Unusual Competition between Nitrogen and Carbon Methylation of Nucleosides by Methyl Radical in Various Aqueous Media [1]

Mona F. Zady and John L. Wong*

Department of Chemistry, University of Louisville, Louisville, Kentucky 40208

Received December 5, 1979

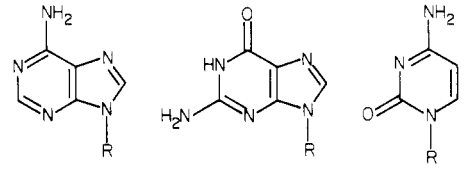
Five nucleosides, adenosine, guanosine, cytidine, thymidine, and uridine, were allowed to react with methyl radical produced by homolysis of *tert*-butyl peracetate. The extent and sites of reaction exhibited a marked dependence on the pH of the aqueous medium. In the region of pH 1–4, the major products arose from C-methylation of the nucleosides. The purines were more reactive than the pyrimidines under these acidic conditions. In the pH range of 4–10, the extent of C-methylation decreased steadily with increasing pH while N-methylated products arising from methylation of the ring nitrogen and/or exocyclic amino groups predominated. In this pH range, the pyrimidine nucleosides were the more reactive. Beyond pH 10, the extent of methylation diminished in all cases as decomposition of *tert*-butyl peracetate became rampant. The C-methylation occurs by way of an addition mechanism while N-methylation appears to proceed via radical abstraction of a hydrogen from the N–H group followed by combination with $\cdot CH_3$. The implications of these reactivity and methylation patterns in radical carcinogenesis are discussed.

Since it is the prevailing opinion that most carcinogens act by damaging DNA,[2] there is intense interest in determining the reaction sites of the carcinogens which covalently bond to the DNA bases by alkylation. The simplest of these are the methylating carcinogens such as *N*-methyl-*N*-nitrosourea and methyl methanesulfonate. They react with the multiple nitrogen and oxygen sites of the nucleosides via the ionic S_N1 or the nonionic S_N2 mechanism. Although these N- and O-methylation patterns vary with reaction parameters,[3,4] none of these agents has been found to attack any carbon position. On the other hand, methyl radical ($\cdot CH_3$)[5] and other alkyl radicals[6] are known to yield only C-alkylation products of the bases. We have reported[5,7] recently that $\cdot CH_3$ generated from *tert*-butyl peracetate (BPA) reacted with nucleosides under acidic conditions to yield exclusively *C*-methyl products. However, as the pH of the reaction medium was raised, we began to observe a multitude of products derived from carbon and nitrogen methylation. The reactivity and methylation patterns of the nucleosides with methyl radical are now elucidated in various aqueous media, and these observations are pertinent to explaining the carcinogenic actions of *N*-acetylaminofluorene, *N*-hydroxyurethane, and the like.

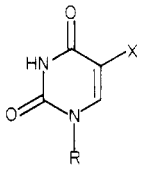
Results

The five nucleosides studied and their pK_a values are shown in Chart I. The methyl radical was generated by photolysis ($\lambda > 300$ nm) of the *tert*-butyl peracetate in an aqueous medium in the pH range of 1–12. The yields of the methylated products were determined by high-pressure LC analyses, and these percent yields are plotted as a function of pH in Figures 1–5. In all cases, at least 80% of the nucleoside was recovered as starting material and products. For adenosine, the profiles of 2-methyl-, N^6-methyl-, and 8-methyladenosine are shown in Figure 1. In Figure 2 is shown the formation of N^2-methyl- and 8-methylguanosine at two different concentrations (0.001 and 0.005 M). Figure 3 shows the yields of the N^3- and N^4-methyl derivatives from cytidine. In Figure 4, N^3-methylthymidine, the only product from thymidine, is featured. Finally, the N^3-methyl- and 5-methyluridine curves are shown in Figure 5. The very small amount of the 6-methyl derivative is not represented, however.

Chart I[a,d]



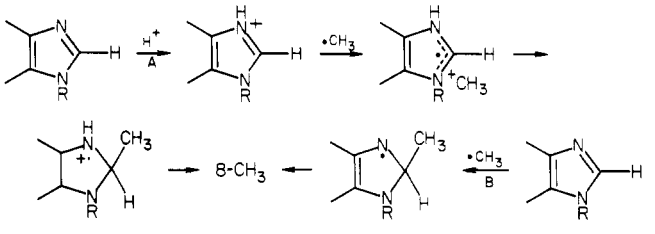
adenosine 3.55, 12.35 | guanosine 1.6, 9.24 | cytidine 4.08, 12.24



thymidine[b] 9.79, 12.85 | uridine[c] 9.3, 12.59

[a] R = β-D-ribofuranose. [b] X = CH_3. [c] X = H. [d] The pK_a values are given under each name.

Scheme I



Discussion

C-Methylation of Nucleosides. The extent of C-methylation of nucleosides is compared in Figure 6. In an acidic solution of pH 1.4, the amount of 8-methylguanosine is almost twice that of all the other methyl nucleosides combined. It drops off rapidly with increasing pH. On the other hand, the yields of 8-methyladenosine and 5-methyluridine are comparable and remain fairly constant over the range of pH 1–7, exceeding that of 8-methylguanosine at pH 4. The amount of 2-methyladenosine, ranking close to that of 5-methyluridine at pH 1.4, becomes smaller at higher pH's while the meager

(1) Reactivities and Electronic Aspects of Nucleic Acid Heterocycles. 9. For Part 8, see ref 7.
(2) B. N. Ames, *Science*, **204**, 587 (1979).
(3) J. P. Sullivan and J. L. Wong, *Biochim. Biophys. Acta*, **479**, 1 (1977).
(4) A. E. Pegg, *Adv. Cancer Res.*, **25**, 195 (1977).
(5) M. F. Zady and J. L. Wong, *J. Am. Chem. Soc.*, **99**, 5096 (1977).
(6) D. Leonov and D. Elad, *J. Org. Chem.*, **39**, 1470 (1974).
(7) M. F. Zady and J. L. Wong, *J. Org. Chem.*, **44**, 1450 (1979).

0022-3263/80/1945-2373$01.00/0

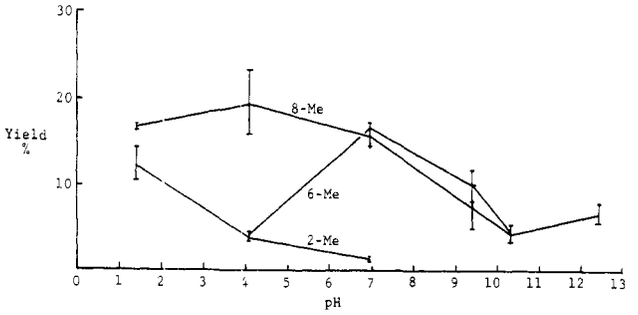


Figure 1. Radical methylation of adenosine: 0.005 M solutions of adenosine in 0.1 M buffers irradiated for 20 h with a 450-W mercury lamp, Pyrex filter, 32 °C, in the presence of a tenfold excess of *tert*-butyl peracetate. The mean and standard deviation of the percentage yields are shown as vertical bars.

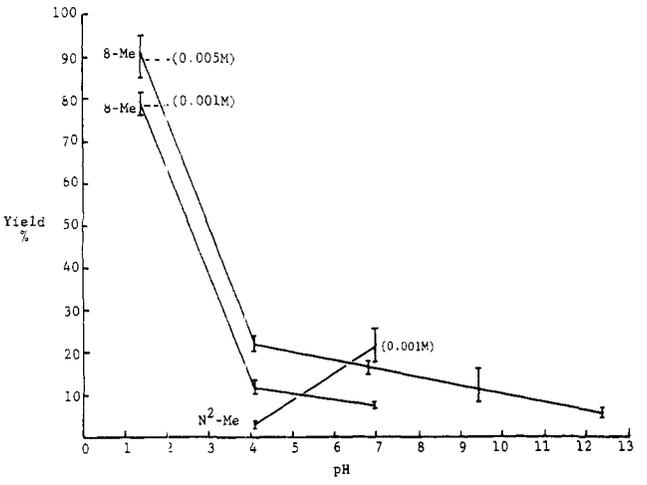


Figure 2. Radical methylation of guanosine: 0.001 and 0.005 M solutions of guanosine in 0.1 M buffers, other conditions as in Figure 1.

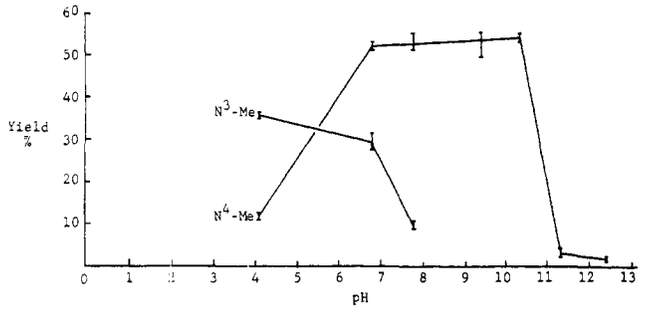


Figure 3. Radical methylation of cytidine: conditions are the same as for Figure 1.

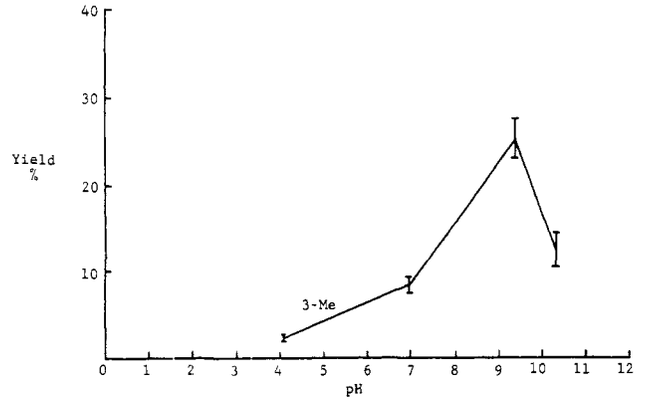


Figure 4. Radical methylation of thymidine: conditions are the same as for Figure 1.

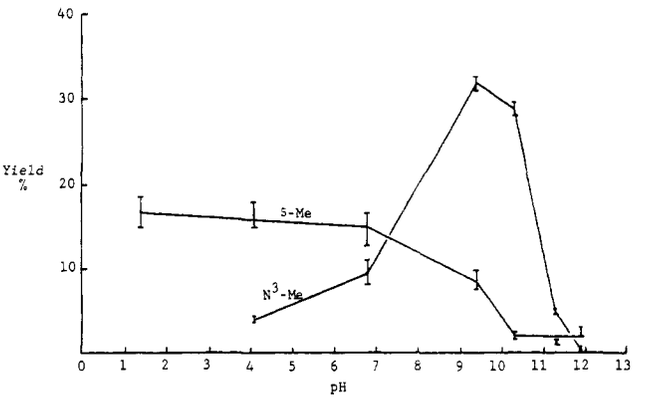


Figure 5. Radical methylation of uridine: conditions are the same as for Figure 1.

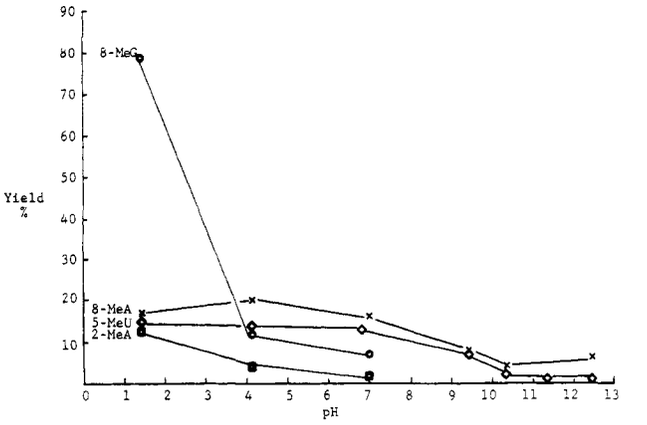
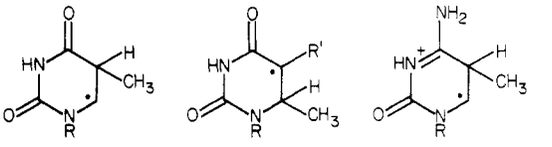


Figure 6. C-Methylation of adenosine, guanosine, and uridine. Refer to Figures 1, 2, and 5 for reaction conditions.

Scheme II



a b, R′ = H c, R′ = CH_3 d

amount of 5-methylcytidine stays at about the 3% level until alkaline pH is reached. These carbon methylation patterns can be rationalized by virtue of the mechanistic Schemes IA,B which have been deduced earlier.[5,7] In general, the charge-transfer radical-cation mechanism in Scheme IA occurring on the conjugate acid form of the heterocycle proceeds faster than the formation of σ-complex radical intermediate from the neutral species as depicted in Scheme IB. Thus, the declining yields of 8-methylguanosine in less acidic solutions reflect the decreasing availability of the N-7 protonated species. Since protonation of adenosine occurs principally at N-1,[8] the C-2 methylation pattern of adenosine is reminiscent of that of 8-methylguanosine. A combination of both mechanisms probably prevails for 8-methyladenosine. The neutral σ complex mechanism is likely the major one for the formation of 8-methyladenosine, hence a leveling of yields with pH. Of the pyrimidine nucleosides, uridine greatly surpasses cytidine in reactivity at the carbon sites. The former yields both 5-methyluridine and 6-methyluridine in a ratio of 8.2:1. Thymidine, however, does not undergo

(8) R. M. Izatt, J. J. Christensen, and J. J. Rytting, *Chem. Rev.*, 71, 439 (1971).

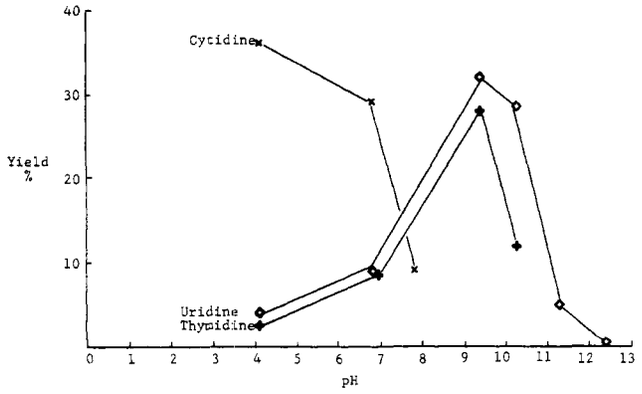
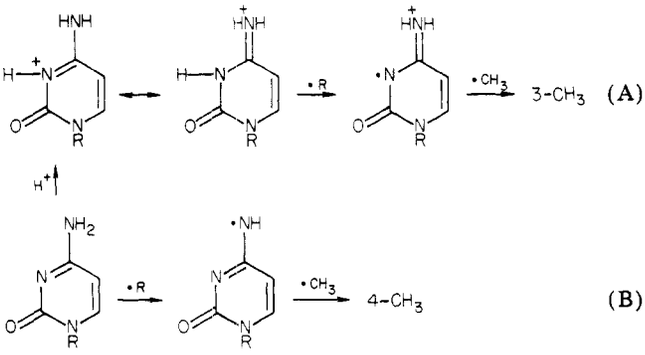


Figure 7. Ring N-methylation of cytidine, thymidine, and uridine. Refer to Figures 3, 4, and 5 for reaction conditions.

Scheme III



carbon methylation at all. The considerable reactivity of the uridine C-5 position suggests that the σ complex mechanism of Scheme IB is operative. Since the stability of the radical intermediate as shown in Scheme II determines the extent of methylation at a particular ring carbon, C-5 methylation of uridine is favored because the intermediate a is stabilized by a "three-electron bond" (C·–N: $\rightleftarrows$ C⁻–N⁺·).[9] Methylation at the 6-position generates the less desirable α-carbonyl radical b. Furthermore, if thymidine, which does not undergo C-methylation, were to methylate at the C-6 position, the intermediate c is made even less tenable because of added steric hindrance. That uridine is more reactive than cytidine may be due to destabilization of intermediate d by the positive charge on N-3 of the cytidine conjugate acid. It should be noted that photodemethylation of thymidine to uridine[10] is a significant side reaction unless the reaction is conducted under oxygen-free conditions. However, the presence of oxygen is not detrimental to the reactions of the other nucleosides.

Ring N-Methylation of Nucleosides. At pH 4 and above, cytidine, thymidine, and uridine yield significant amounts of N^3-methyl derivatives as summarized in Figure 7. Cytidine is more than 10 times as reactive as either thymidine or uridine at pH 7. The situation is reversed at pH 9 where both of the latter pyrimidines react with great facility while the formation of N^3-methylcytidine is suppressed. It appears reasonable to expect that methylation at N-3 should follow an abstraction of the N-3 hydrogen by a radical, e.g., CH_3CO_2·. That the formation of N^3-methylcytidine is at a maximum at pH 4 and declines as the pH is raised indicates the necessity for prior protonation at N-3. This may be followed by hydrogen abstraction as shown in pathway A in Scheme III. A variation of this hypothesis is that the ·CH_3 attacks via electron transfer resulting in a methyl cation (cf. Scheme IA) for methylation at N-3 or N-4. In the case of thymidine and uridine where the N-3 hydrogen is already present, the protonation step is unnecessary, and the hydrogen abstraction Scheme IIIA appears more attractive. Neither adenosine nor guanosine yields any ring N-methylation product, however.

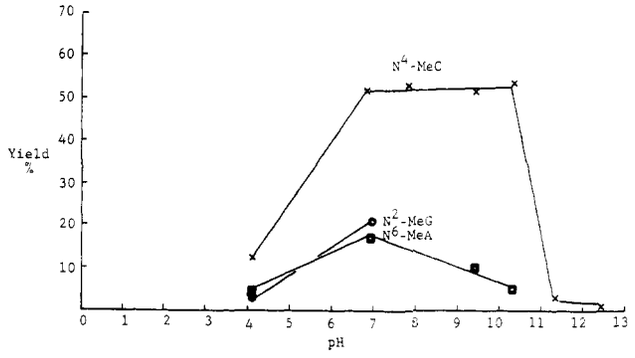


Figure 8. Exocyclic N-methylation of adenosine, guanosine, and cytidine. Refer to Figures 1, 2, and 3 for reaction conditions.

Exocyclic N-Methylation of Nucleosides. Figure 8 shows the exocyclic N-methylation of adenosine, guanosine, and cytidine. Thus, significant yields of N^6-methyladenosine, N^2-methylguanosine, and N^4-methylcytidine are obtained, beginning at pH 4 and peaking at pH 7. Guanosine is unstable to the reaction conditions above pH 7. Also, while it exhibits no significant concentration effect in C-8 methylation, the yields of the N^2-methyl derivative, starting with guanosine at 0.001 M (21.3%) and 0.005 M (2.2%), are different by an order of magnitude. The favorable N-2 methylation at high dilution can be predicted by the well-known tendency toward gel formation in concentrated guanosine solutions.[11] This gel formation usually involves N-1, N-2, O-6, and N-7, hence affecting reaction at the N-2 site more than the C-8 site. Furthermore, the formation of the exocyclic N-methyl products via a Dimroth rearrangement of the ring N-methyl products[12] was considered. Therefore, N^3-methylcytidine was subjected to the same reaction conditions as cytidine. Since no N^4-methylcytidine was detected, the exocyclic N-methyl products must arise from a radical hydrogen abstraction from the exocyclic amino group followed by combination with the methyl radical as shown in pathway B in Scheme III. Methylation of the nucleosides at carbon or nitrogen above pH 10 is not fruitful due to the high thermal ionic decay of *tert*-butyl peracetate, whose rate of decomposition is 6.9×10^{-3} s^{-1} (half-life 1.7 min) at pH 12.5.

Conclusion

The radical methylation patterns of the nucleosides have been determined. This is the first established case in which an alkyl radical is capable of nitrogen and carbon alkylation of a heterocycle. For the nucleoside–methyl radical reaction, the regioselectivity of the radical attack is highly sensitive to the acidity of the aqueous medium. Under acidic conditions, about pH 1, methylation occurs exclusively at carbon sites. In neutral solution, around pH 7, the methyl radical prefers nitrogen, either exocyclic or as part of the ring system. For a perspective of the relative

(9) F. D. Greene, J. D. Burrington, and A. M. Karkowsky, "Organic Free Radicals", W. A. Pryor, Ed., American Chemical Society, Washington, DC, 1978, Chapter 8.
(10) R. Alcantara and S. Y. Wang, *Photochem. Photobiol.*, 4, 473 (1965).
(11) J. F. Chantat and W. Guschlbauer, "The Purines", E. D. Bergmann and B. Pullman, Eds., The Israel Academy of Sciences and Humanities, Jerusalem, Israel, 1972, pp 205–16.
(12) T. Ueda and J. J. Fox, *J. Org. Chem.*, 29, 1770 (1964).

Table I. High-Pressure LC Conditions for Analysis of Nucleoside-Methyl Radical Reaction Mixtures[a]

nucleosides	Partisil 10 column	solvent	flow, mL/min	detection λ, nm	t,[b] min
adenosine	ODS	0.20 N NH_4OAc/10% MeOH	2.0	270	4.1 (A), 5.2 (2-MeA), 6.8 (8-MeA), 7.4 (6-MeA), 9.1 (2,8-diMeA)
guanosine	ODS-2	0.05 N NH_4OAc/7.5% MeOH	3.0	254	2.9 (G), 5.4 (2-MeG), 6.4 (8-MeG)
cytidine	ODS-2	0.05 N NH_4OAc/5% HOAc	1.5	280	3.4 (C), 3.8 (3-MeC), 4.6 (4-MeC)
thymidine	ODS	0.10 N NH_4OAc	3.0	265	2.4 (T), 5.2 (3-MeT)
uridine	ODS-2	0.05 N NH_4OAc/7.5% MeOH	2.0	254	2.3 (U), 3.9 (6-MeU), 4.3 (5-MeU), 5.8 (3-MeU)

[a] Analyzed as the nucleosides for the guanosine, cytidine, and thymidine reactions but as the free bases after acid hydrolysis of the reaction mixtures of adenosine and uridine: A, adenine; 2-MeA, N^2-methyladenine; 8-MeA, 8-methyladenine; 6-MeA, N^6-methyladenine; 2,8-diMeA, 2,8-dimethyladenine; G, guanosine; 2-MeG, N^2-methylguanosine; 8-MeG, 8-methylguanosine; C, cytidine; 3-MeC, N^3-methylcytidine; 4-MeC, N^4-methylcytidine; T, thymidine; 3-MeT, N^3-methylthymidine; U, uracil; 6-MeU, 6-methyluracil; 5-MeU, 5-methyluracil; 3-MeU, N^3-methyluracil. [b] Retention time.

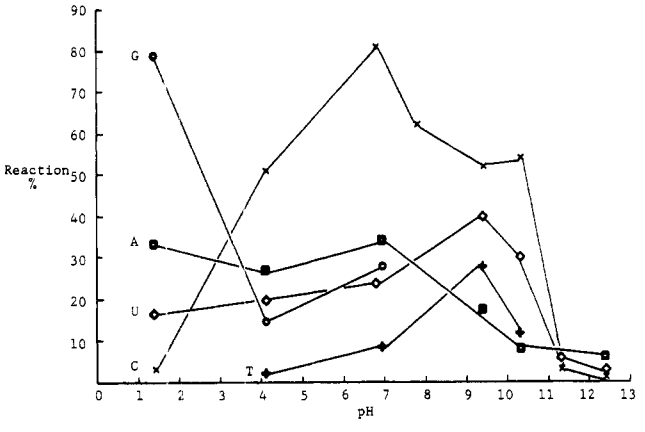


Figure 9. Overall reactions of nucleosides with $\cdot CH_3$. Refer to Figures 1–5 for reaction conditions.

reactivity of the nucleosides toward an alkyl radical, Figure 9 plots the percent reaction of the five nucleosides with $\cdot CH_3$ as a function of pH. In aqueous acids, the ranking is as follows: guanosine > adenosine > uridine > cytidine > thymidine. In the range of pH 4–7 the reactivity order is revised: cytidine > adenosine > guanosine ~ uridine > thymidine. It would be enlightening to apply these reactivity and methylation patterns to further elucidate the chemical behavior of some known carcinogens. Thus, *N*-acetyl-2-aminofluorene (AAF) has been shown to exhibit free-radical character.[13] Its putative metabolite, *N*-OAcAAF, was found to react with DNA in vitro to yield *N*-(deoxyguanosin-8-yl)- and 3-(deoxyguanosin-N^2-yl)-*N*-acetyl-2-aminofluorenes, which are products of C-8 and N-2 alkylation of the guanine base, respectively.[14] These products are in consonance with the radical methylation products of guanosine as shown in Figure 2. In an in vivo experiment involving AAF,[15] these same two compounds were isolated from the enzymatic digests of rat liver DNA, together with a third compound, tentatively identified as an adenine-AAF adduct. The latter product, according to the radical methylation patterns observed and Figure 1 in particular, may be derived from C^8- or N^6-alkylation of the adenine base. Incidentally, it may be speculated that cytosine N^4-alkylation product might also be formed, considering the extreme reactivity of cytidine toward $\cdot CH_3$ in neutral medium as shown in Figure 9. Indeed, *N*-hydroxyurethane, another carcinogen with radical character which damages DNA, was found to modify DNA in vitro, with the cytosine N-4 position being proposed as the tentative target site.[16] In this light, further studies of the products of radical carcinogen–DNA reactions can be made by reference to the radical methylation results described herein.

Experimental Section

Materials. Authentic samples of the methyl nucleosides were used to identify the methylation products. Commercial samples included adenosine, guanosine, cytidine, and 5-methylcytidine from Aldrich Chemical Co., thymidine from Sigma Chemicals, uridine from Nutritional Biochemicals Co., N^3-methylcytidine from Chemalog, and N^2-methylguanosine from Cyclo Chemical Co. Those prepared according to literature methods were 8-methylguanosine[5] and N^3-methylthymidine.[17] Other authentic samples used were obtained as follows: adenine and 6-methyluracil from Aldrich Chemical Co., 2-methyladenine and N^3-methyluracil from Sigma Chemicals, thymine from Nutritional Biochemicals, uracil from ICN Life Sciences, and N^6-methyladenine from Vega Fox. Three methylated bases were prepared by known methods: 8-methyladenine,[5] 2,8-dimethyladenine,[5] and N^4-methylcytosine via 4-thiouracil.[12,18] The *tert*-butyl peracetate was purchased from the K & K division of ICN Life Science Group. The buffer solutions were prepared in distilled water which contained traces of iron and copper according to standard procedures procedures and had the following compositions: pH 1.4, HCl–KCl;[19] pH 4.1, NaOH–CH_3COOH;[19] pH 6.8 and 7.8, KH_2PO_4–NaOH;[19] pH 9.4, KCl–H_3BO_3–NaOH;[19] pH 10.3 and 11.3, $NaHCO_3$–NaOH;[20] pH 12.4, NaOH–KCl.[20]

Product Analysis. The reaction mixtures were analyzed by high-pressure liquid chromatograph (LC) with the previously described equipment[5] and a Tracor 970 variable-wavelength UV detector. The eluting solvents, columns, flow rates, wavelengths of detection, and the pertinent retention times are shown in Table I. The percent yield of each methylated derivative of the five nucleosides was calculated from the peak area and is expressed as a percentage of the total peak area obtained on the chroma-

(13) P. O. P. Ts'o, J. C. Barrett, W. J. Caspary, S. A. Lesko, R. J. Lorentzen, and L. M. Schechtman, "Aging, Carcinogenesis, and Radiation Biology", K. C. Smith, Ed., Plenum, New York, 1976, pp 373–97.
(14) H. Yamaski, P. Pulkrabek, D. Grunberger, and I. B. Weinstein, *Cancer Res.*, **37**, 3756 (1977).
(15) J. G. Westra, E. Krick, and H. Hittenhausen, *Chem.-Biol. Interact.*, **15**, 149 (1976).
(16) K. Mullinix, S. Rosenkrantz, H. Carr, and H. S. Rosenkrantz, *Biochim. Biophys. Acta*, **312**, 1 (1973).
(17) T. Tanabe, K. Yamauchi, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **52**, 204 (1979).
(18) Y. Mizuno, M. Ikehara, and K. A. Watanabe, *Chem. Pharm. Bull.*, **10**, 647 (1962).
(19) "Biochemist's Handbook", C. Long, Ed., Van Nostrand, Princeton, NJ, 1968, pp 30–42.
(20) "Handbook of Biochemistry", R. C. Weast, Ed., CRC Press, Cleveland, OH, 1968, p J194.

togram attributed to the nucleosides. Such data treatment is validated by the great similarity in extinction coefficient observed for the starting nucleoside and its methyl derivatives at the wavelength of detection.

Methylation of Adenosine. Solutions of adenosine (0.005 M) in 0.1 M buffers (pH 1.4–12.4) were prepared. A tenfold excess of BPA was added to each solution which was placed in a clear tube and irradiated for 20 h with a water-cooled 450-W mercury lamp (Pyrex filter) at 32 °C and a distance of 2 cm. Since some deribosylation occurred during this reaction, the reaction mixtures were totally deribosylated to the free bases by acid hydrolysis (1.0 M HCl, 100 °C, 1 h) before analysis by high-pressure LC. This simplifies data analysis without sacrificing the accuracy of the methylation pattern or the product yield as indicated by controls.

Methylation of Guanosine. The methylation of guanosine at 0.001 and 0.005 M concentrations was conducted in the same manner. Guanosine and its methylated derivatives were analyzed by high-pressure LC.

Methylation of Cytidine. The methylation of cytidine was conducted in the same manner. One of the products, N^4-methylcytidine, was isolated from a large-scale reaction by preparative high-pressue LC using a Partisil 10 ODS (Magnum 9) column (50 cm × 9 mm) with 10% methanol in water at 8 mL/min as eluent. The eluted material was deribosylated by acid hydrolysis (4 N HCl, 130 °C, 16 h) and was identified as N^4-methylcytosine by coinjection with an authentic sample.

Methylation of Thymidine. The methylation of thymidine was conducted in the usual manner except a nitrogen atmosphere was maintained. The nucleoside and its methylation product were analyzed by high-pressure LC.

Methylation of Uridine. The methylation of uridine was conducted in the same manner. Since some deribosylation occurred during this reaction, the reaction mixtures were totally deribosylated by acid hydrolysis (4.0 M HCL, 130 °C, 16 h) and analyzed by high-pressure LC. There were no changes observed in either the site or extent of methylation by this acidic workup procedure as indicated by controls.

Acknowledgment. This investigation was supported by Grant CA16182 awarded by the National Cancer Institute, DHEW, for which we are grateful.

Registry No. Adenosine, 58-61-7; guanosine, 118-00-3; cytidine, 65-46-3; thymidine, 50-89-5; uridine, 58-96-8; A, 73-24-5; 2-MeA, 1445-08-5; 8-MeA, 22387-37-7; 6-MeA, 443-72-1; 2,8-Me_2A, 25680-62-0; 2-MeG, 2140-77-4; 8-MeG, 36799-17-4; 3-MeC, 2140-64-9; 4-MeC, 10578-79-7; 3-MeT, 958-74-7; U, 66-22-8; 6-MeU, 626-48-2; 5-MeU, 65-71-4; 3-MeU, 608-34-4.

Vinyl Cation Intermediates in Electrophilic Additions to Triple Bonds. 1. Chlorination of Arylacetylenes

Keith Yates* and T. Andrew Go

Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A1

Received October 30, 1979

The products of ionic addition of chlorine to phenylacetylene, β-methylphenylacetylene, 4-methylphenylacetylene, β-ethylphenylacetylene, and tolan have been investigated in anhydrous acetic acid. The major products are the α,β-dichlorostyrenes arising from simple 1,2 addition, but significant yields of solvent-incoroprated products are also found. In some cases significant yields of β-chlorophenylacetylenes are found, presumably arising from an addition–elimination process. No products arising from addition of 2 mol of Cl_2 were observed. The reactions are clearly nonstereospecific and show only weak stereoselectivity varying from predominant syn to predominant anti addition. However, the reactions are all completely regiospecific in the Markovnikov sense. In the presence of low concentrations of added salts such as lithium chloride, acetate, and perchlorate, the product distribution and stereochemistry are hardly affected. Only at high concentrations of these salts is there any significant change in product distribution. The second-order rates of addition have been measured for five additional phenyl-substituted compounds. The seven ring-substituted phenylacetylenes show an excellent correlation with σ^+, giving a large negative ρ value (−4.19). The effects of β-substitution on the rate of chlorination are very small. The results are interpreted in terms of a simple Ad-E2 process, in which the rate-determining transition state is an open vinyl-cation-like species, with most of the positive charge being developed at C_α. The subsequent product-determining intermediate is considered to be a tight ion pair between an open α-phenylvinyl cation and a chloride counterion. This ion pair can react by ion-pair collapse, solvent attack, or internal proton elimination. Activation parameters determined for three of the above compounds show that the higher rates of chlorination (over bromination) of the acetylene system are due almost entirely to lower ΔH^* values.

Despite the recent wave of activity in studying reactions involving vinyl cations[1] as reactive intermediates and the resurgence of interest in electrophilic additions generally, very little mechanistic work has been reported to date on the addition of molecular chlorine to the triple bond. This reaction presumably involves the formation of vinyl cationic intermediates of some kind, yet a recent review on electrophilic additions to carbon–carbon triple bonds[2] shows relatively little in the way of systematic results in this area.

We have recently completed a detailed study of the kinetics and mechanism of additions of chlorine to two types of acetylene, namely, those substituted with phenyl groups and those substituted only with alkyl groups. Since the reactions of the arylacetylenes appear to be less complex and the results more easily interpreted mechanistically, these will be reported on first in this paper. The accompanying paper[3] reports an analogous study of the chlorinations of alkylacetylenes. All the reactions have been studied in anhydrous acetic acid as solvent to make

(1) M. Hanack, *Angew. Chem., Int. Ed. Engl.*, 17, 333 (1978); P. J. Stang, *Prog. Phys. Org. Chem.*, 10, 205 (1973); G. Modena and U. Tonellato, *Adv. Phys. Org. Chem.*, 9, 185 (1971).

(2) G. H. Schmid, "Electrophilic Additions to Carbon–Carbon Triple Bonds. The Chemistry of the Carbon–Carbon Triple Bond", S. Patai, Ed., Wiley, New York, 1978, Chapter 8, p 279.

(3) K. Yates and T. A. Go, *J. Org. Chem.*, following paper in this issue.

0022-3263/80/1945-2377$01.00/0