R)_X}{(k_R)_H}$$

The product ratios and relative rearrangement rate constants are shown in Table II.

Table II. Product Ratios and Relative Rate Constants

Substituent	Rearranged / Unrearranged	Relative k_R rearrangement aptitude	Rüchardt[a] migration aptitude
OCH_3	3.35	0.785	0.35
CH_3	4.00	0.938	0.65
H	4.26	1.000	1.00
Cl	5.67	1.329	1.82

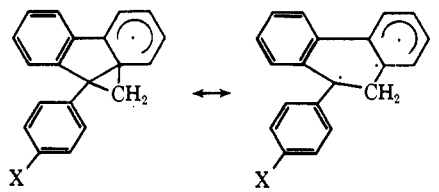
[a] See ref 1.

A good Hammett correlation was obtained by plotting log relative k_R *vs.* σ, and the value of the reaction constant was calculated by the method of least squares to be +0.426. This rearrangement is, therefore, facilitated to a small degree by electron-withdrawing substituents on a benzene ring attached to the migration origin.

Rüchardt's picture of the rearrangement transition state as a semipolar hybrid with partial positive character at the migration origin is, however, incompatible with these results. Based on our data, such a semipolar transition state for our system would require the migration origin to have a partial negative charge. Results on the analogous rearrangement of the 2,2-diphenyl-2-(*p*-nitrophenyl)ethyl radical[3] indicate, however, that no charge reversal is involved.

Interestingly, the present results on the effects of substituents at the migration origin (rearrangement aptitudes) and Rüchardt's results on the effects of substituents attached to the migrating aromatic nucleus (migration aptitudes) are of different magnitudes *but in the same direction* (Table II). This is clearly demonstrated by the linear relationship which is obtained by plotting the logarithms of the relative rearrangement rate constants obtained in the present study against those obtained by Rüchardt. The slope of this line (+3.11) shows that the effect of a substituent on an aromatic ring at the migration origin is approximately one-third the effect of the same substituent on the aromatic ring which is migrating. This could simply be due to the greater distance of the substituent from the radical center in the fluorenyl system.

We have concluded from these results that for the substituents studied the transition state for a free-radical aryl migration is purely radical in character,



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with contributing structures such as shown in **8** for this study.

Rüchardt found that some substituents such as the nitro and cyano groups increased the migration aptitude by a very large extent and consequently did not lie on the straight line. It is likely with very strong election-withdrawing groups that ionic contributions are important.

Further work is in progress with these systems and a complete report is forthcoming.

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Nuclear Magnetic Resonance Determination of Syn and Anti Conformations in Pyrimidine Nucleosides

Sir:

Recently considerable study has been directed toward determination of the relative positions of sugar and base moieties about the glycosidic bond in nucleosides and nucleotide derivatives. Crystallographic data[1] have shown that in most cases the anti conformational range for the torsion angle, ϕ_{CN}, is preferred.[2] However, for purine nucleosides substituted in the 8 position with bulky groups, both X-ray data on the crystals[3] and CD spectra in aqueous solution[4] indicated predominantly syn conformers. In terms of biological significance, it has been shown that certain enzymes catalyzing polynucleotide synthesis will not function with purine and pyrimidine nucleoside di- or triphosphate substrates not having normal anti conformations, including the di- or triphosphate of 6-methylcytidine.[5,6]

We wish to report a facile determination of syn and anti conformation in various substituted pyrimidine nucleosides in solution using nuclear magnetic resonance. Nmr techniques have previously been successful in determination of conformation about the glycosidic bond in some nucleosides, nucleotides, and dinucleoside monophosphates.[7-10] In this communication we make use of the 2-keto anisotropic effect upon ribose proton chemical shifts to determine syn and anti nucleoside conformation.

Chemical shifts for several pyrimidine nucleosides are presented in Table I. Comparison of 5- and 6-methylcytidine and 5- and 6-methyluridine reveals a significant deshielding at H-2′ (0.5–0.6 ppm) and at H-3′ (0.15–0.2 ppm) in the 6-methyl derivatives. Concomitant with

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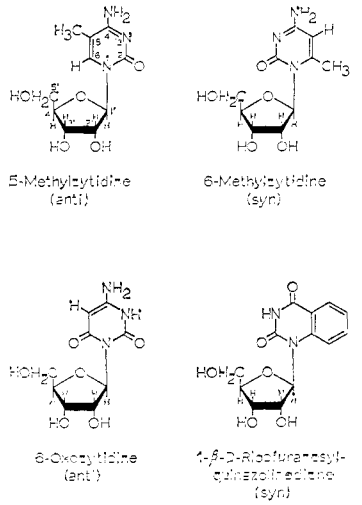

Figure 1. Several pyrimidine nucleosides shown in the preferred conformations as deduced by noting the anisotropic effect of the keto group upon ribose proton chemical shifts (see text).

this deshielding are upfield shifts for H-1′ (0.16–0.25 ppm), H-4′ (0.17 ppm), and H-5′,5″ (0.04–0.10 ppm).

6-Methylcytidine and 6-methyluridine display negative CD curves[11] whereas the 5-methylpyrimidine nucleoside derivatives have the usual positive Cotton effects. These results indicate that 6-methylcytidine and 6-methyluridine are not in the normal anti conformation. Examination of molecular models indicates that intimate van der Waals contact between the 6-methyl and 5′-CH_2OH groups would prevent 6-methylcytidine and 6-methyluridine from assuming the normal anti conformation and that this contact could be relieved by clockwise rotation about the glycosidic bond. These considerations lead one to propose that the deshielding and shielding phenomena displayed at the various ribose protons of the 6-methylated nucleosides result from the anisotropy of the 2-keto group which has been brought in proximity to these protons due to rotation of the base in a clockwise manner.

Table I. Ribose Proton Chemical Shifts for Various Pyrimidine Nucleosides[a]

Nucleoside[b]	Chemical shifts, ppm, from TMS capillary H-1′	H-2′	H-3′	H-4′	H-5′,5″
5-Methylcytidine	6.40	4.71	4.71	4.71	4.41
6-Methylcytidine[c]	6.15	5.30	4.86	4.48	4.31
5-Methyluridine[d]	6.36	4.69	4.69	4.69	4.34
6-Methyluridine[c]	6.10	5.27	4.88	4.46	4.30
6-Oxocytidine[e]	6.67	5.26	4.85	4.50	4.23
1-β-D-Ribofuranosyl-barbituric acid[e]	6.57	5.10	4.85	4.48	4.20
4-Thiouridine	6.33	4.74	4.74	4.74	4.36
1-β-D-Ribofuranosyl-2,4-quinazolinedione[f,g]	6.58	5.02	4.63	*h*	4.14

[a] These compounds were obtained either from commercial sources or by established literature procedures. [b] 10% solutions in D_2O; spectra recorded at 60 MHz on a Perkin-Elmer Hitachi R20A spectrometer. Probe temperature 34°. [c] M. W. Winkley and R. K. Robins, *J. Org. Chem.*, **33**, 2822 (1968). [d] We thank Dr. J. J. Fox, Sloan-Kettering, for his gift of this compound. [e] M. W. Winkley and R. K. Robins, *J. Chem. Soc. C*, 791 (1969). [f] 10% solution in DMSO-d_6. [g] M. G. Stout and R. K. Robins, *J. Org. Chem.*, **33**, 1219 (1968). [h] H-4′ resonance obscured by HDO.

To further elucidate the nature of the keto anisotropy, we have examined several pyrimidine nucleosides considered primarily to be anti conformers which possess 6-keto groups located over the ribose ring. For 6-oxocytidine and 1-β-D-ribofuranosylbarbituric acid (6-oxouridine), the ribose proton chemical shifts shown in Table I are quite similar to those of 6-methylcytidine and 6-methyluridine. These data are in agreement with our data on an additional 6-keto compound, 1-β-D-ribofuranosylcyanuric acid.[12] The 0.2–0.25-ppm downfield shift for H-1′ in the 6-keto-substituted compounds may be due to the electron-withdrawing effect of the additional carbonyl.

Consequently, on the basis of these data, 6-methylcytidine (Figure 1) and 6-methyluridine are considered to exist primarily in the syn conformation in aqueous solution. $J_{1'-2'}$ coupling constants are similar in the two pairs of the 5- and 6-methyl nucleosides which indicates that the ribose conformations are nearly equivalent.

It was of interest to examine the ribose proton chemical shifts of 4-thiouridine, a constituent of several *E. coli* tRNAs.[13] Crystallographic data[14] have shown that this nucleoside exists in the syn conformation whereas in solution the anti conformer of 4-thiouridine 5′-phosphate predominates.[15] The ribose proton chemical-shift data in Table I for this nucleoside are similar to those of *anti*-5-methyluridine and 5-methylcytidine; thus, 4-thiouridine is mostly anti in solution.

In the case of the quinazoline nucleosides, where a benzene ring is fused 5,6 to the pyrimidine ring, one might expect that the conformation would be altered compared with more simple pyrimidine nucleosides. Accordingly, we have studied 1-β-D-ribofuranosyl-2,4-quinazolinedione. Because of solubility, this molecule was studied in DMSO-d_6. Although solvent effects are important in nucleoside conformation, we found that the ribose proton chemical-shift differences between 5- and 6-methylcytidine were of the same nature in DMSO-d_6 as in D_2O, thus the same conformational differences exist in DMSO. Deshielding at H-2′ and H-3′ is observed; thus, 1-β-D-ribofuranosyl-2,4-quinazolinedione appears to exist in the syn conformation with respect to the 2 position of the pyrimidine ring.

Although the data presented here allow a qualitative determination of syn *vs.* anti conformation, the precise geometry in terms of values of the torsion angle cannot be specified due to flexibility of the molecules and to the fact that the exact nature of the keto group anisotropy is not known.[16,17] We have noted a similar keto anisotropic effect on ribose protons in the purine nucleosides 8-oxoadenosine and 8-oxoguanosine and are currently studying purine nucleosides with bulky 8 substituents.

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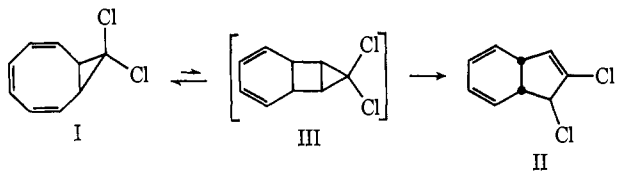
Thn Thermal Bicyclo[6.1.0]nonatrienyl Chloride–Dihydroindenyl Chloride Rearrangement

Sir:

In 1961 Vogel and Kiefer[1,2] reported the first observations dealing with rearrangements of bicyclo[6.1.0]-nonatrienes, a field which subsequently has been rather extensively investigated.[2-8] 9,9-Dichlorobicyclo[6.1.0]-nonatriene (I) upon heating gave 1,2-dichloro-*cis*-8,9-dihydroindene (II); the intermediacy of the tricyclic valence tautomer III was proposed to explain this result.[1,2]



Subsequent investigations have shown that this reaction course is exceptional. For example, 9,9-dideuteriobicyclo[6.1.0]nonatriene gives mainly 1,1-dideuterio-*cis*-dihydroindene,[3] while 9,9-dimethylbicyclo[6.1.0]nonatriene rearranges to 1,1-dimethyl-*trans*-dihydroindene.[6] The behavior of the monochlorides IV and V related to I has appeared not to follow the mechanism proposed by Vogel and Kiefer. Regardless of the stereochemistry at C-9, IV and V were found to rearrange at about equal rates to give the same product, 1-chloro-8,9-dihydroindene (VI).[4,5,9] LaLancette and Benson[5] suggested that "chlorocyclononatetraene (VII) may be a common intermediate in these transformations."

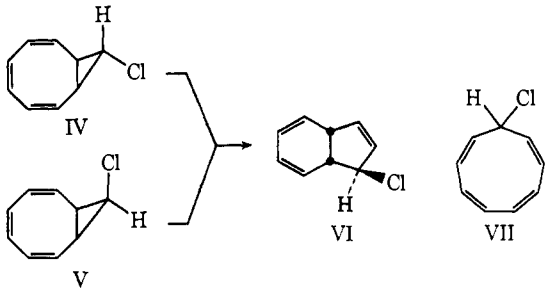
We have investigated the apparent discrepancy between the behavior of dichloride I and monochlorides IV and V. Because of the known propensity of disrotatory *syn*-bicyclocyclopropyl chloride ring opening,[10a] V, at least, might be expected to react *via* the Vogel–Kiefer mechanism.[10b]

Table I. Thermolysis and Solvolysis Rates, 75°

Compd	Solvent	k, sec^{-1}	k_{rel}	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu
IV	CCl_4	2.60×10^{-4} [a]	1.0	25	−2.3
	CH_2Cl_2	6.53×10^{-4} [a]	2.5		
	90% acetone	2.43×10^{-3} [b]	9.4		
	70% acetone	2.97×10^{-3} [b]	11.3		
V	CCl_4	2.46×10^{-4} [a]	0.95	23	−8.7
	CH_2Cl_2	1.13×10^{-4} [a]	0.44		
	90% acetone	2.64×10^{-4} [b]	1.01		
	80% acetone	1.81×10^{-4} [b]	0.70		
I	CCl_4	3.74×10^{-5} [a]	0.14		
	CH_2Cl_2	6.29×10^{-5} [a]	0.41		
	80% acetone	3.80×10^{-5} [b]	0.15		
	70% acetone	4.04×10^{-5} [b]	0.16		

[a] Thermolysis rates were obtained by measuring the rate of disappearance of absorptions in the nmr due to H_1 and H_8. [b] Solvolysis rate, determined conductometrically.

Quantitative measurements (Table I) confirmed that IV and V rearrange to VI at nearly the same rate in aprotic solvents. Furthermore, neither thermolysis was significantly enhanced if more polar solvents like CH_2Cl_2 were employed. This shows that the rate-determining step was in neither case the formation of an ion pair similar to that involved in the thermal rearrangements of di-



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