American Chemical Society

29th NATIONAL ORGANIC CHEMISTRY SYMPOSIUM

Under the auspices of the
Division of Organic Chemistry &
The University of Delaware
June 16–20, 1985
Newark, Delaware

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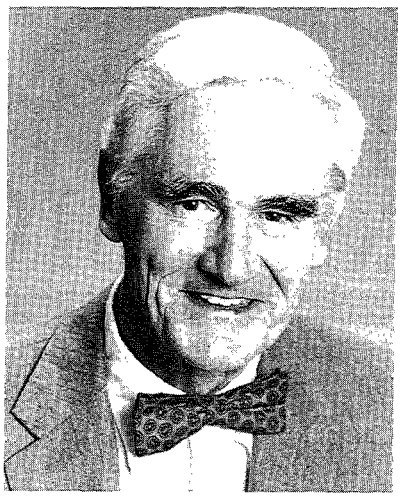
The Roger Adams Award in Organic Chemistry

The Roger Adams Award in Organic Chemistry is sponsored jointly by the American Chemical Society, Organic Reactions, Inc., and Organic Syntheses, Inc. The award recognizes the distinguished career of Roger Adams who played a vital role in each of these three organizations. He was Chairman of the Board of Directors as well as President of the American Chemical Society, and he co-founded Organic Syntheses and Organic Reactions.

The award is made biennially to an individual, without regard to nationality, for outstanding contributions to research in organic chemistry. The award consists of a medal and an honorarium of ten thousand dollars. It is presented at the biennial National Organic Chemistry Symposium of the Division of Organic Chemistry of the American Chemical Society. The awardee is a featured lecturer in the program of the Symposium.

The recipient of this year's Roger Adams Award is Professor Donald J. Cram of the University of California at Los Angeles. His award address is entitled "Molecular Cells, Their Guests, Portals, and Behavior."



Donald J. Cram

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LARRY E. OVERMAN

DAVID A. EVANS

Program

SUNDAY, JUNE 16

Arrival and Checkin.

MONDAY, JUNE 17

8:30 AM Welcome, Response, and Announcements.

9:00 AM C.T. WALSH, Naturally-Occurring Deazaflavin Coenzymes: Structure and Function.

10:30 AM P.A. BARTLETT, Organic Synthesis: Applications to Natural Products and Bioorganic Chemistry.

7:30 PM P.B. DERVAN, Molecular Recognition of DNA by Small Molecules.

TUESDAY, JUNE 18

9:00 AM C.H. DEPUY, The Chemistry of Anions in the Gas Phase.

10:30 AM M.A. FOX, Chemical Control: Combining Photochemistry with Electrochemistry.

7:30 PM D.J. CRAM, Molecular Cells, Their Guests, Portals, and Behavior.

WEDNESDAY, JUNE 19

8:30 AM C.P. CASEY, Hydrocarbation.

10:00 AM J.K. STILLE, Carbon-Carbon Coupling Reactions Catalyzed by Palladium.

11:15 AM J.D. WHITE, Synthetic Studies of Boron-Containing Macrolides.

THURSDAY, JUNE 20

9:00 AM L.E. OVERMAN, Sigmatropic Rearrangements in Heterocyclic Synthesis

10:30 AM D.A. EVANS, Studies in Asymmetric Synthesis.

12 Noon Closing Remarks.

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NATURALLY-OCCURRING DEAZAFLAVIN COENZYMES: STRUCTURE AND FUNCTION

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NATURALLY OCCURRING DEAZAFLAVIN COENZYMES AND THEIR ROLES IN REDOX BIOCHEMISTRY

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This presentation will deal with recently discovered naturally occurring 5-carba-5-deaza analogs of Vitamin B_2, riboflavin, and their roles as redox coenzymes in three specific biological settings: a) methanogenic bacterial metabolism, b) in tetracycline biosynthesis in streptomycetes, and c) in photoreversion of thymine-dimers in UV-damaged DNA.

First some relevant chemical properties of deaza analogs of riboflavin will be analyzed to see how the 5-carba and 8-hydroxy substituents make the 5-deazaflavin coenzymes a hybrid system between nicotinamides and flavins. Then the coenzymatic function of the methanogen cofactor F_{420} will be analyzed in its role as low potential electron acceptor from H_2, catalyzed by methanogen hydrogenase and subsequent transfer of a hydride equivalent from dihydro coenzyme F_{420} to NADP catalyzed by an oxidoreductase. Methanogenic bacteria are killed on exposure to O_2 and on brief exposure to air coenzyme F_{420} is converted in methanogenic cells to F_{390}, shown to be an 8-O-AMP ester of F_{420}. F_{390} could represent an "alarmone" for oxidant stress.

In nonmethanogenic organisms coenzyme F_{420} has been implicated in two other roles. Work at Lederle suggested dihydro F_{420} is the obligate cofactor for conversion of inactive precursor 5a, 11a-dehydrochlortetracycline to the active antibiotic chlortetracycline. A second role is in enzyme-mediated photoreversion of cyclobutane-

ORGANIC SYNTHESIS: APPLICATIONS TO NATURAL PRODUCTS AND BIOORGANIC CHEMISTRY

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Organic Synthesis: Applications to Bioorganic Chemistry

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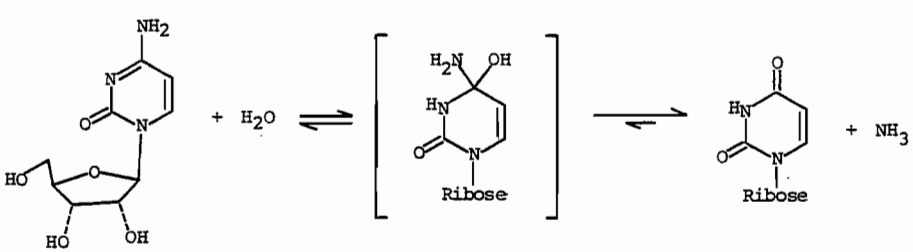
Our work in bioorganic chemistry has a very synthetic basis, in that each of the projects that we undertake starts out with the design and synthesis of a molecule which we think will have a particular effect. My lecture will not focus solely on synthetic chemistry, however, since successful "first-level" solutions to the problems we address seem to raise numerous "second-level" questions. These second level questions, and the implications their answers have for mechanism and structure, often turn out to be more intriguing than the original solutions. I hope I can convince you of this in the course of discussing three projects in the design and synthesis of enzyme inhibitors.

The approach we are using for the design of enzyme inhibitors is to synthesize transition state analogs,[1] taking advantage of the idea that an enzyme has a higher affinity for the transition state of the reaction it catalyzes that it does for the ground state form of the substrate.

I. "Phosphapyrimidines" as Inhibitors of Cytidine Deaminase

Cytidine deaminase catalyzes the conversion shown below; although not much is known about the mechanism of the enzyme-catalyzed process, it presumably involves the carbinolamine intermediate depicted.[2]



MOLECULAR RECOGNITION OF DNA BY SMALL MOLECULES

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Molecular Recognition of DNA by Small Molecules

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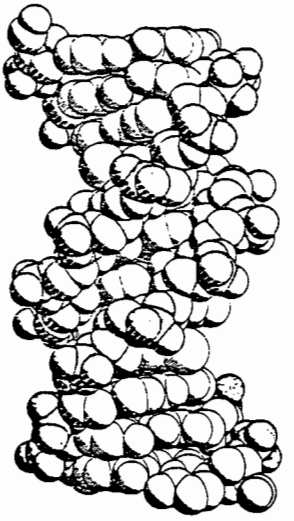
Recent X-ray analysis of crystals of double helical DNA leads to the realization that base sequence information can be stored in the local structure of the helix (1) The question arises whether one could develop a set of rules of recognition for the three dimensional readout of DNA. This would allow the design of synthetic molecules that bind B-DNA of any sequence of any size. We will use the tools of synthetic and mechanistic organic chemistry in combination with nucleic acid techniques such as high resolution gel electrophoresis to define the scope and limitations of this problem. The size of our first synthetic targets will be sufficiently large to cover two to five contiguous base pairs of DNA, up to one half turn of the helix. Because there are four bases possible for each nucleotide position on each strand in the DNA polymer, and within the constraints of the A·T and G·C complementary nature of the helix, the binding site sizes of two to five base pairs means that there are 10, 32, 136, and 512 unique combinations of base pairs or specific binding sites on DNA, respectively. Therefore our first priority was to develop the analytical techniques necessary to analyze the sequence specificities of either natural or designed synthetic DNA binding molecules. These methods are called MPE·Fe(II) footprinting (2-8) and affinity cleaving (9-15). The solution to this design/synthesis/footprinting or affinity cleaving exercise is relevant to a general problem in organic chemistry of refining our understanding of the rules of macromolecular recognition and the nature of intermolecular interactions. What is the combination of multiple weak interactions such as hydrophobic, hydrogen bonding and electrostatic forces that afford optimal macromolecular recognition? Within the nucleic acid area, the development of synthetic molecules that can read DNA of any sequence and size will lead to the development of new research tools for use in molecular biology, diagnosis of disease states at the DNA level, mapping of human chromosomes and novel chemotherapeutic strategies.



THE CHEMISTRY OF ANIONS IN THE GAS PHASE

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THE CHEMISTRY OF ANIONS IN THE GAS PHASE

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The chemical reactivity of an anion in the gas phase is perturbed neither by solvation nor by the presence of a counterion. As a consequence one can examine its intrinsic reactivity, determine its heat of formation and investigate such fundamental properties as its basicity and electron-binding energy. One can also generate a host of ions which have not as yet been prepared in solution, and investigate for the first time their chemical and physical properties.[1,2]

The instrument we use for our gas-phase anion studies is known as a flowing afterglow[3] (FA) and is shown in fig. 1. It consists of a meter-long

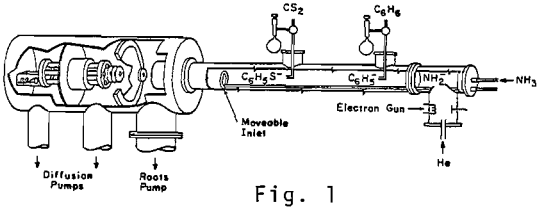

Fig. 1

CHEMICAL CONTROL: COMBINING PHOTOCHEMISTRY WITH ELECTROCHEMISTRY

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CHEMICAL CONTROL:
COMBINING PHOTOCHEMISTRY WITH ELECTROCHEMISTRY

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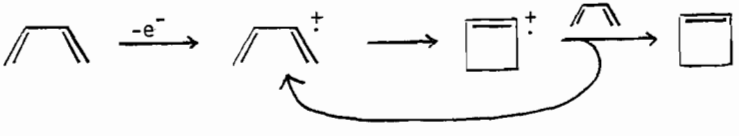
Much of the significant recent work in organic chemistry has sought to discover new chemical pathways in which molecules could be selectively activated, using a reagent in repetitive cycles (i.e., as a catalyst), in a stereocontrolled fashion (i.e., in a defined three dimensional environment). Inherently, electrochemical transformations feature methods by which all three goals might be accomplished. The poised electrode surface thus can selectively oxidize or reduce a specific functional group because of defined redox potentials or preferential adsorption, can provide "switchable" catalysis for reactions initiated by electron transfer, and can provide chemically determinative surface effects.[1] In addition, the ability to switch reactions on or off either by time-controlled application of potential or by photoactivation of light responsive electrodes provides a powerful method for studying the synthetic and mechanistic features of a given transformation.[2]

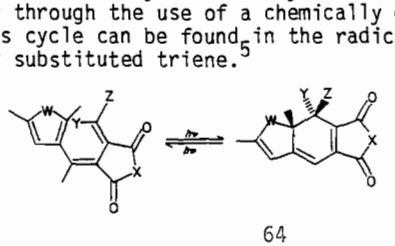
Electrochemical techniques can provide access to new catalytic routes. For example, redox reactions generate radical ions, a class of reactive intermediates whose properties are still poorly understood. A major challenge in fruitfully employing these reactive intermediates lies in restricting their reactivity to the desired path from among the many possible routes open to them: radical cations, for example, are known to dimerize, to disproportionate, to deprotonate, to react with nucleophiles, and so forth. Only if a desired route can be reasonably predicted from among conceivable alternatives can these species become useful in chemical reactions.

One little explored role for radical ions is as catalysts for pericyclic reactions.[3] The dramatic rate acceleration by cation radicals of the Diels-Alder reaction is one example of the profound effects on kinetics which redox reactions can exert. Electrocyclic reactions might also be affected by the addition or removal of an electron. For example, a catalytic cycle might be envisioned



in which a diene ion radical cyclizes, before acting itself as a redox reagent with another molecule of its diene parent to generate ring-closed product and to reform the radical ionic catalyst. In principle, either radical cations or radical anions could function in this way. Initial entry into the cycle could be effected either in an electrochemical cell or through the use of a chemically generated mediator.[4]

One example of this cycle can be found in the radical anionic catalysis of the cyclization of a highly substituted triene.[5]



W = X = O; Y = Z = CH₂

MOLECULAR CELLS, THEIR GUESTS, PORTALS, AND BEHAVIOR

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MOLECULAR CELLS, THEIR GUESTS, PORTALS, AND BEHAVIOR

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In organic chemistry, complexing partners have been divided into two important classes (hosts and guests). Hosts contain convergently arranged binding sites, and are synthetic counterparts of the receptor sites of enzymes, nucleic acids, proteins of the immune system, or ionophores. Guests possess divergently arranged binding sites, and are the synthetic counterparts of substrates, inhibitors, drugs, or cofactors such as metal cations. Complexes are composed of hosts and guests that are held together in solution in a definite structural relationship. Solvation is usually nonstructured complexation which competes with structured complexation between hosts and guests. Forces available for complexation are: hydrogen bonding, ion pairing, pi-acid to pi-base attractions, metal ion to ligand attractions, van der Waals attractions, and the entropic component of desolvation.[1]

Multiple binding sites are needed for the structuring of complexes since the binding energy and orienting power at a single contact site are low compared to the energy of a covalent bond. The design of complexes is aided by two guiding principles. The principle of complementarity states that "to complex, hosts must have binding sites which cooperatively contact and attract the binding sites of guests without generating strong nonbonded repulsions." The principle of preorganization states that "the smaller the changes in organization of host, guest, and solvent required for complexation, the stronger will be the binding."[2]

HYDROCARBATION

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HYDROCARBATION

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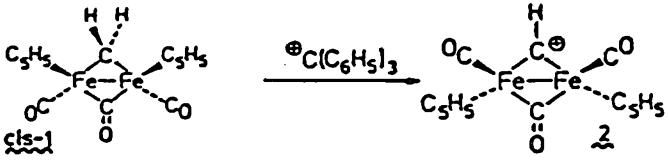
Several years ago we synthesized the first complex with a CH ligand bridging between two metals by reaction of the bridging methylene complex 1 with the hydride abstracting reagent $(C_6H_5)_3C^+ PF_6^-$.[1] This methylidyne complex, 2, which is characterized by the remarkably far downfield chemical shifts of the methylidyne proton (δ 22.8) and the methylidyne carbon (δ 490.2), can be viewed as a relatively stabilized carbocation--certainly more stable than its precursor, $(C_6H_5)_3C^+$. Electron donation from two iron centers accounts for the thermodynamic stability of 2. As expected, 2 reacts with amines, alcohols, and CO to form 1:1 adducts.



CARBON-CARBON COUPLING REACTIONS CATALYZED BY PALLADIUM

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CARBON-CARBON COUPLING REACTIONS CATALYZED BY PALLADIUM

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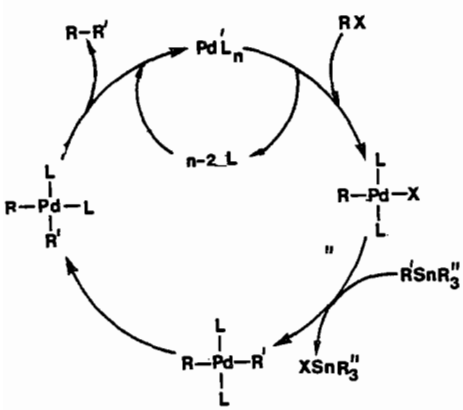
A new palladium catalyzed cross-coupling reaction of organotin reagents with a variety of organic electrophiles that generates a new carbon-carbon bond has been developed recently. Because this mild, versatile reaction is tolerant of a wide variety of organic functionality on either coupling partner, is stereospecific, and gives high yields, it is ideal for use in the synthesis of functionalized organic molecules.

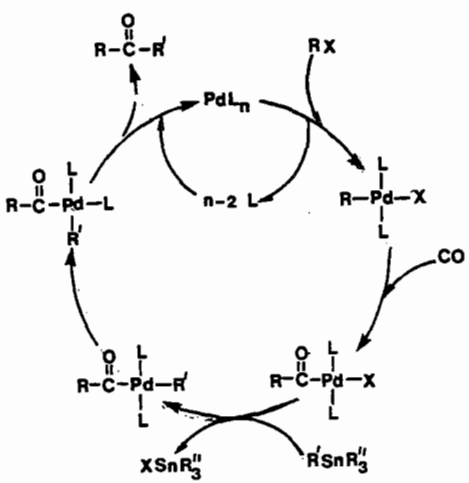
Two general types of catalytic coupling reactions have been carried out. In direct catalytic coupling reactions, acid chlorides, organic halides, and vinyl triflates have been utilized. The proposed catalytic cycle (Scheme 1) serves to illustrate how this coupling reaction works; the mechanisms of some of the individual steps in this cycle have been established.

If, however, carbon monoxide is present in the reaction, CO insertion can take place subsequent to the oxidative addition step to yield an acylpalladium complex (Scheme 2). Thus, a ketone synthesis can be obtained by running the coupling reaction in the presence of CO (carbonylative coupling).



Scheme 1

Direct Coupling



Scheme 2

Carbonylative Coupling

SYNTHETIC STUDIES OF BORON-CONTAINING MACROLIDES

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SYNTHETIC STUDIES OF BORON-CONTAINING MACROLIDES

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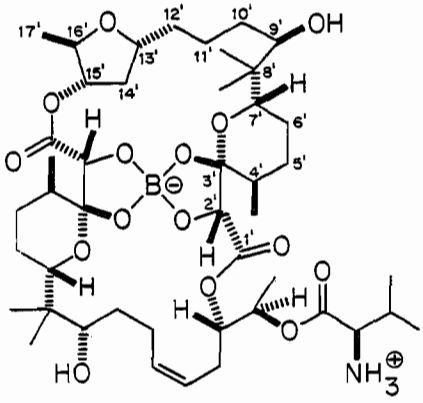
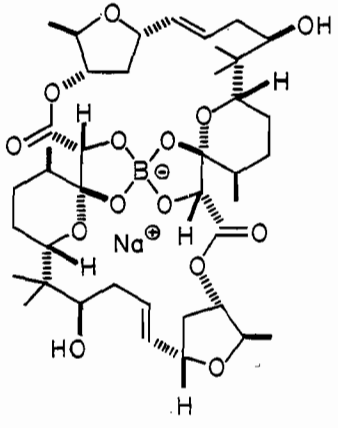
The ionophores boromycin and aplasmomycins A, B, and C are unique among natural products for their incorporation of the element boron. The function of borate at the core of these Streptomyces metabolites appears to be primarily that of a counterion to the encapsulated alkali metal cation (Na^+).



Boromycin



Aplasmomycin A

Structural studies on boromycin [Dunitz, Prelog et al., Helv. Chim. Acta, 1971, 54 1709] and aplasmomycin [Okami et al., J. Antibiot. (Tokyo), 1978, 31, 632] reveal a close stereochemical correspondence between these macrolides. In particular, the identical halves of aplasmomycin differ from the upper ("northern") half of boromycin only in the presence of unsaturation at C-11',12'. The lower ("southern") half of boromycin contains a structurol unit which, in principle, can give rise to the tetrahydrofuran moiety of the upper

SIGMATROPIC REARRANGEMENTS IN HETEROCYCLIC SYNTHESIS

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SIGMATROPIC REARRANGEMENTS IN HETEROCYCLIC SYNTHESIS

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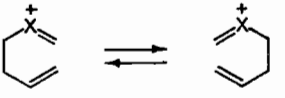
University of California, Irvine, CA 92717

The development of versatile methods for forming carbon-carbon bonds under mild conditions is a central objective of synthetic organic chemistry. For several years,[1] our laboratory has been investigating cationic 2-hetero-Cope rearrangements (Fig 1) as useful vehicles for developing new transformations of this type. Three features of these rearrangements

Figure 1.

CATIONIC 2-HETERO-COPE REARRANGEMENTS



X = NR : cationic aza-Cope rearrangement

2-azonia-[3,3]-sigmatropic rearrangement

must be irreversible to be of use in synthesis

are particularly attractive: (a) they occur under remarkably mild conditions, typically near room temperature and often at neutral pH, (b) a variety of methods are available for preparing the starting iminium ions (or oxonium ions, etc.) and (c) [3,3]-sigmatropic rearrangements occur with a predictable high level of stereocontrol. This lecture will examine some of the highlights our investigations of cationic aza-Cope rearrangements as well as our very recent studies of cationic oxa-Cope rearrangements.

The cationic aza-Cope rearrangement (2-azonia-[3,3]-sigmatropic rearrangement) was first described by Horowitz and Geissman in 1950[2] (Fig 2). For cationic aza-Cope rearrangements to be of general use in synthesis,

RECENT ADVANCES IN ASYMMETRIC SYNTHESIS

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RECENT ADVANCES IN ASYMMETRIC SYNTHESIS

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The polyether antibiotics represent the newest significant class of naturally occurring substances that have been discovered during the last decade.[1] The important chemical property associated with this group of substances stems from their ability to readily complex with inorganic ions. As a consequence, the term "ionophore" has evolved to associate this property with this class of natural products. The coincident pioneering, but accidental, discovery of the crown ethers by Pederson (1967) and the subsequent development of this class of ion-complexing ligands by Cram and related aza-analogs (Cryptands) by Lehn has collectively demonstrated the importance of ion-complexing organic molecules to the fields of both chemistry and biology. Relevant reviews covering the isolation, structure and synthesis of the naturally occurring ionophore antibiotics,[2] as well as the synthetic crown ethers[3] should provided the reader with an excellent background to this topic.

The challenges associated with the rational design and synthesis of this class of naturally occurring compounds places one at the limits of current technology in the area of chemical synthesis. By inspection, target structures such as lasalocid, calcimycin and ionomycin contain not only a multitude of asymmetric centers (7-14) but also an array of heteroatom functionality. Any contemplation of the syntheses of these molecules rapidly identifies