Nomenclature of Macrocyclic Compounds by Sequential Citation

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A nomenclature is proposed for cyclic compounds in general, with specific applicability to macrocyclic systems such as "crown ethers" or "cryptands". The nomenclature is based on approved IUPAC names for bivalent radicals and follows the concepts of structure-based polymer names. A macrocycle is named, beginning with the prefix cyclo, by citing from an established order of seniority the most senior unit in the cycle, followed by sequentially citing the remaining units in order in the direction of the nearest unit next lower in seniority. Bridges are also cited sequentially, while substituents are cited by substitutional principles.

During the last 15 years, the field of macrocyclic chemistry has grown rapidly. A large part of this evolution has been concerned with large ring systems containing heteroatoms. The simpler systems have acquired trivial names, e.g., "18-crown-6", that cannot accomodate substituents or other complexities. Family names, e.g., "crown ethers", "chorands", "cryptands", "cavitands", etc., clearly have their limitations, and a comprehensive nomenclature cannot be designed around them.

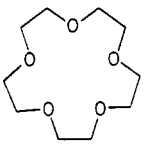
This is not to say that there is no systematic nomenclature for macrocyclic compounds. Conventional IUPAC rules[1] for organic nomenclature lead to unequivocal but frequently cumbersome and complicated names. While indexing and retrieval have been adapted to the IUPAC names, the names are often difficult to use in speech or writing.

The purpose of the nomenclature proposed here is to provide a systematic way to name not only macrocycles but, in principle, any cyclic structure. Because it is systematic and unambiguous, the nomenclature can be handled by computer. Because it is simple in concept, utilizes accepted bivalent radical names, and requires few unfamiliar conventions outside the IUPAC organic and polymer rules, it leads to readily recognized names, relatively easily used in all forms of chemical communication.

It is stressed that although the IUPAC Commission on Nomenclature of Organic Chemistry has reviewed this proposal, it has not been adopted; the Chairman of that Commission urged that it be published. It is hoped that the usefulness of the proposal will be demonstrated through acceptance by the chemical community.

This nomenclature system is based on the view that cyclic compounds are chains of atoms with the chain ends joined together. A macrocycle with repeating units in the structure is seen to be a polymer chain without end groups. Thus, a structure-based polymer nomenclature can be adapted to cyclic structures. Such a system exists, and it has IUPAC approval.[2]

Conceptually, generation of a name under this proposal amounts to sequentially reciting the constitutional units in the cyclic structure by using conventional bivalent radical names and multiplying prefixes where repetition occurs. "Cyclo" is prefixed to the name of the cycle. Wherever the cycle has more than one kind of constitutional unit such as a heteroatom, a unit containing unsaturation or substitution, or an integral ring, it is necessary to define a starting point (an order of seniority) and a direction in which to proceed with the sequential citation. For example, because O is senior to C the simple compound known as "15-crown-5" is



cyclo[pentakis(oxyethylene)]
IUPAC name: 1,4,7,10,13-pentaoxacyclopentadecane

A full explanation of this principle and the method, in rule form (Chart I) through which names of cyclic compounds can be generated are presented in the remainder of this paper.

(1) MACROCYCLIC CONSTITUTIONAL UNIT (MCU)

(1.1) General Principles. To generate the name of a macrocyclic compound under this nomenclature system, a stepwise analysis of the structure must first be carried out in the following order: (1) select the base cycle; (2) minimize bridges by combination with the base cycle to yield an expanded base cycle; (3) identify the macrocyclic constitutional unit (MCU). A sequential citation of the individual constitutional units of the MCU gives the name of the MCU; the name of the macrocyclic compound is cyclo(MCU).

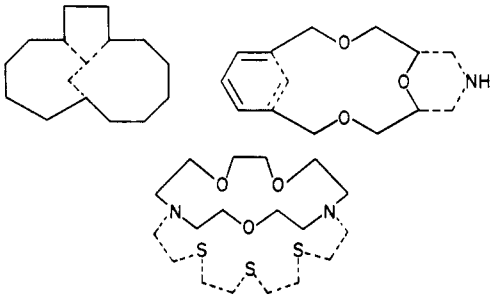
(1.1.1) Base Cycle. Every cyclic compound contains at least one continuous circle of atoms bound together in a specific sequence. The circle of atoms has no terminus, but the atoms may have substituents bound to them, and often, two atoms in the circle are bound to each other through an entity that acts as a bridge between them. Under the latter circumstance, more than one continuous circle is possible. This nomenclature rests on the initial selection of a preferred circle of atoms termed the *base cycle*.

Definition of the base cycle depends only on the number and kind of atoms in a continuous sequence. The base cycle will be one that contains the highest number of the most senior atom in the declining series O, S, Se, Te, N, P, As, Sb, Bi, C, Si, Ge, Sn, Pb, B, Al, with other atoms placed in the list as indicated by their positions in the periodic table (see p 459 of footnote 1). Where there is further choice, successive preference is given to (a) the cycle having, in addition, the highest number of each of the next senior atoms, in order, (b) the cycle with the longest continuous sequence of atoms, and (c) the cycle that ultimately provides the minimum number of bridges (see rule 1.1.2).

Chart I. Rules for Sequential Citation Nomenclature for Macrocyclic Compounds

(1) macrocyclic constitutional unit (MCU)
  (1.1) general principles
    (1.1.1) base cycle
    (1.1.2) treatment of bridges
    (1.1.3) identification of the MCU
    (1.1.4) generic name
  (1.2) seniority and direction of citation in the MCU
  (1.3) replacement nomenclature
  (1.4) fixed numbering in the units of the MCU
  (1.5) inclusion of substituents in trivial names of units
(2) sequences of repeated units in the MCU
  (2.1) generic names with repeating unit citations
  (2.2) seniority in a MCU containing constitutional repeating units
  (2.3) maximization of repetition in citations
(3) substitution in the MCU
  (3.1) numbering of the MCU
    (3.1.1) radical names for macrocyclic systems
  (3.2) bridges as part of the MCU

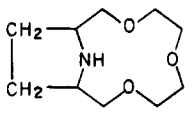
In the following structures, the base cycle is indicated by solid lines:



In each case, the dashed lines indicate bridging units that are not part of the base cycle.

(1.1.2) Treatment of Bridges. A bridge is a valence bond, an atom, or an unbranched chain of atoms connecting two different parts of a molecule (Organic Rule A-31 of footnote 1). After the base cycle is selected, the number of bridges between any two atoms in the base cycle is minimized by combining, as far as possible, each of them with atoms of the base cycle to form ring structures. Of the two possible rings thus formed in each case, the one with the smaller number of ring atoms will become a ring unit in the now-expanded base cycle.

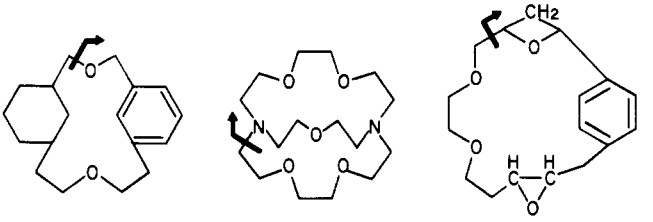
The general rule is that the expanded base cycle will have within it, in addition to atoms or chains of atomic groups, only monocyclic rings, the bivalent radicals of which can be the named by conventional organic nomenclature, or polycyclic rings that have accepted trivial names allowed by Organic Rules A-21.2, A-23,1, B-2, or D-Table IV of footnote 1:



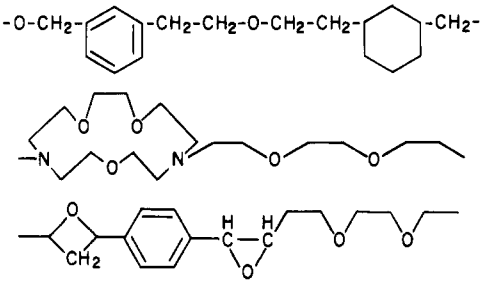
In this structure, the $-CH_2CH_2-$ bridge connecting two carbon atoms in the base cycle is considered to be part of a pyrrolidine ring. The ring unit, 2,5-pyrrolidinediyl, is part of the expanded base cycle.

(1.1.3) Identification of the MCU. The MCU is the polyvalent (but usually bivalent) sequence of atoms and/or rings that results when the expanded base cycle undergoes *one* hypothetical scission of a bond outside of a ring unit and adjacent to the most senior unit in the sequence. Where there is a choice, the scission is made to place the most senior unit as close as possible to the nearest unit of equal or next lower seniority. Valency of the MCU is minimized only after all other orders of seniority have been observed.

In the following structures, the point of hypothetical scission and the direction of decreasing seniority is indicated by the arrow:



Seniority rules are elaborated below. The MCU for these structures are



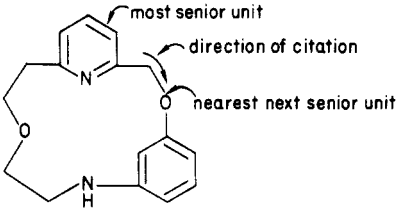
(1.1.4) Generic Name. The MCU identified by the above procedures consists of a series of constitutional units that can be named by IUPAC organic nomenclature rules.[1] The entire MCU can be named within the restrictions of directional citation given by the IUPAC structure-based polymer nomenclature rules.[2] The name of the macrocycle is formed by citing consecutively, in the sequence in which they appear, the names of the individual, usually bivalent, constitutional units, beginning with the most senior unit and proceeding in the direction of the nearest next most senior unit. Thus, the generic name of A–C–B–D–E, where the order of seniority is A, B, C, D, and E, is cyclo(ACBDE), in which the letters each represent the name of an individual unit.

(1.2) Seniority and Direction of Citation in the MCU. The order of seniority among the classes of bivalent units in a MCU is (1) *heterocyclic rings*, followed by (2) *heteroatoms*, (3) *carbocyclic rings*, and (4) *carbon atoms*, in that order. This order is unaffected by the presence of substituents that are not part of the main sequence of the MCU, even though such substituents could be expressed as part of a trivial name for a bivalent unit. Within a class, the order of seniority is that delineated in the IUPAC structure-based polymer rules.[2] Cyclic bivalent units are chosen to minimize the number of bridges cited (see rules 1.1.2 and 3.2) in the macrocycle. Unsaturation other than in ring units in the main sequence will be used to designate the most senior unit in the MCU only after all other orders of seniority have been observed; in such cases, seniority decreases with decreasing degree of unsaturation.

Among heterocyclic ring systems, the descending order of seniority is (a) a ring system with nitrogen in the ring, (b) a ring system containing a heteroatom (in absence of nitrogen) as high as possible in the order given in rule 1.1.1, (c) a ring system containing the greatest number of rings, (d) a ring system having the largest individual ring, (e) a ring system having the largest number of heteroatoms of any kind, (f) a ring system containing the greatest variety of heteroatoms, and (g) the ring system having the greatest number of heteroatoms highest in the order given in rule 1.1.1. Further examples of the application of seniority in heterocyclic ring systems are given elsewhere.[2]

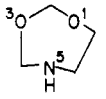
Macrocycles in which the senior unit is a carbocyclic ring system are named by citing first the carbocyclic ring of highest seniority and proceeding by the shorter path, in descending order of seniority, to (a) another of the same carbocycle, (b) the carbocyclic system next in seniority, and (c) the acyclic group appearing earliest in the alphabet. Carbocyclic ring system seniority decreases with increasing degree of hydrogenation or decreasing number of double bonds, irrespective of ring size, and within a group of rings with the same degree of hydrogenation decreases with decreasing ring size or number of rings. The basis for further choice is found in Organic Rule C-14.1 of the IUPAC rules.[1]

The name of the MCU is formed by citing the name of the most senior unit, followed in turn by the names of each of the succeeding units, proceeding along the MCU in the direction of the nearest unit of equal or next lower seniority. Choice of shortest path is determined by the rules of structure-based polymer nomenclature:[2]



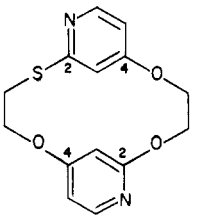
cyclo(2,6-pyridinediylmethyleneoxy-1,3-phenyleneiminoethyleneoxyethylene)

(1.3) Replacement Nomenclature. As an alternative to these rules, the MCU may be named by replacement nomenclature wherever the MCU consists only of carbon atoms and heteroatoms, and a shorter name results:

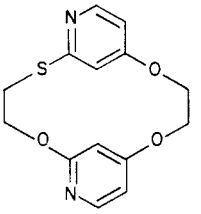


cyclo(1,3-dioxa-5-azaoctamethylene)
or cyclo(oxymethyleneoxyethyleneiminoethylene)

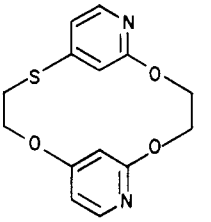
(1.4) Fixed Numbering in Units of the MCU. Units of the MCU that have fixed numbering retain that numbering in naming the individual units of the MCU; these units are usually derived from heterocyclic ring systems, polycyclic hydrocarbons, bridged hydrocarbons, and spiro systems. Free valences in the bivalent units are numbered as low as possible, consistent with the fixed numbering:



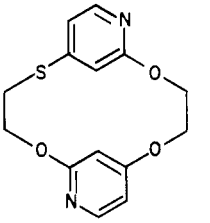
cyclo(2,4-pyridinediyloxyethyleneoxy-2,4-pyridinediyloxyethylenethio)



cyclo(2,4-pyridinediyloxyethyleneoxy-4,2-pyridinediyloxyethylenethio)



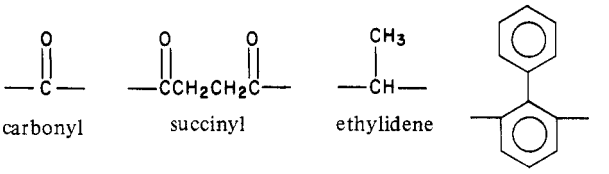
cyclo(4,2-pyridinediyloxyethyleneoxy-2,4-pyridinediyloxyethylenethio)



cyclo(4,2-pyridinediyloxyethyleneoxy-4,2-pyridinediyloxyethylenethio)

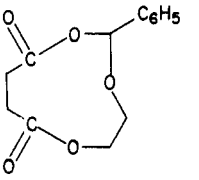
Locants for substitution in the macrocycle are independent of fixed numbering of the individual units (see rule 3.1).

(1.5) Inclusion of Substituents in Trivial Names of Units. The MCU and its directional orientation are established on the basis of all of the atoms and rings that form a part of the base cycle or the expanded base cycle. Under some circumstances, a simplified name can result if certain substituents are expressed in a trivial name of a unit. Examples of such units are



2,6-biphenylylene

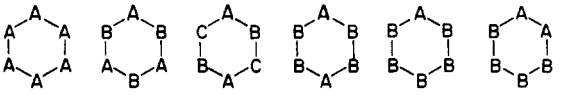
If no other kind of substitution is present in the macrocycle, such trivial names may be used in forming the name of the MCU; in all other cases, the name is formed according to rule 3 with all appended moieties cited as substituents:



cyclo(oxybenzylideneoxyethyleneoxysuccinyl)

(2) SEQUENCES OF REPEATED UNITS IN THE MCU

(2.1) Generic Names with Repeating Unit Citations. A MCU may contain sequences of constitutional repeating units (CRU). Examples are for MCU



and for CRU

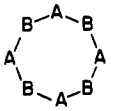
-A- -AB- -ABC- -ABB- -B- -A-, -B-

These MCU's are named according to rule 1 except that an appropriate multiplying prefix is placed ahead of the name

of each CRU. The generic names of the above examples are cyclo(hexaA), cyclo[tris(AB)], cyclo[bis(ABC)], cyclo[bis-(A-diB)], cyclo(A-pentaB), cyclo(diA-tetraB), where A, B, and C are the names of units in that order of decreasing seniority. Additional examples are

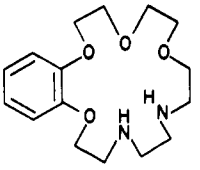
cyclo[tris(Abis(BC)B)]

cyclo[bis(diA-B)]

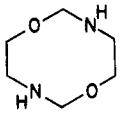


cyclo[tetrakis(AB)]
not cyclo[bis[bis(AB)]]
not cyclo[Atris(BA)B]
not cyclo[bis(ABAB)]

(2.2) Seniority in a MCU Containing Constitutional Repeating Units. Seniority and direction of citation in the MCU are determined by the principles given in the preceeding rules; this determination is made before the name is generated:

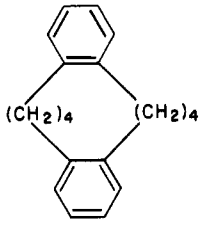


cyclo[oxy-1,2-phenylenetris-(oxyethylene)bis(iminoethylene)]

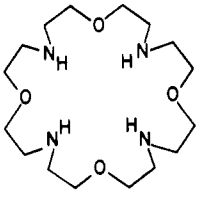


cyclo[bis(oxymethylene-iminoethylene)]

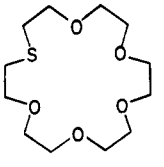
(2.3) Maximization of Repetition in Citations. After seniority and direction of citation have been established, the preferred name will maximize the multiplying prefix denoting the number of times a CRU is repeated in a sequence in the MCU:



cyclo[bis(1,2-phenylenetetramethylene)]
not cyclo(1,2-phenylenetetramethylene-1,2-phenylenetetramethylene)

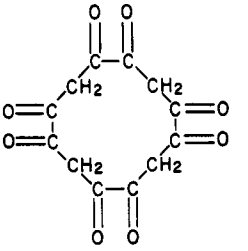


cyclo[tetrakis(oxyethyleneiminoethylene)]
not cyclo[bis[bis(oxyethyleneiminoethylene)]]
not cyclo[bis(oxyethyleneiminoethyleneoxy-ethyleneiminoethylene)]



cyclo[pentakis(oxyethylene)thioethylene]
not cyclo[tetrakis(oxyethylene)oxyethylene-thioethylene]

The smallest CRU will be selected for repetition:

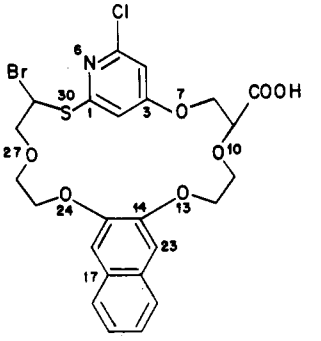


cyclo[tetrakis(1,2-dioxotrimethylene)]
not cyclo[bis(1,2,4,5-tetraoxohexamethylene)]
not cyclo[bis(3,4-dioxoadipoyl)]
not cyclo[tetrakis(malonyl)]

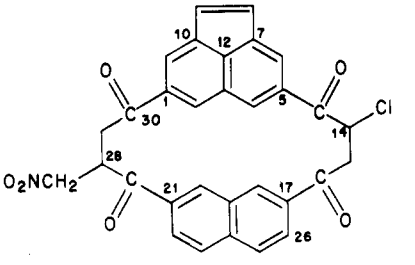
(3) SUBSTITUTION IN THE MCU

Substituents to the MCU and its unit parts are cited by prefixing the name(s) of the substituents in alphabetical order, with appropriate locants, to the term "cyclo" followed by the name of the MCU: *x*-P-*y*-Qcyclo(ABC), where *x* and *y* are locants and P and Q are substituents. The structure, directional orientation, and name of the MCU are established before locants for substituents are determined; where there is a choice, lowest numbers will be used for substituents.

(3.1) Numbering of the MCU. Following the selection of the MCU, its atoms, including those in rings that form part of the MCU, are numbered beginning with the most senior unit in the cycle and proceeding in the direction of the next most senior unit. If the most senior unit is a ring system, numbering will begin at the ring atom that is furthest by the shortest path from the next most senior unit and proceed around the ring system beginning with that shortest path:



29-bromo-9-carboxyl-5-chlorocyclo[2,4-pyridinediylbis(oxyethylene)oxy-2,3-naphthylenebis(oxyethylene)thio]

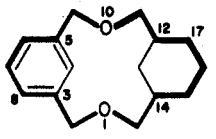


14-chloro-22,28-bis(nitromethyl)-13,16,27,30-tetraoxocyclo(4,7-acenaphthylenetetra-methylene-2,7-naphthylenetetramethylene)

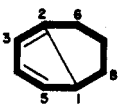
Additional examples of numbering are shown in rule 3.2.

(3.1.1) Radical Names for Macrocyclic Systems. Radicals derived from macrocyclic systems by removal of one or more hydrogen atoms from one or more atoms in a MCU or a bridging unit are named by adding "-yl", "-ylidene", "-diyl", "-triyl", etc., as appropriate, to the name of the system. Locants are determined by the numbering of the entire system.

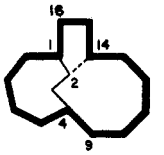
Chart II



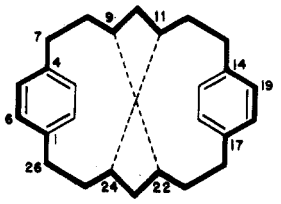
cyclo(oxymethylene-1,3-phenylenemethyleneoxymethylene-1,3-cyclohexylenemethylene)



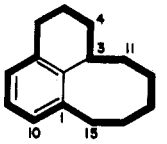
cyclo(2,4-cyclopentadien-1,2-ylenetrimethylene)



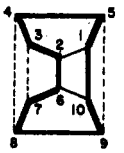
$O^{2,14}$-cyclo(1,4-cyclooctyleneoctamethylene)



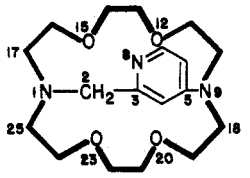
$O^{9,22},O^{11,24}$-cyclo[bis(1,4-phenyleneheptamethylene)]



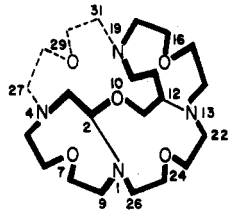
cyclo(1,8-tetrahydronaphthalenediylpentamethylene)



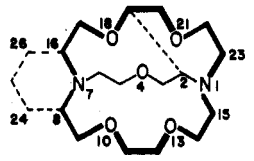
$O^{3,7},O^{4,8},O^{5,9}$-cyclo[di(1,2-cyclopentylene)]



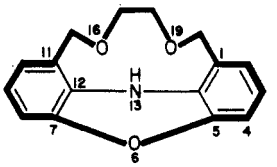
cyclo[[2,4-pyridinediyliminoethylenebis(oxyethylene)iminomethylene]-7,16-diylbis(ethyleneoxy)ethylene]



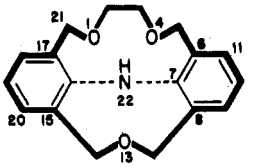
4,19-ethyleneoxyethylenecyclo[cyclooxyethylenebis(iminoethylene)]-4,5-diyloxymethylenecyclo(oxyethyleneiminotrimethyleneiminoethylene)-5,4-diylethyleneoxyethylene]



8,16-trimethylene-$O^{2,19}$-cyclo[cyclo[bis(oxyethyleneiminoethylene)thioethylene]-4,10-diylbis(ethyleneoxy)ethylene]

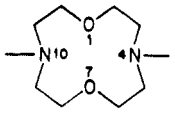


cyclo(1,9-phenoxazinediylmethylene-oxyethyleneoxymethylene)



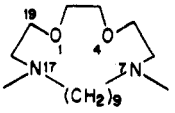
7,16-iminocyclo[oxyethylenebis(oxymethylene-1,3-phenylenemethylene)]

Free valences are treated in the same way as substituents in determining seniority of units:

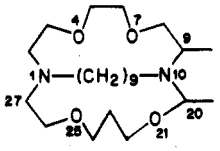


cyclo[bis(oxyethyleneiminoethylene)]-4,10-diyl

Radical names are useful in naming ring units in a MCU. In such cases, the ring unit, as an MCU in its own right, is treated in the same way as any other heterocyclic unit with regard to numbering or seniority:

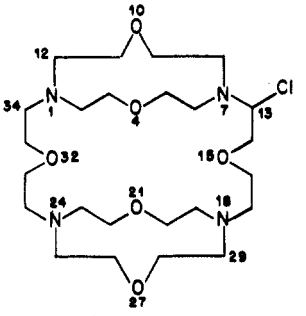


cyclo[bis(oxyethylene)iminononamethyleneiminoethylene]-7,17-diyl



cyclo[cyclo[bis(oxyethylene)iminononamethyleneiminoethylene]-7,17-diylmethyleneoxytrimethyleneoxyethylene]-9,20-diyl

To maximize repetition (rule 2.3) and minimize bridging (rule 3.2), the names of macrocyclic polyvalent radicals are used in the formation of names of macrocyclic systems:



13-chlorocyclo[bis[cyclo[bis(oxyethyleneiminoethylene)]-4,10-diylethyleneoxyethylene]]

(3.2) Bridges as Part of the MCU. Following selection of the base cycle in a given structure, bridges, if any, are combined with the base cycle to form an expanded base cycle containing ring units. This process is subject to the following conditions:

(a) Combination is made in a way that yields the minimum number of uncombined bridges. Where there is a choice, combination is to provide units of highest seniority (subject to the following paragraphs) in the expanded base cycle; for

further choice, the bridge with lowest locants will remain uncombined.

(b) The expanded base cycle may have as ring units only monocyclic rings, or where they have trivial names allowed by Organic Rules A-21.3, A-23.1, B-2, or D-Table IV in footnote 1, polycyclic rings are permitted.

(c) When a bridge is combined with another part of the structure, the ring with the least number of atoms will be the choice as a unit in the expanded base cycle unless the larger unit is part of a polycyclic ring having an allowed trivial name. In a choice between the rings of the same size, the more senior ring will be taken as part of the expanded base cycle.

(d) Bridges will be combined with other parts of the structure in the following order: (1) bridges between atoms in the base cycle; (2) bridges between atoms within one bridge; (3) bridges between atoms in the base cycle and a ring unit of the expanded base cycle; (4) bridges between atoms in different ring units. The minimum number of bridges remaining after the above combinations have been carried out will be treated in the same way as substituents in forming the name of the macrocycle. A zero-atom bridge will be cited in the form $O^{x,y}$, where x and y are locants for the bridge.

In the examples of cyclic structures containing bridges shown in Chart II, the base cycle is shown in heavy lines; numbering is that of the system after bridge combinations have been made.

ACKNOWLEDGMENT

I express my appreciation to Joy E. Merritt for her many valuable criticisms and suggestions; she contributed in a major way to the improvement of the nomenclature system proposed in this paper.

REFERENCES AND NOTES

(1) International Union of Pure and Applied Chemistry "Nomenclature of Organic Chemistry"; Pergamon Press: Oxford, 1979; Sections A–F and H.
(2) "Nomenclature of Regular Single-Strand Organic Polymers". *Pure Appl. Chem.* **1976**, *48*, 373–385.

Voice-Operated Microcomputer-Based Laboratory Data Acquisition System To Aid Handicapped Students in Chemistry Laboratories

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A voice-entry microcomputer system is described that consists of a Voice-Operated Isolated Command Entry (VOICE) terminal connected to a previously developed talking microcomputer-based data acquisition system. The system has been used to carry out a titration experiment with voice commands, and it can be used to aid a student in performing a number of undergraduate chemistry experiments as well as function as a voice-entry scientific calculator. This system will enable students with upper limb disabilities to participate in chemistry laboratory experiments that use standard chemical instruments.

INTRODUCTION

Students with disabilities of the upper limbs face high occupational barriers if they plan to enter technical fields where manipulative skills are required. We have attempted to lower some of the barriers by applying microcomputer technology to the problems of giving them access to genuinely instructive laboratory experiences in chemistry. Since chemistry courses are required as cognates for degrees in all the natural sciences, in every branch of engineering, and in most of the health professions, lowering the barriers that keep persons with upper limb disabilities from taking chemistry courses will improve their access to many other fields. Because of the great and ever-increasing importance of instrumental measurements in chemistry and in other fields in which chemistry is a useful tool, we have chosen to concentrate on the objective of facilitating the use of chemical instruments by students with upper limb disabilities in order to increase their independence in chemistry laboratories. Microcomputers and voice-recognition technology provide effective means of realizing this objective. Using commercially available technology, we have developed a voice-command recognition system that will enable persons with upper limb disabilities to acquire laboratory data and control chemistry experiments by giving voice commands to an existing laboratory microcomputer.

We have previously described a microcomputer-based Universal Laboratory Training and Research Aid (ULTRA) that we developed to aid blind students in undergraduate chemistry laboratories.[1,2] This system consists of a portable microcomputer equipped with voice output, keyboard input, and a variety of analog and digital inputs and outputs. It comes with an extensive software package designed to perform most of the instrumental measurements now done in freshman and sophomore chemistry laboratories.

The ULTRA system can be interfaced with a wide variety of instruments and sensors and is programmed to assist the student during experiments and during subsequent data analysis tasks. The ULTRA software includes a program that functions as a talking scientific calculator so handicapped students can perform calculations on the data they collect during a laboratory experiment. The blind student controls the computer and enters data through a standard keyboard; the computer's principal means of communication with blind students is spoken words generated by a speech synthesizer. The ULTRA system is also capable of functioning as a talking terminal to a large central computer, so students can use it to obtain access to other educational materials.

In this paper, we discuss extensions we have made to the ULTRA system by adapting it to accept voice commands, and we discuss a voice-operated titration we carried out by using

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