Properties of Retinoids

Structure, Handling, and Preparation

Arun B. Barua* and Harold C. Furr

Abstract

Retinoids are unstable compounds being readily oxidized and/or isomerized to altered compounds, especially in the presence of oxidants including air, light, and excessive heat. They are labile toward strong acids and solvents that have dissolved oxygen or peroxides. In this review, procedures for handling and storage of retinoids and biological samples containing them have been described. The physical and chemical properties of retinoids have been reported. Simplified procedures for derivatizations and purification, and methods for quantitation of retinoids have been presented.

Index Entries: Retinoids; retinoic acid; retinol; properties; storage; handling; derivatization.

1. Structure

Retinoids have been defined as a class of compounds consisting of four isoprenoid units \( (H_2C=C(CH_3)-CH=CH_2) \) joined in a head-to-tail manner. The retinoid molecule can be divided into three parts: a trimethylated cyclohexene ring, a conjugated tetraene side chain, and a polar carbon-oxygen functional group. Retinol (I), retinaldehyde (II), and retinoic acid (III), as well as their derivatives whose structures are shown in Structure 1, are included by this definition.

The conventional numbering of carbon atoms in the retinoid molecule is shown in the structure of retinol (I). On the basis of this numbering scheme, geometric isomers and substituted compounds can be named unambiguously, e.g., 13-cis retinoic acid (IV), 3-hydroxyretinoic acid (V), and 9-cis retinoic acid (VI).

To name retinoids systematically (IUPAC nomenclature), however, a different numbering scheme must be used: the carbon atom bonded to the functional group is given number 1. The numbering of carbon atoms by this scheme is shown in structure III for all-trans retinoic acid. Accordingly, the systemic name for all-trans retinoic acid is (all-trans) 3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)-nona-2,4,6,8-tetraen-1-oic acid, or more simply (all-trans) 3,7-dimethyl-9-(2,6,6-trimethylcyclohexene-1-yl)-2,4,6,8-nonautraenoic acid.

Also note that the terms E and Z are used frequently for trans and cis, respectively. Thus all-trans retinoic acid is also known as all-E retinoic acid. Other names for all-trans and 13-cis (or 13-Z) retinoic acid are tretinoin and isotretinoin, respectively. The same numbering system is also used for the aromatic retinoids, such as etretinate (VII) and acetretin (VIII).

Retinoids are essential for several biological processes, including growth and development, reproduction, and cellular differentiation. However, retinoids are toxic when taken in excess, are irritating to the skin, and are highly teratogenic.

In an attempt to produce retinoids that are efficacious, yet lack toxicity, many new retinoids have been synthesized and tested biologically. Molecular modifications have been made to all three units of the retinoid molecule: the cyclohexene ring, the polyene chain, and the polar end group. Many such retinoids, such as TTNPB (IX), TTNN (X),

*Author to whom all correspondence and reprint requests should be addressed. Department of Biochemistry and Biophysics, Iowa State University, Ames, IA 50011. E-mail: abarua@iastate.edu
Ch-55 (XI), and Am-580 (XII)—which are cyclic, nonpolyisoprenoid compounds—have been shown to be more active than retinol or retinoic acid in several accepted assays for retinoid activity.

Hence the above definition of retinoids has become obsolete. Sporn et al. (2) recently redefined a retinoid as a substance that can elicit specific biological responses by binding to and activating a