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Research Article

Development of a New Spectral Tool for Identification of *E* and *Z* Isomers of Retinoids

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Abstract

A spectral study of a new series of fifteen retinoids based on the dimethyltetralin ring system, leading to the development of a new "Spectral Tool" for identification of *E* and *Z* isomers, is reported. Four types of retinoids (A-D), promising therapeutic agents for the treatment of epithelial cancer, were reported recently, in which various side-chain double bonds are rigidly held in specific conformations. Among the most active retinoids, the 9*E* isomers are 40-60 times more active than the corresponding 9*Z* isomers. In this study, a complete assignment of the ^{1}H and ^{13}C NMR signals of the retinoids to specific hydrogen and carbon atoms was achieved on the basis of chemical shifts, multiplicity, coupling constants, and assessment of substituent effects (*i.e.* shift changes upon alteration of the chemical structure), and comparisons of chemical shifts from compound to compound and of related compounds, and by proton noise-decoupled spectra and single frequency off-resonance decoupled spectra. The chemical shift differences between the 9*E* and the corresponding 9*Z* isomers are discussed, and interesting chemical shift patterns are observed. The distinct chemical shift patterns of the 9*E* and the 9*Z* retinoids in the ^{1}H and ^{13}C NMR could be used as a spectral tool to identify the *E* and *Z* isomers of other retinoids and vitamin A analogs.

Keywords: *cis*-and *trans*-retinoids; ^{1}H and ^{13}C NMR of *E* and *Z* isomers of retinoids

Introduction

The retinoids, a large class of polyunsaturated diterpenes structurally related to vitamin A, have aroused much interest because of their diverse biological properties [2] and versatile isomeric structures. In particular, the effect of vitamin A on epithelial tissues [2] has attracted much attention because vitamin A deficiency leads to hyperkeratosis of the skin and to metaplastic changes in the epithelia of gastrointestinal, respiratory, and urogenital tracts.

A number of synthetic retinoids have proven to be extremely effective in the treatment of various types of keratinization disorders [2]. Although a large number of retinoids have been synthesized, only limited work has been done on the NMR spectral study of retinoids and vitamin A derivatives [3,4].

The retinoic acid molecule is composed of three building units – a nonpolar cyclic end group, a polyene chain and a polar head group. Although it is relatively easy to probe structure-activity relationships involving the cyclic end group and polar head group, side-chain effects on biological activity are more difficult to study. The conformational flexibility of the side chain makes it possible for retinoids to adopt a large number of conformations, some of which are biologically active while others are inactive.

We recently reported [5] the development of four types of new retinoids containing dimethyltetralin end groups (A-D in Chart 1), in which various side-chain double bonds are rigidly held in specific conformations. Bicyclic type A analogs have the 5,6 and 7,8 double

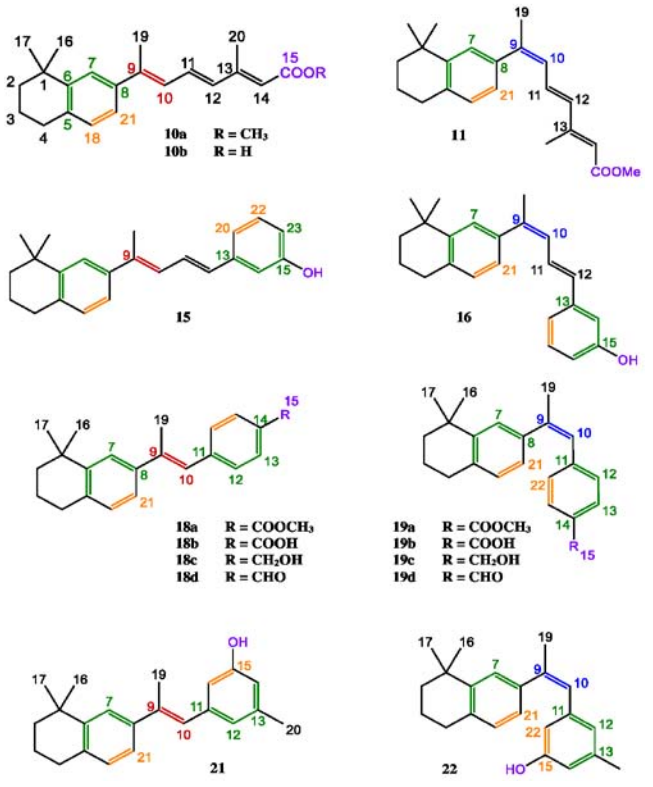

Chart 1: Structures of new Retinoids.
(Type **A: 10-11**, Type **B: 15-16**, Type **C: 18-19**, and Type **D: 21-22**)

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Table 1: ^{1}H NMR Spectral Shifts of Retinoids 10a, 10b and 11.

Retinoid No.→ Hydrogen No. ↓	**10a** (9*E*) (R = CH_3)	**11**(9*Z*) (R = CH_3)	**10b** (9*E*) (R = H)
H-2	1.67 (dt, 2, 5.8)	1.68 (dt, 2.2, 5.7)	1.67 (dt, 2, 5.8)
H-3	1.80 (m)	1.81 (m)	1.80 (m)
H-4	2.77 (t, 6.2)	2.78 (t, 6.0)	2.77 (t, 6.2)
H-7	**7.42** (d, 1.8)	**7.20** (d, 1.6)	**7.43** (d, 1.7)
H-10	**6.54** (d br, 11.1)	**6.23** (d, 11.0)	**6.56** (d br, 11.2)
H-11	7.04 (dd, 11.3, **15.1**)	6.80 (dd, 11.1, **15.2**)	7.08 (dd, 11.1, **14.9**)
H-12	6.38 (d, **15.2**)	6.26 (d, **15.1**)	6.41 (d, **15.1**)
H-14	5.81 (s br)	5.75 (s br)	5.84 (s br)
H-16 & 17	1.31 (s)	1.29 (s)	1.32 (s)
H-18	7.03 (d, 8.1)	7.06 (d, 8.1)	7.04 (d, 8.0)
H-19	2.25 (d, 0.8)	2.18 (s)	2.26 (s)
H-20	2.39 (d, 0.8)	2.18 (s)	2.40 (s)
H-21	**7.19** (dd, 1.9, 8.0)	**6.98** (dd, 1.7, 7.9)	**7.20** (dd, 1.8, 7.9)
H-Functional Group	3.72 (s, -$COOCH_3$)	3.69 (s, -$COOCH_3$)	-

Table 2: ^{1}H NMR Spectral Shifts of Retinoids 15, 16, 21 and 22.

Retinoid No. → Hydrogen No. ↓	**15** (9*E*)	**16** (9*Z*)	**21** (9*E*)	**22** (9*Z*)
H-2	1.67 (m)	1.69 (m)	1.66 (m)	1.61 (m)
H-3	1.79 (m)	1.82 (m)	1.79 (m)	1.77 (m)
H-4	2.76 (t, 6.3)	2.79 (t, 6.3)	2.75 (t, 6.3)	2.74 (t, 6.3)
H-7	**7.44** (d, 1.8)	**7.25** (d, 1.8)	**7.44** (d, 1.8)	**7.11** (s br)
H-10	**6.58**[a] (d br, 11)	**6.27** (d, 11)	**6.52** (s br)	**6.21** (s br)
H-11	7.17[b] (m)	6.99[b] (m)	-	-
H-12	6.58[a] (d br, **15**)	6.45 (d, **15.4**)	**6.75** (s br)	**6.41** (s br)
H-14	6.93 (d, 2.2)	6.75 (d br, 2.2)	6.65 (s br)	6.34 (s br)
H-16 & 17	1.32 (s)	1.31 (s)	**1.31** (s)	**1.10** (s)
H-18	7.01[a] (d, 8.1)	6.99[b] (m)	7.01 (d, 7.7)	6.99 (d, 8)
H-19	2.25 (s)	2.18 (s)	2.24 (d, 1.1)	2.17 (d, 1.5)
H-20	7.01[a] (d, 8.1)	6.99[b] (m)	2.29 (s)	2.13 (s)
H-21	**7.17**[b] (m)	**6.99**[b] (m)	**7.19** (dd, 1.8, 7.7)	**6.94** (dd, 1.8, 8)
H-22	7.17[b] (m)	6.99[b] (m)	**6.68** (s br)	**6.37** (s br)
H-23	6.68 (dd, 1.8, 7.4)	6.62 (dd, 2.2, 8.1)	-	-
-OH	5.08 (br)	4.7 (br)	5.24 (br)	4.33 (br)

[a]merged with other signals; [b]not resolved, merged with other signals.

bonds of the retinoic acid locked into an s-cis conformation without disturbing the rest of the molecule, while tricyclic analogs of types B–D have additional constraints on double bond geometry imposed by introduction of a third ring.

In all of the fifteen new synthetic retinoids reported [5], three of which (18a, 18b, and 10b) exhibited ED_{50}(M) values in the (3-5) $x10^{-11}$ range, and are promising candidates for the prevention and treatment of epithelial cancer. In this series of retinoids, the 9-*trans* retinoids (*E* isomers) are more active than their 9-*cis* retinoids (*Z* isomers). Comparing the ED_{50}(M) values of the most active retinoids, the 9*E* isomers are 40-60 times more active than the corresponding 9*Z* isomers.

In this paper, we report the high resolution ^{1}H and ^{13}C NMR spectral study of these four types of retinoids leading to the development of a new "Spectral Tool" for identification of *E* and *Z* Isomers. We were able to use the interesting chemical shift patterns of the 9*E* and the 9*Z* retinoids in the ^{1}H NMR as a tool to pinpoint the 9*E* and 9*Z* isomers. The distinct chemical shift patterns of the 9*E* and the 9*Z* retinoids in the ^{13}C NMR were used as a better tool to distinguish between 9*E* and 9*Z* isomers.

Numbering the skeletal atoms of retinoids

Numbering the skeletal atoms of retinoids is based on standard retinoid numbering. Carbon numbering of the retinoids closely resembles that for retinoic acid. The numbering the new synthetic

Table 3: ^{1}H NMR Spectral Shifts of Retinoids 18a-d and 19a-d.

Retinoid No. →	**18a** (9*E*)	**19a** (9*Z*)	**18b**(9*E*)	**19b**(9*Z*)	**18c**(9*E*)	**19c**(9*Z*)	**18d**(9*E*)	**19d**(9*Z*)
Hydrogen No. ↓	(R=COOMe)		(R=COOH)		(R=CH_2OH)		(R=CHO)	
H-2 (m or dt, 2,6)	1.68	1.60	1.69	1.60	1.68	1.61	1.68	1.61
H-3 (m)	1.81	1.77	1.82	1.78	1.81	1.77	1.81	1.78
H-4 (t, 6.3)	2.78	2.73	2.78	2.75	2.78	2.73	2.78	2.74
H-7 (d, 1.8)	**7.47**	**6.98**[a](m)	**7.47**	**6.99**[a](m)	**7.46**	**7.08**[a](m)	**7.47**	**7.05**
H-10 (s br)	**6.79**	**6.45**	**6.81**	**6.48**	**6.77**	**6.43**	**6.80**	**6.47**
H-12&22 (d, 8)	**7.43**	**6.98**[a](m)	**7.46**	**6.99**[a](m)	**7.37**(s br)	**6.96**(m)	**7.51**	**7.11**
H-13&23(d,8)	**8.03**	**7.77**	**8.12**	**7.83**	**7.37**(s br)	**6.96**(m)	**7.87**	**7.61**
H-16&17 (s)	**1.33**	**1.08**	**1.34**	**1.08**	**1.33**	**1.09**	**1.33**	**1.06**
H-18 (d, 8)	7.06	6.98[a](m)	7.06	6.99[a](m)	7.05	7.08[a](m)	7.06	7.00
H-19 (d, 1.1)	2.29	2.21	2.30	2.23	2.27	2.19	2.31	2.23
H-21(dd, 2,8)	**7.23**	**6.98**[a](m)	**7.24**	**6.99**[a](m)	**7.24**	**7.08**[a](m)	**7.23**	**6.92**
H-Functional Group (R=)	3.92 (s) ($COOCH_3$)	3.83 (s) ($COOCH_3$)	-	-	4.71 (s) (CH_2OH)	4.54 (s) (CH_2OH)	9.81 (s) (CHO)	9.87 (s) (CHO)

[a]not resolved, merged with other signals.

Table 4: Significant Chemical Shift Differences $\delta_{9E} - \delta_{9Z}$ (abs. value > 0.05 ppm) in the ^{1}H NMR Signals of Retinoids.

Retinoid No. → Hydrogen No. ↓	**10a - 11** R=Me	**15-16**	**21-22**	**18a - 19a** R=COOMe	**18b - 19b** R=COOH	**18c - 19c** R=CH_2OH	**18d - 19d** R=CHO
H-2	-	-	-	0.08	0.09	0.07	0.07
H-7	**0.22**	**0.19**	**0.33**	**0.49**	**0.48**	**0.38**	**0.42**
H-10	**0.31**	**0.31**	**0.31**	**0.34**	**0.33**	**0.34**	**0.33**
H-11	0.24	0.18	-	-	-	-	-
H-12	0.12	0.13	**0.34**	**0.45**	**0.47**	**0.41**	**0.40**
H-13	-	-	-	**0.26**	**0.29**	**0.41**	**0.26**
H-14	0.06	0.18	0.31	-	-	-	-
H-16 & 17	-	-	**0.21**	**0.25**	**0.26**	**0.24**	**0.27**
H-18	-	-	-	0.08	0.07	-	0.06
H-19	0.07	0.07	0.07	0.08	0.07	0.08	0.08
H-20	0.21	-	0.16	-	-	-	-
H-21	**0.21**	**0.18**	**0.25**	**0.25**	**0.25**	**0.16**	**0.31**
H-22	-	0.18	**0.31**	**0.45**	**0.47**	**0.41**	**0.40**
H-23	-	0.06	-	**0.26**	**0.29**	**0.41**	**0.26**
H-Functional Group (R=)	-	-	-	0.09 (COOMe)	-	0.17 (CH_2OH)	0.06 (CHO)

retinoids were done with assistance from the editor of Nomenclature, Chemical Abstract Service [6].

Experimental

^{1}H NMR spectra were run at 300 MHz on a Bruker WM 300 spectrophotometer in $CDCl_3$ with Me_4Si as internal standard. ^{13}C NMR spectra were run at 22.49 MHz on a JEOL FX 90Q spectrometer at 25 °C in $CDCl_3$ with Me_4Si as internal standard. Chemical shifts were reported in ppm relative to Me_4Si (d=0).

Spectral Study leading to the development of a new "Spectral Tool" for identification of *E* and *Z* isomers

^{1}H NMR Studies: Tables 1-3 list the chemical shifts (d, ppm), multiplicity, and coupling constants (J, Hz) of synthetic retinoids 10a-22. A complete assignment of the ^{1}H NMR signals of the retinoids to specific hydrogen atoms in Tables 1-3 was achieved on the basis of chemical shifts, multiplicity, coupling constants, and assessment of substituent effects (*i.e.* shift changes upon alteration of the chemical structure), and comparisons of chemical shifts from compound to compound and of related compounds. ^{1}H NMR data and their assignment to specific hydrogen atoms for retinoids 10a, 10b and 11 are reported in Table 1, for retinoids 15, 16, 21 and 22 in Table 2, and for retinoids 18a-19d in Table 3. Significant chemical shifts differences between the 9*E* and the 9*Z* isomers of retinoids [absolute value of $(d_{9E} - d_{9Z}) > 0.05$ppm] are summarized in Table 4.

The 11*E* double-bond configuration for retinoids 10a, 10b, and 11 was established from the 15 Hz coupling constants for H-11 and H-12. The *all-E* configuration for 10a and 10b was established by comparison of their ^{1}H and ^{13}C NMR spectra with those of known retinoids [3,4]. In the known retinoids, a strong downfield shift (~1.4ppm) of H-12 and a significant upfield shift (~0.3ppm) of H-20 relative to those of

Table 5: ^{13}C NMR Chemical Shifts of Retinoids 10a, 10b, and 11.

Retinoid No. → Carbon No. ↓		**10a** (9*E*) (R=CH_3)	**11** (9*Z*) (R=CH_3)	**10b** (9*E*) (R=H)
C-1	(s)	33.95	33.85	34.00
C-2	(t)	39.31	39.22	39.31
C-3	(t)	19.61	19.61	19.66
C-4	(t)	30.49	30.54	30.54
C-5	(s)	140.68	143.55	141.36
C-6	(s)	145.70	145.41	145.80
C-7	(d)	**122.83**	**126.59**	**122.88**
C-8	(s)	**140.09**[a]	**138.19**[a]	**140.04**[a]
C-9	(s)	136.04[a]	135.70[a]	136.24[a]
C-10	(d)	129.07	128.98	129.12
C-11	(d)	131.36	132.97	132.14
C-12	(d)	135.41	134.19	135.26
C-13	(s)	152.96	153.30	155.30
C-14	(d)	118.15	117.71	117.71
C-15	(s)	167.49	167.54	172.13
C-16 & 17	(q)	31.85	31.80	31.90
C-18	(d)	125.76	127.12	125.76
C-19	(q)	**16.44**	**25.51**	**16.54**
C-20	(q)	13.86	13.77	14.11
C-21	(d)	123.90	124.73	124.00
-COO**C**H_3	(q)	50.92	50.87	-

[a]assignments interchangeable with the value marked *a* in the same column.

Table 6: ^{13}C NMR Chemical Shifts of Retinoids 15, 16, 21 and 22.

Retinoid No. → Carbon No. ↓		**15** (9*E*)	**16** (9*Z*)	**21** (9*E*)	**22** (9*Z*)
C-1	(s)	33.90	33.90	33.95	33.70
C-2	(t)	39.31	39.36	39.36	39.31
C-3	(t)	19.61	19.76	19.66	19.76
C-4	(t)	30.44	30.58	30.44	30.54
C-5	(s)	140.43	140.48	141.51	141.80
C-6	(s)	145.55	145.50	145.60	145.50
C-7	(d)	**122.69**	**127.61**	**123.03**	**125.76**
C-8	(s)	137.56	138.78	138.00	138.97
C-9	(s)	135.41	135.26	135.26	134.83
C-10	(d)	128.98[a]	128.88[a]	128.93	129.02
C-11		126.34[a] (d)	126.93[a] (d)	139.95 (s)	139.31 (s)
C-12	(d)	131.71	130.34	122.73	122.69
C-13	(s)	139.60	139.75	139.31	139.12
C-14	(d)	112.69	112.59	114.15	113.76
C-15	(s)	155.60	155.65	155.11	154.91
C-16 & 17	(q)	31.80	31.90	31.85	31.51
C-18	(d)	126.15	126.93	126.44	127.17
C-19	(q)	**16.20**	**25.51**	**17.66**	**26.83**
C-20		119.17 (d)	119.13 (d)	21.32 (q)	21.27 (q)
C-21	(d)	123.71	125.17	124.15	124.59
C-22	(d)	129.71	129.66	112.98	112.50
C-23	(d)	114.35	114.01	-	-

[a]assignments interchangeable with the value marked *a* in the same column.

all-E retinoids are characteristic of 13*Z* configuration. Although H-20 of retinoid 11 is shifted upfield (0.21ppm) relative to that of 10a, the absence of a downfield shift of H-12 (shifted upfield 0.12ppm) relative to that of 10a favors a13*E* geometry for 11. The 13*E* configuration is also supported by the ^{13}C NMR spectra (discussed infra). A significant upfield shift (0.31ppm) of H-10 in 11 relative to that of 10a favors a 9*Z* geometry for 11, which was established from the ^{13}C NMR spectra (discussed infra).

The 15 Hz coupling constant for H-12 in retinoids 15 and 16 is indicative of an 11*E* configuration. An upfield shift of H-10 (0.31-0.34ppm) in retinoids 16, 22, and 19a-19d, relative to that of the corresponding *all-E* isomers favors a 9*Z* geometry. The 9*Z* configuration was further established by the ^{13}C NMR spectra discussed later.

A study of the chemical shift differences between the 9*E* and the 9*Z* isomers of retinoids reported in Table 4 reveals interesting chemical shift patterns that make it possible to achieve the development of a new "spectral tool" to distinguish between 9*E* and 9*Z* isomers:

i) Most of the protons of 9*Z* retinoids exhibit an upfield shift relative to those of the corresponding 9*E* isomers. An overall greater steric interaction between hydrogen atoms occurs in the case of 9*E* retinoids leading to downfield shifts. Conversely, an overall reduction of specific steric compressions in the 9*Z* retinoids leads to corresponding upfield shifts in the ^{1}H NMR spectra.

ii) A pronounced upfield shift of H-7 [Dd (9*E*-9*Z*): 0.2-0.5ppm] occurs in all 9*Z* isomers of new retinoids.

iii) All 9*Z* retinoids exhibit an upfield shift (0.3ppm) of H-10.

iv) A significant upfield shift (0.2-0.3ppm) of H-21 is displayed in all 9*Z* retinoids.

v) A slight upfield shift (0.07ppm) of H-19 is experienced by all 9*Z* retinoids.

vi) An upfield shift [Dd (9*E*-9*Z*): 0.2-0.3ppm] of H-16 and H-17 is observed in tricyclic retinoids 18a-19d, 21, and 22.

vii) H-12 and H-22 show a pronounced upfield shift [Dd (9*E*-9*Z*): 0.3-0.5ppm] in tricyclic retinoids 18a-19d, 21, and 22.

viii) H-13 and H-23 also show a pronounced upfield shift [Dd (9*E*-9*Z*): 0.3-0.4ppm] in tricyclic retinoids 18a-19d.

^{13}C NMR Studies: Tables 5-7 list the chemical shifts (d, ppm) of synthetic retinoids 10a-11, 15-16, 18a-19d, and 21-22. A complete assignment of the ^{13}C NMR signals of the retinoids to specific carbon atoms in Tables 5-7 was achieved on the basis of proton noise-decoupled spectra, single frequency off-resonance decoupled spectra, assessment of substituent effects, and comparisons of chemical shifts from compound to compound and of related compounds. ^{13}C NMR data and their assignment to specific carbon atoms for retinoids 10a-11 are reported in Table 5, for retinoids 15-16 and 21-22 in Table 6, and for retinoids 18a-19d in Table 7. Significant chemical shift differences between the 9*E* and the 9*Z* isomers of retinoids, a value of

Table 7: ^{13}C NMR Chemical Shifts of Retinoids 18a-d and 19a-d.

Retinoid No. →		**18a**(9*E*)	**19a**(9*Z*)	**18b**(9*E*)	**19b**(9*Z*)	**18c**(9*E*)	**19c**(9*Z*)	**18d**(9*E*)	**19d**(9*Z*)
Carbon No. ↓		R=COOMe		R=COOH		R=CH_2OH		R=CHO	
C-1	(s)	34.00	33.61	34.05	33.75	34.00	33.66	34.00	33.75
C-2	(t)	39.31	39.12	39.36	39.22	39.41	39.22	39.31	39.17
C-3	(t)	19.61	19.61	19.66	19.66	19.71	19.66	19.66	19.66
C-4	(t)	30.39	30.44	30.54	30.54	30.49	30.49	30.49	30.54
C-5	(s)	141.16	141.75	141.12	142.38	141.51	139.12	140.87	142.97
C-6	(s)	145.75	145.70	145.80	145.89	145.65	145.55	145.80	145.89
C-7	(d)	**123.08**	**125.27**	**123.12**	**125.27**	**123.08**	**125.66**	**123.08**	**125.22**
C-8	(s)	**139.90**	**138.43**	**140.43**	**138.43**	138.82	138.87	**140.87**	**138.34**
C-9	(s)	135.80	135.17	135.95	135.41	135.36	134.78	136.04	135.56
C-10	(d)	129.02	129.17	128.83	129.32	128.98	128.98	129.12	129.41
C-11	(s)	143.26	142.82	144.24	143.89	138.00	138.34	144.92	144.72
C-12 & 22	(d)	129.02	128.68	129.17	128.88	126.83	126.54	129.61	129.41
C-13 & 23	(d)	129.41	129.07	130.15	129.80	129.32	128.98	129.61	129.41
C-14	(s)	127.76	127.17	125.76	126.39	138.00	137.46	134.24	133.95
C-15		167.01(s)	166.86(s)	171.73(s)	172.17(s)	65.15 (t)	65.05 (t)	191.68(d)	191.73(d)
C-16 & 17	(q)	31.85	31.51	31.90	31.56	31.90	31.56	31.90	31.56
C-18	(d)	125.90	126.83	125.90	126.98	126.44	126.98	125.76	126.98
C-19	(q)	**17.76**	**26.88**	**17.86**	**26.98**	**17.61**	**26.83**	**17.91**	**27.02**
C-21	(d)	124.20	124.50	124.29	124.54	124.15	124.68	124.25	124.54
-COO**C**H_3	(q)	51.94	51.74	-	-	-	-	-	-

Table 8: Significant Chemical Shift Differences $\delta_{9E} - \delta_{9Z}$ (value > 0.5 ppm) in the ^{13}C NMR Signals of Retinoids.

Retinoid No. → Carbon No. ↓	**10a -11** (R=Me)	**15-16**	**21-22**	**18a - 19a** R=COOMe	**18b - 19b** R=COOH	**18c - 19c** R=CH_2OH	**18d-19d** CHO
C-5	-2.9	-	-	-0.6	-1.3	2.4	-2.1
C-7	**-3.8**	**-4.9**	**-2.7**	**-2.2**	**-2.2**	**-2.6**	**-2.1**
C-8	1.9	-1.2	-1.0	1.5	2.0	-	2.5
C-9	-	-	-	0.6	-	0.6	-
C-11	-1.6	-0.6	0.6	-	-	-	-
C-12	1.2	1.4	-	-	-	-	-
C-14	-	-	-	0.6	-0.6	-	-
C-18	-1.4	-0.8	-0.7	-0.9	-1.1	-	-1.2
C-19	**-9.1**	**-9.3**	**-9.2**	**-9.1**	**-9.1**	**-9.2**	**-9.1**
C-21	-0.8	-1.5	-	-	-	-	-

($d_{9E} - d_{9Z}$) > 0.5ppm, are summarized in Table 8.

The *all-E* configuration for 10a and 10b was established by comparison of their ^{13}C NMR spectra with those of known retinoids [4]. The C-12 and C-20 resonances occurring at 134-135 and 14ppm in retinoids 10a-11 supports a 13*E* configuration. The C-10 signal at 129ppm in retinoids 10a-11 and 15-16 is in agreement with 11*E* geometry. Changing the stereochemistry at the 9, 10-double bond from *E* to *Z* is expected to cause an upfield shift of C-8 and a downfield shift of C-19. A 9ppm downfield shift of C-19 is observed for all 9*Z* retinoids. An upfield shift [Dd (9*E*-9*Z*): 1.5-2.5ppm] of C-8 is also observed in the 9*Z* retinoids 11, 19a, 19b, and 19d.

A study of the chemical shift differences between the 9*E* and the 9*Z* isomers of retinoids reported in Table 8 reveals distinctive chemical shift patterns that make it possible to achieve the development of a new "spectral tool" to distinguish between 9*E* and 9*Z* isomers:

i) Most of the carbons of 9*Z* retinoids exhibit a downfield shift relative to those of the corresponding 9*E* isomers. An overall reduction of specific steric compressions occurs in the 9*Z* retinoids leading to downfield shifts in the ^{13}C NMR spectra.

ii) All the 9*Z* retinoids exhibit a pronounced downfield shift [Dd (9*E*-9*Z*): -9ppm] of C-19.

iii) The C-7 resonance shows a downfield shift of 2-5ppm in all 9*Z* retinoids.

iv) A slight downfield shift (0.5-1.2ppm) of C-18 is displayed for all 9*Z* retinoids.

Conclusion

The complete assignment of the ^{1}H and ^{13}C NMR signals of the fifteen new retinoids to specific hydrogen and carbon atoms was achieved. We were able to use the distinctive chemical shift patterns of the 9*E* and the 9*Z* retinoids in the ^{1}H and ^{13}C NMR to achieve a new "spectral tool" to pinpoint the 9*E* and 9*Z* isomers. This spectral tool could be utilized to identify the *E* and *Z* isomers of other retinoids and vitamin A analogs.

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