Ab initio molecular dynamics of retinals

Bifone, A.; Groot, H.J.M. de; Buda, F.

ELSEVIER

12 January 1996

Chemical Physics Letters 248 (1996) 165–172

CHEMICAL PHYSICS LETTERS

Ab initio molecular dynamics of retinals

Angelo Bifone [a], Huub J.M. de Groot [a], Francesco Buda [b,*]

[a] *Leiden Institute of Chemistry, Gorlaeus Laboratoria, University of Leiden, 2300 RA Leiden, The Netherlands*

[b] *Istituto Nazionale per la Fisica della Materia, Laboratorio Forum, Scuola Normale Superiore, Piazza dei Cavalieri 7, 56126 Pisa, Italy*

Received 22 September 1995; in final form 10 November 1995

Abstract

A Car–Parrinello ab initio molecular dynamics calculation is presented of all-trans and 11-cis retinals. The minimum energy configurations of the two isomers have been determined by a simulated annealing procedure. The backbone conjugation is properly described within the local density approximation. The vibrational frequencies have been determined from the molecular dynamics trajectories. The theoretical results show an excellent agreement with experiment and provide grounds for an analysis of the retinal vibrations in terms of localized modes.

1. Introduction

Two distinct light-transducing proteins, rhodopsin and bacteriorhodopsin, present an isomer of retinal as a chromophore [1]. Rhodopsin, which is responsible for the black and white vision in vertebrates, consists of an 11-cis-retinal covalently bound via a protonated Schiff base to the apoprotein opsin. The first step in light-transduction is the 11-cis to all-trans isomerization of the chromophore upon absorption of a photon. Bacteriorhodopsin is present in the purple membrane of the *Halobacterium halobium* and serves as a light-driven pump of protons through the cell membrane. The primary event in the proton-pumping photocycle involves an all-trans to 13-cis isomerization of the retinal protonated Schiff base.

Although these two proteins play significantly different roles, it is remarkable how natural selection has led to similar chromophores and design. This suggests that the high efficiency and quantum yield of these molecular devices are related to the fundamental properties of the retinyl chromophore. Unfortunately, the lack of information about the structure of the chromophore and its interaction with the protein makes it difficult to substantiate the models for the molecular mechanisms involved in the energy transduction process. Thus, although many hints and structural constraints are available from NMR, Raman and IR spectroscopy [1,2], a comprehension of these mechanisms still necessitates a reliable theoretical treatment, which provides a basis for modelling the process by taking into account the spectroscopic information.

In this Letter we present a study of the ground state properties and vibrations of two isomers of retinal by Car–Parrinello ab initio molecular dynamics [3,4], based on density functional theory within the local density approximation [5] (DFT-LDA). This first-principles technique allows us to fully optimize the geometry of the molecule by a simulated annealing procedure, an efficient approach for overcoming

* Corresponding author.

SSDI 0009-2614(95)01312-1

local minima on the Born–Oppenheimer hypersurface. Moreover, ab initio molecular dynamics makes it possible to study simultaneously the dynamical evolution of the atomic positions and the electronic ground state. This may be of crucial important when studying retinal in the protein chromophore, as mechanisms such as energy storage and isomerization involve a dynamical electron distribution rearrangement.

Although the Car–Parrinello approach within DFT is well established in solid state and cluster physics [3], it is still matter of discussion whether the LDA provides an accurate description of finite conjugated systems, such as retinals. In this Letter we apply this technique to the 11-cis and the all-trans isomers of retinal (Fig. 1), which are involved in the primary step in vision. These isomers have been fully characterized by infrared and resonance Raman spec-

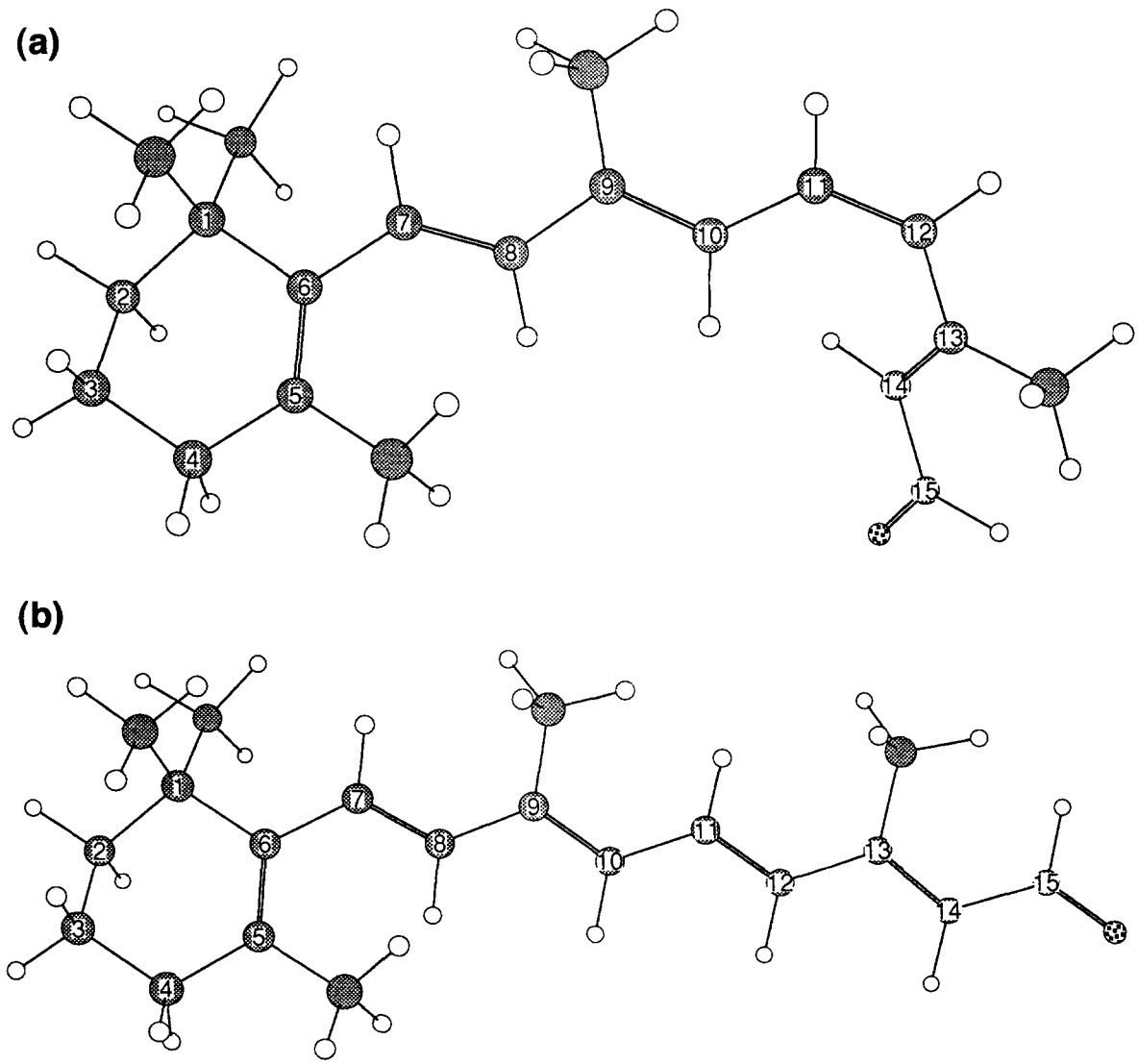

Fig. 1. Structures of the (a) 11-cis and (b) all-trans-retinal, showing the numbering system used in this Letter.

troscopy [6], and provide an excellent test of the reliability of the LDA approach to this sort of system. The total, HOMO and LUMO charge distributions have been determined for the equilibrium structures of the retinals. We also present a vibrational analysis for both isomers and discuss the localization of normal modes. The good agreement with experiment makes this approach promising for a future study of chromophore–protein interactions and the fundamental mechanisms involved in the energy-transduction process.

In Section 2 we describe briefly the computational method and the technical details. In Section 3, the geometric and electronic structures at zero temperature are reported and compared with the experimental data. The vibrational properties obtained by finite temperature molecular dynamics are discussed in Section 4. Section 5 is devoted to concluding remarks and perspectives for the future study of retinal–protein interactions.

2. Computational methods

The ab initio molecular dynamics approach describes the Newtonian dynamics of a system by using an interatomic potential obtained at each time-step from the instantaneous electronic ground state [3]. This is achieved by introducing an extended Lagrangian which includes both the ionic and electronic degrees of freedom. By choosing an appropriate fictitious mass for the electronic degrees of freedom, the electrons follow adiabatically the ionic motion staying close to the Born–Oppenheimer surface [4]. The electronic ground state is obtained within the local density approximation, where the exchange–correlation energy is described in terms of the Perdew and Zunger [7] parametrization of numerical quantum Monte Carlo results [8]. We explicitly treat only the valence electrons and describe the interaction with the inner core by using soft first-principles pseudopotentials in the form proposed by Vanderbilt [9]. The Kohn–Sham single particle wavefunctions are expanded on a plane wave basis set with an energy cut-off of 20 Ry. The convergence of the calculation relative to the energy cut-off has been tested on a C_2H_6 molecule up to 30 Ry. At 20 Ry the C–C bond length and the C–C stretch frequency are already close to the fully converged values within $\approx 1.0\%$.

The expansion in terms of plane waves implies the use of periodic boundary conditions (pbc). The simulation box has been chosen large enough to avoid interaction with the images, specifically $36 \times 18 \times 18$ au for all-trans-retinal and $30 \times 20 \times 20$ au for 11-cis-retinal.

We took a fictitious electronic mass $\mu = 500$ au and a time-step for the molecular dynamics simulations of 6 au. Each time-step takes about 3 min of CPU time on IBM RISC/6000 workstation with 256 Mb of RAM. The vibrational analysis has been carried out on the atomic trajectories generated with MD runs of about 600 fs.

In a classical MD simulation the vibrational frequencies are usually computed by the Fourier transform (FT) of the velocity autocorrelation function. In ab initio molecular dynamics the simulation time is necessarily limited by the computational burden and the thermodynamic equilibrium of the system is not usually achieved. A vibrational analysis scheme for short non-thermally equilibrated molecular dynamics trajectories has been presented recently by Kohanoff [10]. This approach is based on a self-consistent application of the multiple signal classification (MUSIC) algorithm [11]. We exploited this method for the spectral analysis of the global vibrational modes in retinals, while the standard FT technique has been applied to characterize more localized modes.

3. Ground state properties

A first minimization of the total energy of the system has been performed with a steepest descent algorithm followed by simulated annealing. The total energy of the all-trans isomer turns out to be lower than the 11-cis one by about 8 kcal/mol, compatible with experiment [12]. The 11-cis form is non-planar due to a dihedral angle of 38° around the C12–C13 single bond. This results in an increase in the C12–C13 bond length of ≈ 0.01 Å in 11-cis-retinal. The C11=C12 bond presents a twist of 2.1° in the 11-cis isomer, while it is planar in all-trans-retinal. The conjugation of the carbon backbone is well reproduced, as shown in Table 1. This result is noticeable

Table 1
Theoretical and experimental C–C bond lengths for the 11-cis and all-trans retinals. All distances are in Å

Distance (Å)	11-cis (theory) LDA	all-trans (theory)		11-cis (exp. [a])	all-trans (exp. [b])
		LDA	GC		
C5=C6	1.371	1.370	1.372	1.327	1.329
C6–C7	1.452	1.451	1.459	1.460	1.483
C7=C8	1.366	1.366	1.363	1.350	1.317
C8–C9	1.442	1.441	1.446	1.426	1.469
C9=C10	1.380	1.381	1.381	1.355	1.346
C10–C11	1.425	1.422	1.420	1.427	1.444
C11=C12	1.376	1.372	1.372	1.347	1.339
C12–C13	1.448	1.437	1.442	1.481	1.455
C13=C14	1.375	1.379	1.376	1.318	1.346
C14–C15	1.443	1.440	1.445	1.474	1.458
C15=O	1.254	1.255	1.256	1.173	1.200
aver. = bond	1.374	1.374	1.373	1.342	1.337
aver. – bond	1.442	1.438	1.442	1.453	1.462

[a] From Ref. [20]. [b] From Ref. [21].

in view of the well known limitations of the LDA in describing infinite conjugated chains [13–15]. DFT-LDA calculations on polyacetylene yield a bond alternation much smaller than the experimental value [13,14], or even no dimerization at all [15], and vanishing stabilization energy. This lack of accuracy is usually ascribed to the underestimation of gaps characteristic of the DFT-LDA approach [13]. The case of retinals presents substantial differences. In fact, the breaking of symmetry that determines the bond alternation is caused by the oxygen that terminates the tail of the molecule and by the β-ionon ring. Moreover, the bond alternation is further stabilized by the side methyl groups. The theoretical dimerization amplitude (defined as the difference between the single and double bond lengths) is still slightly underestimated, but presents a satisfactory agreement with experiment.

Recently, it has been shown that gradient corrections (GC) [16,17] to the LDA can substantially improve the description of weak bonds [18]. Including GC in our calculation did not result in any substantial change of the dimerization amplitude in the retinal isomers, as shown in Table 1.

The HOMO-LUMO energy gap is 1.76 eV for 11-cis-retinal and 1.68 eV for all-trans. The HOMO and LUMO are well separated in energy from the other electronic states and, therefore, an analysis of the corresponding electronic densities can be performed. In Fig. 2, we report the HOMO and the LUMO charge densities for all-trans-retinal. The charge in the HOMO is mainly localized on the β-ionon ring and on the double bonds of the conjugated system. In the LUMO, the electronic charge is depleted from the ring and is localized mainly on the single bonds of the tail. This is particularly relevant in connection with the isomerization of the chromophore of rhodopsin upon excitation of one electron in the LUMO, and supports the idea that this process is driven by a net positive charge transfer to the ring [1]. On the C5=C6 double bond the HOMO displays a π-like character that gradually turns p-like when approaching the terminal oxygen. The reverse occurs for the LUMO.

Similar results hold for 11-cis-retinal and are reported in Fig. 3. It is interesting to notice that the π-like lobes of the LUMO are wrapped around the C12–C13 bond, as a consequence of the bond twist.

4. Finite temperature properties

An extensive resonance Raman (RR) and infrared study of the vibrational properties of retinal isomers is reported in Ref. [6]. The analysis of the vibrational spectra of retinals presents special difficulties because of the size and low symmetry of the molecule. The assignment of the vibrational modes in Ref. [6]

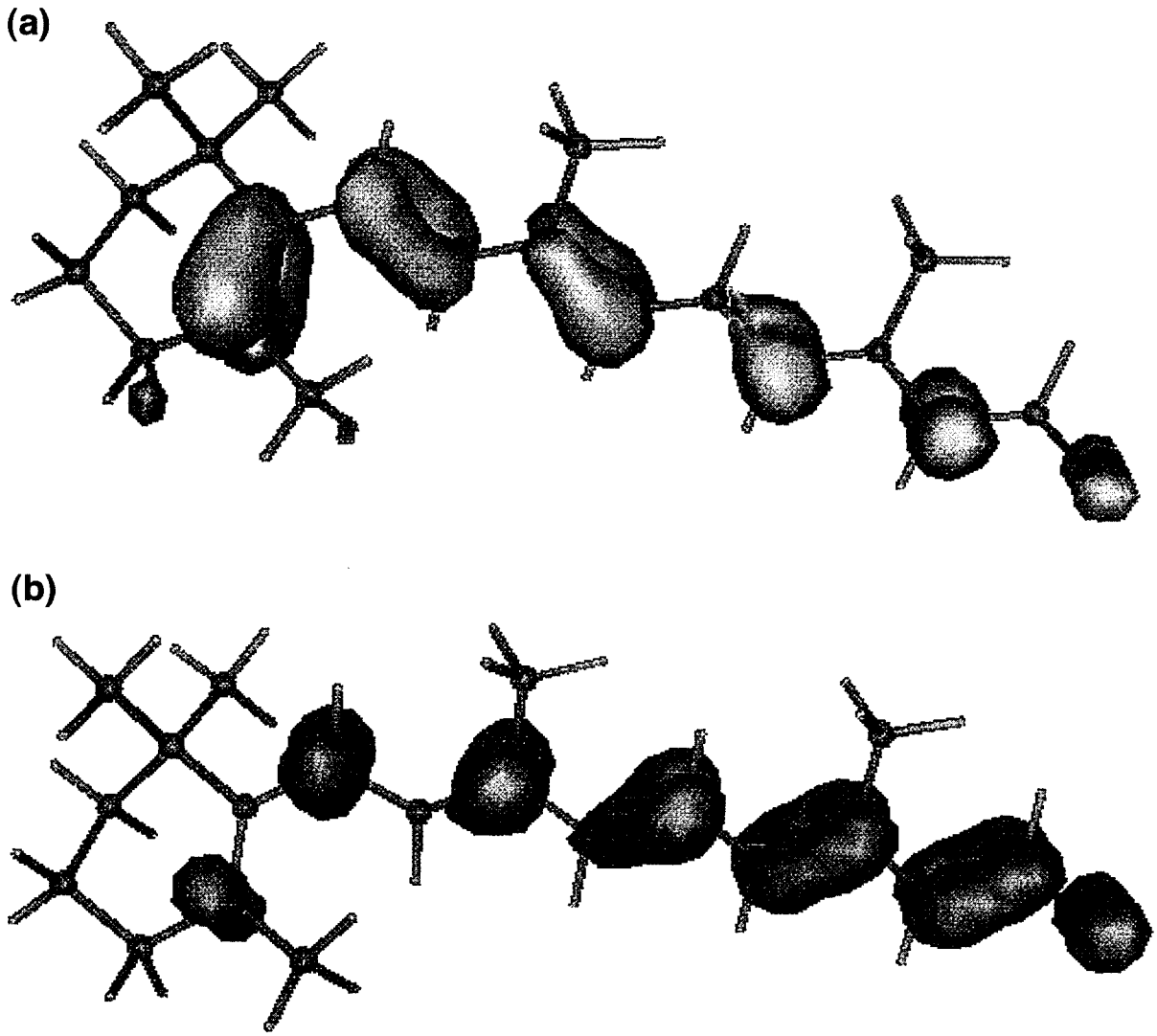

Fig. 2. HOMO (a) and LUMO (b) electron charge density distribution in all-trans-retinal. The isosurfaces shown in the pictures correspond to an electron density of 0.005 e/au^3 and delimit a total electronic charge of about 1 electron.

was made possible by a systematic isotopic substitution in specific sites of the retinals. The substitution alters the reduced masses involved in the modes and allows one to identify the vibrational bands. This analysis has revealed the presence of highly localized modes, namely C–C and C–CH_3 stretches, vinyl and methyl rocks and out-of-plane wags. This localization was attributed to the presence of the side methyl groups, which decouple the backbone modes.

In this section we present a vibrational analysis for the two isomers 11-cis and all-trans-retinal, carried out on the atomic trajectories calculated with the first-principles MD simulation at 80 K temperature for about 600 fs. We concentrate on the most representative vibrational features, with emphasis on the differences between the two isomers, mainly determined by the non-planarity of the 11-cis. A global search of the modes of the carbon backbone has been

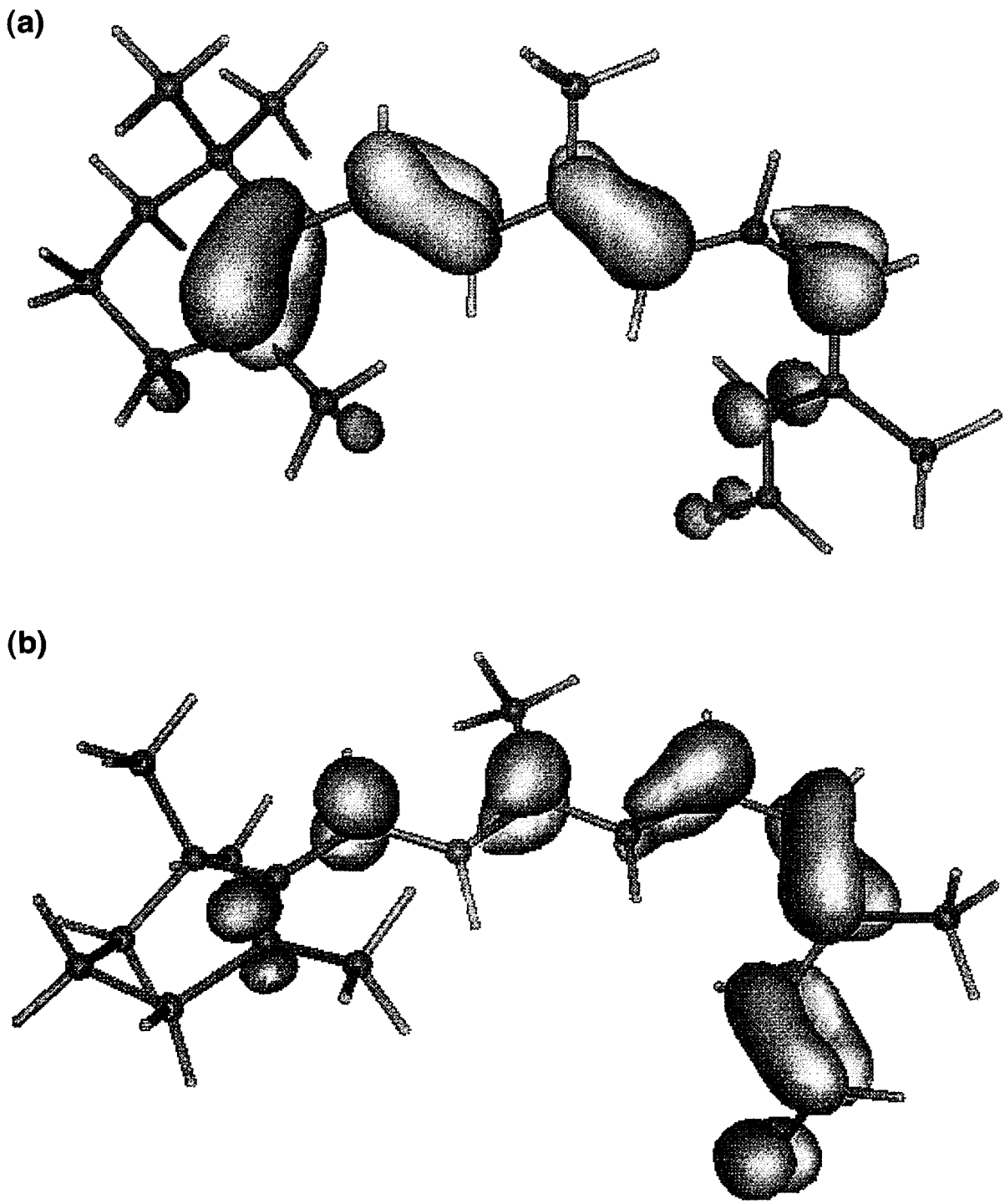

Fig. 3. HOMO (a) and LUMO (b) electron charge density distribution for 11-cis-retinal. Same visualization criteria as in Fig. 2.

performed using Kohanoff's algorithm [10]. The most prominent feature is the ethylenic stretch mode at 1572 and 1577–1581 cm^{-1} in the all-trans and 11-cis isomers respectively. These modes are highly delocalized and involve a concerted motion of the chain even in 11-cis retinal, despite the twist around the 10–11 and 12–13 bonds. The global analysis on 11-cis-retinal does not reveal any other delocalized mode. This is not the case for all-trans-retinal, where two delocalized modes are detected at 841 and 1333 cm^{-1}. Both modes are connected with correlated motions of the methyl groups (see below). The twisted backbone prevents the coupling of these modes in 11-cis-retinal.

As pointed out by Curry et al. [6], the vibrational spectra of the retinals are dominated by localized vibrational modes. In order to make a comparison with the assignments reported in Ref. [6], we have analyzed local vibrations by defining opportune local coordinates, typically atomic distances, and by Fourier transforming the autocorrelation functions of the corresponding velocities. Although this procedure is not formally rigorous and the advantages of Kohanoff's approach are lost, nevertheless, it provides a description consistent with the experimental data and confirms the experimental evidence of highly localized vibrational modes. The results of this analysis are reported in Table 2.

Table 2
Vibrational analysis in terms of local coordinates. Only the frequencies of the most prominent vibrational bands are reported. All frequencies are in cm^{-1}

Stretching C=C	11-cis	all-trans
C5=C6	1580	1590
C7=C8	1585	1580
C9=C10	1574	1574
C11=C12	1595	1574
C13=C14	1585	1537
Stretching C–C	**11-cis**	**all-trans**
C6–C7	1128, 1277	1106, 1234
C8–C9	1186	1218
C10–11	1112	1223
C12–13	1144	1239
C14–15	1090	1117
$C–C_{methyl}$	**11-cis**	**all-trans**
C9–C19	846, 1362	814, 1340
C13–C20	1324	846, 1335

The local C=C stretching modes along the chain of the the isomers present frequencies in the range 1570–1590 cm^{-1}, except the C13=C14 stretch of all-trans-retinal, which is shifted to 1537 cm^{-1}, presumably due to the reduced electron density in the bond caused by the strong electronegativity of the terminal oxygen.

By analogy with the isolated β-ionon ring, the C5=C6 stretch in all-trans-retinal was assigned to the weak experimental infrared peak at 1611 cm^{-1} [19]. However, as shown in Ref. [6], this assignment must be revised, as no shift was observed upon isotopic substitution of C5 and C6. Our simulation shows that this mode lies in the ethylenic band at 1590 cm^{-1}.

The C–C stretches represent the most characteristic part of the vibrational spectra and form the 'fingerprint region' in the range 1000–1400 cm^{-1}. In polyenes these stretches are strongly coupled, because they interact through the π backbone electrons. In our analysis, no significative correlation has been found. This is consistent with the general idea that side groups, such as the two methyl groups, couple with these modes and contribute to their localization. The local modes of C8–C9 and C12–C13 in both isomers present a strong mixing with the $C–CH_3$ stretches and with the CCH rocks, which result in a strong peak in the region 1330–1350 cm^{-1}. The C6–C7 stretch presents slow vibrations, probably connected with the motion of the ring, and two main peaks with comparable intensities at 1106 and 1234 cm^{-1} (all-trans) and 1128 and 1277 cm^{-1} (11-cis).

The most prominent features of the vibrations of the methyl groups have been detected around 1340 and 846 cm^{-1}, corresponding respectively to the methyl deformations and $C–CH_3$ stretches. These peaks are also revealed in the global motion of the backbone chain in the case of all-trans-retinal.

The C=O stretching mode in both isomers is underestimated by about 4%, probably due to the energy cut-off in the plane wave expansion. In fact, the pseudopotential for the oxygen is stiffer than the one for carbon and, therefore, the C=O stretch frequency is more sensitive to the number of plane waves than the C=C stretches.

5. Conclusions and perspectives

The ground-state properties of two isomers of retinals have been computed by Car–Parrinello ab initio molecular dynamics. The LDA provides an excellent framework to study this sort of finite conjugated system, despite its limitations in describing infinite polyenes. Including gradient corrections to the LDA does not result in any significant improvement in the description of the dimerization amplitude in the retinals, suggesting that this is not the clue for the problems in infinite polyenes. A good agreement with the experimental data has been obtained for both zero and finite temperature properties. The equilibrium structures have been determined by simulated annealing, which allows for an efficient energy minimization of systems with many local minima. The analysis of the molecular dynamics trajectories provides theoretical grounds for the assignment of the experimental vibrational spectra in terms of localized modes.

This work paves the way for future studies of the retinal chromophores of rhodopsin and bacteriorhodopsin. The chromophore–protein interactions, in fact, can only be inferred from their effects in the vibrational and NMR spectra. Due to the excellent description of vibrations and ground state electron density distribution, this approach seems promising for testing the effects of the protein binding pocket on the chromophore, which ultimately determines the function of these molecular devices.

Acknowledgement

We wish to thank J. Kohanoff for providing the program for the vibrational analysis and J. Shelley for the graphic package (MOVIE) used to visualize the results of the simulations. We are grateful to J. Lugtenburg for encouraging this project and for many invaluable discussions. Financial support from the EC Biotechnology program, contract CT930467, is gratefully acknowledged.

References

[1] R.R. Birge, Biochim. Biophys. Acta 1016 (1990) 293.
[2] J. Lugtenburg, R.A. Mathies, R.G. Griffin and J. Herzfeld, TIBS 13 (1988) 388.
[3] R. Car and M. Parrinello, Phys. Rev. Letters 55 (1985) 2471; G. Galli and M. Parrinello, in: Computer simulations in material science, eds. M. Meyer and V. Pontikis (Kluwer, Dordrecht, 1991) p. 283.
[4] G. Pastore, E. Smargiassi and F. Buda, Phys. Rev. A 44 (1991) 6334.
[5] R.G. Parr and W. Yang, Density-functional theory of atoms and molecules (Oxford Univ. Press, Oxford, 1989); R.O. Jones and O. Gunnarson, Rev. Mod. Phys. 61 (1989) 689.
[6] B. Curry, I. Palings, A.D. Broek, J.A. Pardoen, J. Lugtenburg and R. Mathies, in: Advances in infrared and Raman spectroscopy, Vol. 12, eds. R.J.H. Clark and R.E. Hoester (Wiley, New York, 1985) p. 115.
[7] J.P. Perdew and A. Zunger, Phys. Rev. B 23 (1981) 5048.
[8] D.M. Ceperley and B.J. Alder, Phys. Rev. Letters 45 (1980) 566.
[9] D. Vanderbilt, Phys. Rev. B 43 (1990) 7892.
[10] J. Kohanoff, Comput. Mater. Sci. 2 (1994) 221.
[11] S. Lawrence Marple, Jr., Digital spectral analysis with applications (Prentice-Hall, New Jersey, 1985).
[12] P.S. Bernstein, C.L. Wing and R. Rando, Proc. Natl. Acad. Sci. US 84 (1987) 1849.
[13] J.W. Mintmire and C.T. White, Phys. Rev. B 35 (1987) 4180.
[14] P. Vogl and D.K. Campbell, Phys. Rev. Letters 62 (1989) 2012.
[15] J. Ashkenazi, W.E. Pickett, H. Krakauer, C.S. Wang, B.M. Klein and S.R. Chubb, Phys. Rev. Letters 62 (1989) 2016.
[16] J.P. Perdew, Phys. Rev. B 33 (1986) 8822.
[17] A.D. Becke, Phys. Rev. A 38 (1988) 3098.
[18] C. Lee, D. Vanderbilt, K. Laasonen, R. Car and M. Parrinello, Phys. Rev. B 47 (1993) 4863).
[19] B. Curry, A. Broek, J. Lugtenburg and R. Mathies, J. Am. Chem. Soc. 104 (1982) 5274.
[20] G. Drikos, H. Ruppel, H. Dietrich and W. Sperling, Fed. Eur. Biochem. Soc. Letters 131 (1981) 23.
[21] T. Hamanaka, T. Mitsui, T. Ashida and M. Kakudo, Acta Crystallogr. B 28 (1972) 214.