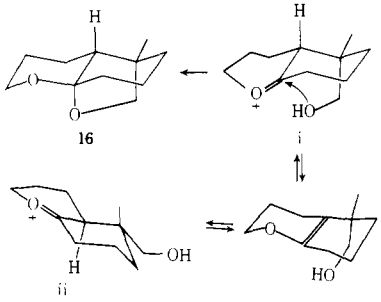
nique and which markedly reduced the yields of the alkylation processes. Alkylation of ketone enolates and other substances with approximate pK_a of ≤ 24 were not markedly affected.
(14) All new compounds exhibited consistent spectral data (IR, NMR (^1H, ^{13}C)) and correct combustion or exact mass analytical data. Yields cited are for distilled or carefully chromatographically purified materials. Yields have not been optimized and in several cases crude materials of acceptable purity are obtained directly without purification (yields in parentheses, losses occur upon purification). Selected spectral data: **3**, ^1H NMR δ 4.55 (t, 1H), 3.97 (t, 2H), 2.75 (m, 2H), 2.3–1.4 (m, 8H), 1.3 (d, 3H); **5**, ^1H NMR δ 4.73 (m, 1H), 4.02 (t, 2H), 2.4–1.6 (m, 8H), 2.1 (s, 3H), 1.04 (d, 3H); **9**, ^1H NMR δ 4.55 (t, 1H), 3.97 (t, 2H), 2.73 (t, 1H), 2.35–1.42 (m, 8H), 1.31 (s, 3H), 1.27 (s, 3H); **10**, ^1H NMR δ 3.90 (t, 2H), 3.52 (t, 1H), 2.25–1.35 (m, 9H), 1.05 (s, 3H), 1.00 (s, 3H); **13**, ^1H NMR δ 4.50 (t, 1H), 3.98 (t, 2H), 2.60 (s, 2H), 2.25–1.4 (m, 10H), 1.35 (s, 3H); **15** characterized as the acetate, ^1H NMR δ 3.95 (m, 4H), 2.1 (s, 3H), 2.25–1.20 (m, 10H), 1.03 (s, 3H); **16**, ^1H NMR δ 3.6 (m, 4H), 2.17–1.06 (m, 12H), 0.88 (s, 3H), and IR 2900, 1450, 1375 cm^{-1}; **21**, ^1H NMR δ 5.37 (m, 1H), 4.82 (m, 1H), 3.86 (m, 2H), 2.13 (s, 3H), 1.12 (d, 3H).
(15) Agitated magnetic stirring for 8 h followed by standing for 16 h. This heterogeneous reaction was found to depend on the activity of the Al_2O_3 utilized.
(16) The ^{13}C NMR spectrum of **3** exhibited only 10 resonances, with no doubling characteristic of a diastereomeric mixture, particularly at the carbons bearing the side chain and hydroxyl.
(17) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).
(18) The structure of **16** follows from consideration of the possible conformations available to the intermediate oxonium ions i and ii. Only i is capable of



cyclization and only the trans ring junction can result since the sp^2 nature of the ring junction carbon bearing the positive charge permits the adjacent hydrogen to occupy only an axial environment if effective overlap of the adjacent oxygen lone pairs is to occur.
(19) M. Chaney, P. Demarco, N. Jones, and J. Occolowitz, *J. Am. Chem. Soc.*, **96**, 1932 (1974).
(20) D. A. Evans, C. E. Sacks, R. A. Whitney, and N. G. Mandel, *Tetrahedron Lett.*, 727 (1978).
(21) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976), and references therein; (b) cf. ref 1j.
(22) For a related cyclization of an epoxy ketone under acidic conditions, see W. K. Anderson and T. Veysoglu, *J. Org. Chem.*, **38**, 2267 (1973); under basic conditions, see T. Masamune, M. Ono, S. Sato, and A. Murai, *Tetrahedron Lett.*, 371 (1978).
(23) (a) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966); (b) I. J. Borowitz, G. J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco, and R. D. G. Rigby, *ibid.*, **37**, 581 (1972).
(24) (a) A. P. Schaap and P. D. Bartlett, *J. Am. Chem. Soc.*, **92**, 6055 (1970); (b) P. D. Bartlett, G. D. Mendenhall, and A. P. Schaap, *Ann. N.Y. Acad. Sci.* **171**, 79 (1970).
(25) It was observed that even in CH_3CN the ratio of dioxetane to ene modes is only 85:15 for dihydropyran[24] and it is the generally observed trend for more highly substituted olefins to prefer the ene pathway; cf. W. Fenical, D. R. Kearns, and P. Radlick, *J. Am. Chem. Soc.*, **91**, 3396 (1969).
(26) Singlet oxygen was generated by irradiation of the solution (CH_3CN) containing Rose Bengal at 10–15 °C with a sodium vapor lamp through a filter with a cut-off at ≤ 500 nm. The presence of the dioxetane was confirmed by the observation of chemiluminescence upon heating.
(27) J. Cartlidge and C. F. H. Tipper, *Anal. Chim. Acta*, **22**, 106 (1960). The hydroperoxide results in an immediate postive test; dioxetanes show a positive test after a short time.
(28) E. J. Corey, D. J. Brunelle, and K. C. Nicolaou, *J. Am. Chem. Soc.*, **99**, 7359 (1977).
(29) Further studies and applications will be reported in subsequent papers.
(30) For one recent approach to this problem, see T. Wakamatsu, K. Akasaka, and Y. Ban, *Tetrahedron Lett.*, 2751, 2755 (1977).
(31) For a recent review, see K. C. Nicolaou, *Tetrahedron*, **33**, 683 (1977).
(32) Fellow of the Alfred P. Sloan Foundation (1976–1980); recipient of a Career Development Award (CA-00273) from the National Cancer Institute of the National Institutes of Health (1976–1981).

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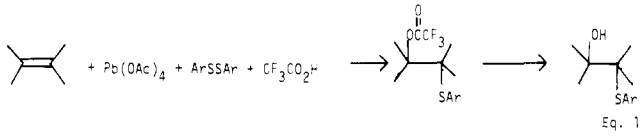
Hydroxysulfenylation of Olefins. An Olefin Cleavage with Functional Group Differentiation

Sir:

We report that combination of a lead (+4) salt and a disulfide provides a convenient general approach to hydroxysulfenylation of olefins.[1,2] The importance of vicinal oxygen and sulfur substitution stems from the great flexibility for structural elaboration.[3] Among such reactions is the ability to cleave the C–C bond bearing these substituents.[4] The combination of the hydroxysulfenylation with an improved cleavage of a β-hydroxylsulfide allows an olefin cleavage with differentiation of regiochemistry and functional groups. The application of this latter reaction toward a precursor of (±)-verrucarinic acid, a portion of the macrocyclic chain of verrucarin A,[5] is reported. An unusual conversion of a hydroxysulfide to an epoxide which can represent a net epoxidation from the sterically hindered face of an olefin is also noted.

Lead tetraacetate (1.0–1.5 equiv) and diphenyl disulfide (1.0–1.5 equiv) in the presence of 8–15 equiv of trifluoroacetic acid (generating a lead (+4) trifluoroacetate in situ)[6] in methylene chloride at 0 or −40 °C form a blue solution which rapidly turns yellow. Addition of 1 equiv of an olefin at this stage leads to smooth and rapid reaction at 0 or −40 °C to produce initially the β-trifluoroacetoxysulfide which upon basic workup generates the thiohydrin as summarized in eq 1 and



Eq. 1

Table I.[7] The chemoselectivity as well as the electrophilic nature of the reaction is illustrated by the case of carvone (Table I, entry 11) in which only the isolated double bond reacts.

The regiochemistry is dependent upon the temperature, the olefin, and the disulfide. Thus, with 1-methylcyclohexene, the regioselectivity increases from 4:1 to 27:1 of **3**:**4** by dropping the temperature of the reaction from 0 to −40 °C. In the case of cholesteryl benzoate, an ~1:1 mixture of the regio- and stereoisomers **10** and **11** is obtained even at −40 °C. Increasing the steric hindrance of the sulfenylating agent by switching to di-*o*-anisyl disulfide improved the selectivity to 1:3. That this enhanced regiochemistry represents a steric and not an electronic effect is evidenced by the nearly 1:1 ratio obtained with di-*p*-anisyl disulfide.[8]

The stereochemistry has been proven for a few cases and assumed for the remaining examples. In the case of the additions to cyclopentene, cyclohexene, and 4-*tert*-butylcyclohexene, the adducts are identical with authentic samples of the trans isomers available by independent methods. In the case of steroid **9** the protons at C(2) and C(3) are broadened singlets at δ 4.06 and 3.45, indicative of these protons being equatorial.

The mechanism of the reaction is obscure. It does involve transfer of an equivalent of ArS^+.[9] Thus, unsaturated acids (Table I, entry 8 and 14) lead to sulfenyllactonization. The ease of this procedure and the avoidance of handling benzenesulfenyl chloride give this method some advantage over a recently reported version of this reaction.[10] The stereo- and regiochemistry are also in accord with initial complexation of an ArS^+ species to the least hindered side of an olefin to generate the equivalent of an episulfonium ion followed by nucleophilic opening with trifluoroacetate. In this regard, the cholesteryl system is of great interest since the isomer ratio is dependent upon the initial complexation. The bulkier *o*-anisyl reagent leads to reaction via preferential β side attack and thus accounts for the enhanced selectivity.

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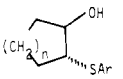
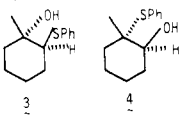
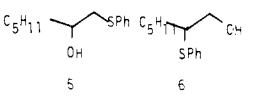
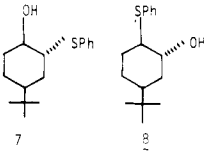
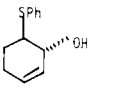
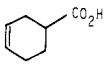
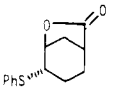
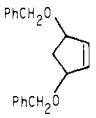
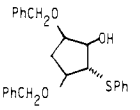
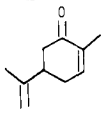
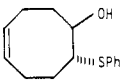
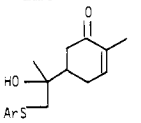
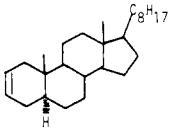
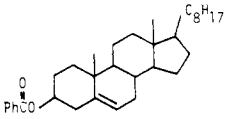
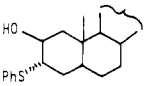
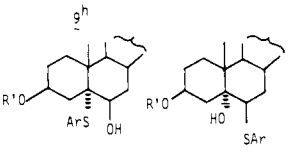
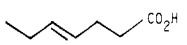
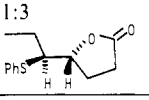
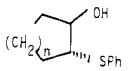
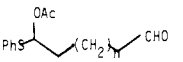
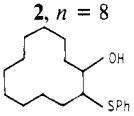
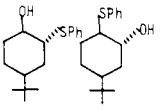
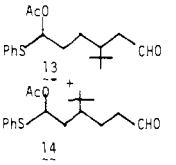
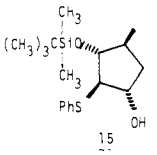
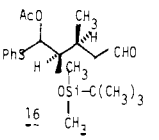
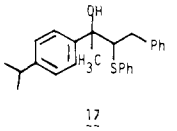
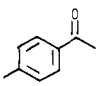
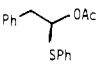
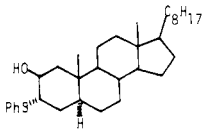
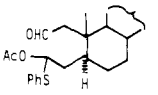
Table I. Hydroxysulfenylation of Olefins

entry	olefin	$(ArS)_2$	temp, °C	product	% yield[b]
	 1			 2	
1	**1**, $n = 1$	$(PhS)_2$	0	**2**, $n = 1$	61
2	**1**, $n = 2$	$(PhS)_2$	0	**2**, $n = 2$	74
3	**1**, $n = 4$	$(PhS)_2$	0	**2**, $n = 4$	80
				 3 4	
4a		$(PhS)_2$	0	4:1	78
4b		$(PhS)_2$	−40	27:1  5 6	63
5a		$(PhS)_2$	0	2:1	87
5b		$(PhS)_2$	−40	3:2	62
6		$(PhS)_2$	−40	 7 8	94
7		$(PhS)_2$	−40		52
8		$(PhS)_2$	0		60[e]
9		$(PhS)_2$	0 → RT[c]		75
10	 	$(PhS)_2$	−40	 	42
11a		$(PhS)_2$	−40	Ar = Ph	92
11b		$(o\text{-}CH_3OC_6H_4S)_2$	−40	Ar = o-$CH_3OC_6H_4$	96
12	 	$(PhS)_2$	−40	 9[h]  10 11	82
13a		$(PhS)_2$	−40	1.2[d]:1[d]	81[f]
13b		$(p\text{-}CH_3OC_6H_4S)_2$	−40	1[d]:1.4[d]	95[g]
13c		$(o\text{-}CH_3OC_6H_4S)_2$	−40	1:3	68
14		$(PhS)_2$	−78		91[i]

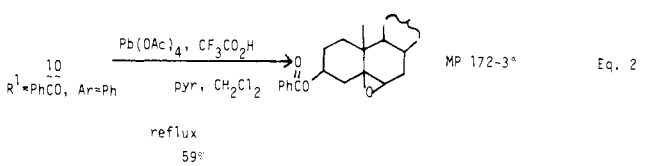
[a] Reaction times of from 20 to 30 min were employed. [b] All yields are for isolated products. Compounds have been fully characterized. [c] 1 h at 0 °C and overnight at room temperature. [d] A mixture of R′ = COPh and R′ = H resulted from incomplete hydrolysis. [e] Product had mp 94 °C. [f] **10** (R′ = PhCO, Ar-Ph), mp 109-112 °C. [g] **10** (R′ = PhCO, Ar = p-$CH_3OC_6H_4$), mp 149-50 °C. [h] A small amount of the 2β-phenylthio-3α-hydroxy isomer was detected in the NMR spectrum. [i] A small amount of 5-phenylthio-6-ethyl-γ-valerolactone (<10%) was detected by NMR spectroscopy.

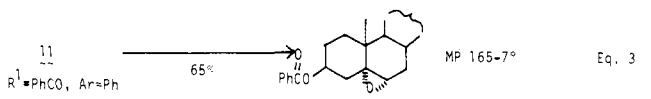
Table II. Oxidative Cleavage of α-Hydroxysulfides

entry	hydroxysulfide (HS)	ratio of HS:LTA:PY:HOAc[a]	product	% yield[b]
1	 **2**, n = 1	1:1.8:3:0	 **12**, n = 1	88
2	**2**, n = 4	1:2:4:3	**12**, n = 4	*c*
3	**2**, n = 8	1:2:4:3	**12**, n = 8	72
4		1:2:4:3	**12**, n = 8	79
5		1:2:4:3	 **13** + **14**	64
6	 **15**	1:2:4:3	 **16**	83
7	 **17**	1:2:4:3	 	82 64
8		1:5:25:50		40[d]

[a] HS:LTA:PY:HOAc = mole ratio of β-hydroxysulfide:lead tetraacetate:pyridine:acetic acid. [b] All yields are for isolated pure products. Since these products do decompose to some extent on chromatography, the isolated yields reported are lower than the actual yields. All compounds have been fully characterized. [c] In this case, the product is contaminated with an unidentified substance and thus a yield was not obtained. [d] This cleavage was performed under an earlier set of conditions as evidenced by the ratio of reagents. It is anticipated that a significantly higher yield would be obtained under the best conditions reported herein.

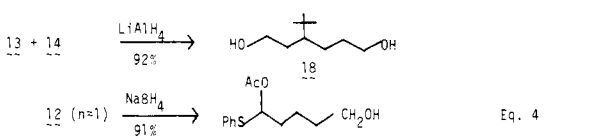
The ready accessibility of the thiohydrins (and by extension the β-ketosulfides) from olefins greatly expands their utility as synthetic intermediates. Most interesting to us is an oxidative cleavage which previously was restricted to strained ring systems.[4a] A greatly expanded scope for this reaction results by the following procedure. To a solution of 2 equiv of lead tetraacetate and 3 equiv of acetic acid in refluxing benzene is added 4 equiv of pyridine. Thirty seconds after addition of the pyridine, 1 equiv of the hydroxysulfide is added and reflux is maintained for 10–15 min, at which point the reaction is worked up in the normal fashion. As can be seen from Table II six-membered and larger rings do cleave under these conditions. A trans diaxial arrangement appears to be required. Thus, the hydroxysulfide from cyclohexene which has the substituents diequatorial fails to cleave, whereas the hydroxysulfides **7** and **8** which have the substituents rigidly diaxial cleave nicely. Steric hindrance also appears to play an important role as exemplified by the difference between **9** and **10** or **11**. Thus, the former cleaves to give the desired aldehyde-acetoxysulfide, whereas the latter two do not cleave. Attempts to increase the oxidizing power of lead tetraacetate by converting it to $Pb(O_2CCF_3)_n(OAc)_{4-n}$ also fails to lead to cleavage. Instead, a rather interesting conversion to the corresponding epoxide occurs (see eq 2 and 3) and constitutes





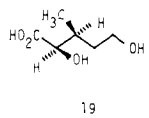
a net olefin epoxidation. Apparently, coordination of the lead (+4) with sulfur makes it a good enough leaving group to be displaced by the neighboring hydroxyl group. Acyclic compounds also cleave as demonstrated by **17** (Table II, entry 7).

The structures of the products are easily discerned spectroscopically. In contrast to our earlier work, only open-chain compounds (i.e., no lactol acetates) are observed.[4] In the case of hydroxysulfides **7** and **8**, the regioisomeric products **13** and **14** are characterized by reduction to the single diol **18**. Of



course, the functional group differentiation allows selective reduction of the free aldehyde (eq 4). In this regard, the cleavage of **15** to **16** (Table II, entry 6) is most interesting, since

the product can serve as an excellent precursor of verrucarinic acid **19**.[11]



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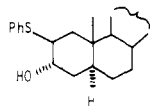

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This direct hydroxysulfenylation of olefins offers a very convenient and general approach to β-hydroxysulfides, particularly useful synthetic intermediates. In addition, this method provides a regio- and stereochemistry not available by alternative procedures. For example, whereas Δ^2-5α-cholestene gives **9** under our conditions, epoxidation and nucleophilic opening gives the isomeric **20**. This difference proved critical for the ring cleavage since **9** does cleave but **20** does not. The ring cleavage provides just one illustration of the utility of this methodology since the combined procedures allow the use of lead tetraacetate in effecting a net olefin cleavage[12] and also maintaining an intrinsic difference between the ends of the chain in the case of cyclic olefins. The question of the nature of the oxidizing agent remains one of the goals of future work.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health (General Medical Sciences) for their generous support of our programs. We also express our thanks to Miss D. Kapadia for her participation in this project.

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(1) Sulfenic acids generally add to olefins to give sulfoxides rather than β-hydroxysulfides: E.g., Jones, D. N.; Hill, D. R.; Lewton, D. A.; Sheppard, C. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 1574. Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929. 2,4-Dinitrobenzenesulfonyl acetate has been reported to add very slowly (16 days, 50 °C) to cyclohexene: Havlik, A. J.; Kharasch, N. *ibid.* **1956**, *78*, 1207. Putnam, R. E.; Sharkey, W. *ibid.* **1957**, *79*, 6526. The penicillin–cephalosporin interconversion involves such a reaction: Cooper, R. D. G.; Hatfield, L. D.; Spry, D. O. *Acc. Chem. Res.* **1973**, *6*, 32. For related work see the following. Szmant, H. H.; Najundiah, R. *J. Org. Chem.* **1978**, *43*, 1835. Uebel, J. J.; Milaszewski, R. F.; Arlt, R. E. *ibid.* **1977**, *42*, 585. Davis, F. A.; Friedman, A. J. *ibid.* **1976**, *41*, 897. Nederlof, P. J. R.; Moolenaas, M. J.; de Waard, E. R.; Huisman, H. O. *Tetrahedron Lett.* **1976**, 3175.

(2) For selenenic acids and carboxylates and their additions to olefins, see the following. Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697. Horio, T.; Sharpless, K. B. *ibid.* **1978**, *43*, 1689. Clive, D. J. *J. Chem. Soc., Chem. Commun.* **1974**, 100. Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *39*, 429. Reich, H. J. *ibid.* **1974**, *39*, 428.

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(4) (a) Trost, B. M.; Hiroi, K. *J. Am. Chem. Soc.* **1975**, *97*, 6911. (b) Also see the following. Trost, B. M.; Hiroi, K. *ibid.* **1976**, *98*, 4313. Trost, B. M.; Tamaru, Y. *ibid.* **1977**, *99*, 3101. Trost, B. M.; Massiot, G. S. *ibid.* **1977**, *99*, 4405.

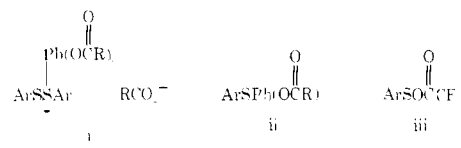
(5) Tamm, Ch. *Fortschr. Chem. Org. Naturst.*, **1974**, *31*, 63.

(6) Jones, S. R.; Meller, J. M. *J. Chem. Soc., Perkin Trans. 2*, **1977**, 511.

(7) Omission of the trifluroacetic acid led to a 10% yield of β-acetoxysulfide after 60 h at reflux in acetonitrile.

(8) The regioisomer formed is normally evident from the NMR spectrum. Further confirmation arose by acetylation to shift the absorption for the methine proton adjacent to the hydroxyl group. For example, in the cyclohexadiene adduct, the pertinent protons appear at δ 3.13 (ddd, J = 9.2, 6.5, and 2.7 Hz) and 4.02 (d, J = 6.5 Hz). Acetylation shifts these absorptions to δ 3.3 and 5.21. The larger shift of the allylic methine proton assigns the hydroxyl group to the allylic carbon.

(9) Several intermediates appear reasonable (i-iii). Trifluoromethanesulfenyl



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trifluoroacetate and relatives have been isolated: Haas, A.; Oh, D. Y. *Chem. Ber.* **1969**, *102*, 77. These reactions can be compared with the addition of sulfenyl halides to olefins. For a recent paper see Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208.

(10) Nicolaou, K. C.; Lysenko, Z. *J. Chem. Soc., Chem. Commun.* **1977**, 293.

(11) The transformation of **16** to verrucarinic acid only requires adjustment of the oxidation level—i.e., reduction of the aldehyde to an alcohol and oxidation of the protected aldehyde to a carboxylic acid.

(12) Cf. Huber, F.; El-Meligy, M. S. A. *Chem. Ber.* **1969**, *102*, 872.

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X-ray Evidence for the Metal Ion Bridged Intra- and Intermolecular Stacking Interactions between Nucleotide Bases and Aromatic Heterocyclic Rings within the Ternary Complex $[Cu(5'\text{-AMP})(bpy)(H_2O)]_2\cdot(NO_3)_2\cdot 6H_2O$

Sir:

The involvement of the charge-transfer interactions between nucleic acid bases and aromatic amino acid residues in biological systems is now widely recognized,[1] but such stacking adducts are usually weak unless they are additionally stabilized by polar interactions, e.g., proton or ionic bridges.[2] In a solution study[3] of the spectroscopic properties of the ternary complexes such as Cu(bpy[4])L (L = 5′-AMP, 5′-IMP, ATP, and ITP), which are known to be possible models for substrate–metal ion–enzyme complexes, it has been demonstrated that the metal ion bridge formation between the two constituents of the adducts can stabilize them in the following way: the metal ion is coordinated to the nitrogen donors of the bpy ligand and to the phosphate chain of the nucleotide, bridging and stabilizing the stacking between the aromatic amine and the purine moiety. In order to substantiate the formation of such a metal ion bridged stacking adduct and to elucidate its stereochemistry, we have undertaken a systematic X-ray crystallographic study[5] of the ternary complexes containing various metal ions, aromatic amines, and nucleotides. We report here the preparation and the structure of the ternary 5′-AMP-Cu^{II}-bpy complex, which is the first example providing the direct evidence for the existence of such a metal ion bridged stacking adduct.[6]

The complex was prepared from 5′-AMP (3×10^{-4} M), $Cu(NO_3)_2\cdot 2H_2O$ (9×10^{-4} M), and bpy (9×10^{-4} M), adjusting pH to ~4 with dilute NaOH solution, and the mixture was allowed to stand at room temperature. Blue columnar crystals formed after ~3 weeks. They were collected, washed with a little water, and air dried. Crystals of $[Cu(5'\text{-AMP})(bpy)(H_2O)]_2\cdot(NO_3)_2\cdot 6H_2O$ are triclinic, space group $P\bar{1}$, with a = 10.195 (2), b = 12.305 (4), c = 11.805 (1) Å; α = 88.92 (1), β = 108.99 (1), γ = 104.41 (1)°; Z = 1; V = 1353.2 Å^3; D_m = 1.70 and D_c = 1.673 g cm^{-3}. Intensity data were collected on a Rigaku automated diffractometer with Mo Kα radiation up to a 2θ limit of 45°. The structure was solved by Patterson and difference-Fourier methods and refined to present discrepancy indices R_F[7] and R_{wF} of 0.046 and 0.051, respectively, for 3567 reflections with $F_o \geq 3\sigma(F_o)$.[8]

Figure 1 shows the molecular structure of the dimeric $[Cu(5'\text{-AMP})(bpy)(H_2O)]_2^{2+}$ unit, where each AMP molecule exists as a monovalent anion with the N(1) of the adenine base being protonated,[9] and with the phosphate group doubly ionized.[10] The two independent $[Cu(5'\text{-AMP})(bpy)(H_2O)]^+$ units are approximately related by a noncrystallographic center of inversion except the sugar parts. The most remarkable features in this structure are that the nucleotide is coordinated to the metal ion through the phosphate group only and not through the base moiety[11] and that the complex forms a metal ion bridged intramolecular stacking adduct, in which the imidazole part of the purine base is stacked on one of the pyridyl

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