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Conformational analysis of retinoic acids: Effects of steric interactions on nonplanar conjugated polyenes

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ABSTRACT

Retinoic acids and other vitamin A analogs contain a trimethylcyclohexenyl ring in conjugation with a polyene chain joined at carbon-6 (C6) and carbon-7 (C7). A MP2-SCS/cc-pVDZ//B3LYP/6-31G(d) 2-D potential energy surface was computed for all-*trans* retinoic acid, which had 6 minima (3 enantiomeric pairs). The global minima were distorted *s-gauche* enantiomers ($\tau_{6-7} = \pm 53°$) with half-chair conformations of the ring. Distorted *s-gauche* enantiomers ($\tau_{6-7} = \pm 55°$) with inverted half-chair ring conformations were 1.7 kJ/mol above the global minima. The *s-trans* enantiomers ($\tau_{6-7} = \pm 164°$) were 11.3 kJ/mol above the global minima. Steric energies were computed by the method of Guo and Karplus to identify key structural elements in retinoic acids which determines their conformation. Small molecule crystal structures in the CCDC database with trimethylcyclohexenyl ring and exocyclic double bonds have ring-chain geometries near to one of the six energy minima of retinoic acids, except for retinaldehyde iminium cations.

1. Introduction

Well before the discovery of vitamin A by McCollum in 1907, many cultures recognized that dietary intake of liver/fish oils reversed night blindness [1]. Today it is well recognized that adequate dietary intake of vitamin A (retinol) from animal sources or provitamin A from plants (carotenoids like β-carotene) is essential for normal nutrition [2]. In mammals, vitamin A dependent tissues first oxidize retinol to retinaldehyde (vitamin A aldehyde), which is the chromophore used in the visual system. Retinaldehyde is irreversibly oxidized to retinoic acid (vitamin A acid), which is essential for normal epithelial tissue growth and differentiation. Retinoic acid prevents epithelial tissues from developing cancer-like lesions first observed in vitamin A deficient animals [3], but it cannot restore vision in vitamin A deficient animals. In 1987, the discovery of nuclear retinoic acid receptors (RARs) independently by the Chambon and Evans groups highlighted the role of retinoic acid as a hormone whose signaling controls epithelial cell growth, differentiation and development [4,5]. Three retinoic acid isomers (all-*trans*-retinoic acid or ATRA; 13-*cis*-retinoic acid or 13cRA; 9-*cis*-retinoic acid or 9cRA – Fig. 1) are potent agonists for RARs and are currently used clinically to treat skin diseases or cancers [6].

Naturally occurring vitamin A analogs (retinol, retinaldehyde, retinoic acid), carotenoids (α-carotene, β-carotene, γ-carotene), and some terpenes (e.g., β-ionone) contain a common structural feature: one or two trimethylcyclohexenyl rings in conjugation with a polyene chain (Fig. 1A). In 1963 Stam and MacGillavry [7] determined the first crystal structure of ATRA in a triclinic crystal. The C5—C6 double bond of the trimethylcyclohexenyl ring of ATRA was in a non-planar *cis*-like conformation relative to the conjugated polyene chain (C6—C7 torsion angle of ~35°). Since this first observation 50 years ago, non-planar polyene structures about the trimethylcyclohexenyl ring have also been observed in X-ray crystal structures of 13-*cis*-retinoic acid [8], retinaldehydes [9–11], and β-carotenes [12–14]. Ten years after the first observation of a distortion in the polyene chain of ATRA, Stam solved the crystal structure of ATRA in a monoclinic crystal [15]. In contrast to their previous structure, the C5—C6 double bond of the trimethylcyclohexenyl ring of ATRA was nearly planar and more conjugated with the polyene chain (C6—C7 torsion angle of 193°). Interestingly, the monoclinic crystal was meta-stable and irreversibly converted to the triclinic form upon heating to 80 °C. Other vitamin A analogs crystallize with a nearly planar *s-trans* conformation between the polyene chain and the trimethylcyclohexenyl ring. These structures are fewer in number and include retinaldehyde iminium salts[16,17].

In 1971, Honig et al. [18] used semi-empirical methods to establish that the distorted *s-cis* geometries (*s-gauche*) of β-ionone

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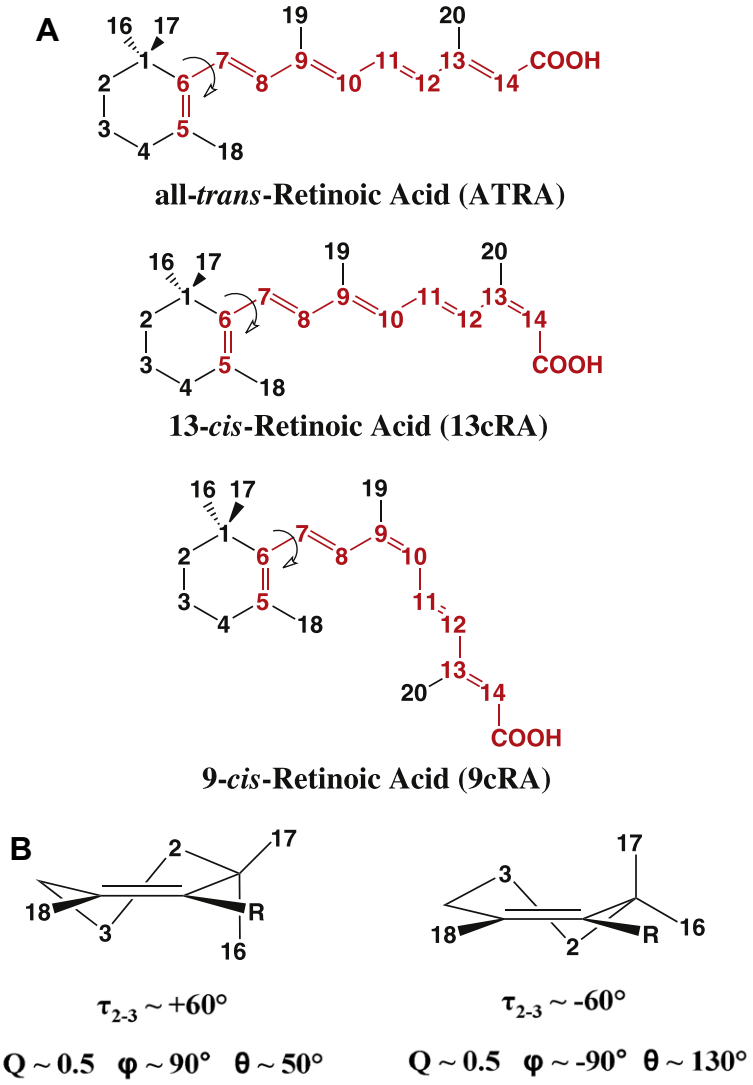

Fig. 1. (A) Chemical structures of 9cRA and ATRA. The structure used for an electronic energy reference in the steric energy calculations are highlighted in red. The retinoic acids are shown in the *s-cis* conformer about the C6—C7 torsion angle. (B) Two low-energy ring conformations of the trimethylcyclohexenyl ring in both 9cRA and ATRA. Also provided are the C2—C3 torsion angles and the ring puckering coordinates (Q, φ, and θ) of the two ring conformations. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and retinaldehydes were lower in energy than the planar *s-trans* geometries by about 20 kJ/mol. Their NMR measurements (NOE and J-coupling analyses) supported significant populations of the non-planar conformers of β-ionone and retinaldehydes. The Poirier group executed a series of Hartree–Fock investigations of retinal analogues, including rotation about the *12-s* bond [19] and rotation about the *6-s* bond [20]. The analog that Poirier and Yadav used in the latter study is almost identical to our compound **11** (*vide infra*). In 2008, 6 low-energy conformers of β-ionone were determined using the B3LYP/6-31G(d,p) level of theory, but the *s-gauche* conformers were similar in energy to the *s-trans* conformers (only 2 kJ/mol higher in energy than *s-gauche*) [21]. Using a variety of semi-empirical or *ab initio* computational approaches, the low-energy conformers of carotenes (including β-carotene) have also been reported in the literature. For β-carotene, the low energy conformers had a distorted *s-gauche* orientation of the trimethylcyclohexenyl ring relative to the polyene chain, but the stability of the *s-gauche* conformer relative to the *s-trans* conformer ranged considerably (4–30 kJ/mol) [22–25]. Over the past twenty years, many high-level computational studies were performed on retinaldehyde and corresponding Schiff bases to better understand their spectroscopic and chiro-optical properties, or to examine their role in photochemistry as chromophores for rhodopsin and bacteriorhodopsin [26–33]. The conformational analysis of retinoic acids were studied to a lesser extent. Recently, an important study by Merz and coworkers thoroughly searched the polyene chain conformations of retinoic acids at a high level of theory. They showed significant errors in the conformations of the polyene chain in crystal structures of retinoic acid bound to proteins [34,35].

In this study we address how the trimethylcyclohexenyl ring inversion influences the potential energy about the C6—C7 torsion in retinoic acids. Experimental [36] and computational methods [37] have established that cyclohexenes interconvert rapidly between two half-chair conformations with C2—C3 torsion angles (vitamin A numbering) of about ±60°. In 2002, Shishkina et al. [38] demonstrated that cyclohexene inverts through a twisted-boat intermediate, with an activation energy of 23 kJ/mol at the MP2 level of theory. The trimethylcyclohexenyl rings of vitamin A analogs or β-carotene are expected to invert between similar half-chair conformations with the C16 and C17 methyl groups at C1 (*gem*-dimethyl groups) flipping between *pseudo*-axial and *pseudo*-equatorial positions (Fig. 1B). Guo and Karplus evaluated