(*E*/*Z*) Stereoisomer Assignment by ^{13}C NMR in Trifunctional Phosphonate α-Oximes and α-Arylhydrazones

Charles E. McKenna,* Boris A. Kashemirov and Jing-Yue Ju

Department of Chemistry, University of Southern California, Los Angeles, California 90089-0744, USA

^{13}C NMR $^1J_{PC}$ coupling constants have predictive value in determining (*E*) *vs.* (*Z*) isomerism in oxophosphonoacetate α-oximes and α-hydrazones, and in distinguishing *syn* from *anti* phosphorus atoms in carbonyldiphosphonate α-hydrazones.

Oxophosphonoacetate (phosphonoglyoxylate, COPAA)[1] and carbonyldiphosphonate (COMDP)[2,3] are inhibitors of some nucleic acid polymerases,[3,4] suggesting to us exploration of cognate derivatives such as α-hydrazones[5,6] and α-oximes.[7] These novel trifunctional compounds are expected to display (*E*/*Z*) stereoisomerism, and their structural geometry should markedly influence their chemical behaviour as seen, *e.g.*, with bifunctional benzoylphosphonate[8,9] and benzoylphenylphosphinate[10] α-oxime stereoisomers. We recently determined structures for the novel COPAA oximes **1** [both (*E*) and (*Z*) isomers][7] and hydrazones **6** and **7** [(*E*) isomers],[6] by X-ray crystallography. In search of a more rapid and general solution phase method to make (*E*/*Z*) assignments for these types of compounds, we have examined the NMR parameters of the oximes **1**–**5**[7] and the hydrazones **6**–**8**[5,6] for structural correlations that might have predictive value.

Previously, Breuer and his coworkers assigned the (*E*)- and (*Z*)-isomers of dimethyl α-hydroxyiminobenzylphosphonate and methyl α-hydroxyiminobenzylphenylphosphinate by X-ray crystallography, noting that the (*E*) isomers displayed their ^{31}P NMR signals at lower field than the corresponding (*Z*)-isomers.[8,10] This observation was used to assign the (*E*/*Z*)-isomers of related compounds.[8,10] We therefore first compared the ^{31}P spectra† of the COPAA derivatives **1** and **2** [Fig. 1 (*a*)]. For the pair of C-monoesters **1** at low pH (**1a**), the (*E*)-isomer was seen at lower field than the (*Z*)-isomer, as expected. However, at slightly alkaline pH (**1b**) the assignment was reversed, with the (*E*) isomer resonating at higher field (this effect was reproduced reversibly in each of two cycles of the same pH adjustment). The ^{31}P NMR of the oximes **2** which are completely de-esterified (isomer assignments were derived from the corresponding known (*E*/*Z*) precursors **1**), correctly assigns the two isomers at high pH (they are unstable near neutral pH).[7] In the light of these results, we sought an alternative (or reliable complement) to ^{31}P NMR for (*E*/*Z*) isomer assignments.

We find that the ^{13}C NMR $^1J_{PC}$ coupling constants of both **1** (at either pH for samples **1a**, **1b**) and **2** consistently distinguish their (*E*)- and (*Z*)-isomers, the (*E*)-isomer displaying the larger value [ΔJ 40–49 Hz; Fig. 1(*b*)]. On the same basis, the (*E*/*Z*)-isomers of the COPAA arylhydrazone **6** [ΔJ 78 Hz; Fig. 1(*b*)] are readily assigned [the ^{31}P method also gives the correct assignment for this neutral ester, *cf.* Fig. 1(*a*)]. Comparison of the NMR data for **1**, **2**, **6** and a group of similar COPAA oximes **3**–**5** and hydrazones **7**, **8** [Figs. 1(*a*), (*b*)] shows that the ^{13}C NMR $^1J_{PC}$ values for the (*E*)-isomers fall in the range 171–242 Hz, whereas those for the (*Z*)-isomers fall in the range 127–164 Hz, and thus form two non-overlapping domains (ΔJ 44 ± 4 Hz for oxime salts **1a**/**1b** and **2**, 60 Hz for the oxime triesters **4** and **5**, 78 Hz for the hydrazone triester **6**; all samples were (*E*/*Z*) pairs except for **3**, **7** and **8** of which only the (*E*)-isomers were available). Although the ensemble of examples is modest in size, it does suggest that for structures of the types analysed here, ^{13}C NMR $^1J_{PC}$ coupling constants less

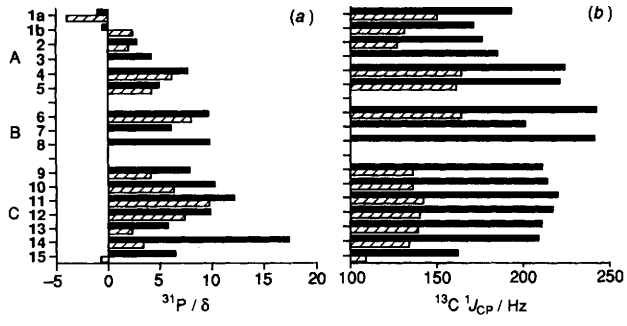
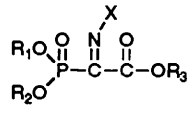
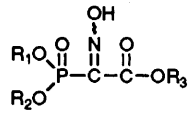


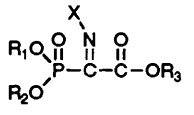
Fig. 1 ^{31}P NMR data (145.78 MHz) A: COPAA oximes; B: COPAA hydrazones; C: COMDP hydrazones: ■ (*E*)-isomers, **1**–**8**; *anti* P, **9**–**15**; ▨ (*Z*)-isomers, **1**–**8**; *syn* P, **9**–**15**. Solvents: **1**–**3**, **15**: D_2O (pH **1a**, 1.5; **1b**, *ca.* 7.5; **2**, *ca.* 13.5); others $DCCl_3$. Independent stereoisomeric assignments based on X-ray crystallographic analysis [(*E*), (*Z*)-**1**, (*E*)-**6**,**7**] or synthetic correlation [(*E*), (*Z*)-**2**, (*Z*)-**6**)]; for others see text.



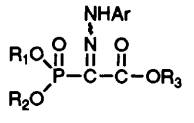
(*E*) Oxime (X = OH)
(*E*) Hydrazone (X = NHAr)



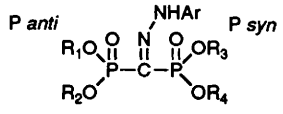
(*E*)-**1**; R_1 = dcha[a]; R_2 = H; R_3 = Me
(*Z*)-**1**; $R_1 = R_2$ = dcha; R_3 = Me
(*E*),(*Z*)-**2**; $R_1 = R_2 = R_3$ = Na[b]
(*E*)-**3**; R_1 = Me, $R_2 = R_3$ = dcha
(*E*),(*Z*)-**4**; $R_1 = R_2 = R_3$ = Me[c]
(*E*),(*Z*)-**5**; $R_1 = R_2$ = Et, R_3 = Me[c]



(*Z*) Oxime (X = OH)
(*Z*) Hydrazone (X = NHAr)



(*E*), (*Z*)-**6**; $R_1 = R_2 = R_3$ = Et, Ar = 2-MeO-4NO_2Ph[d]
(*E*)-**7**; $R_1 = R_3$ = dcha; R_2 = H, Ar = Ph
(*E*)-**8**; $R_1 = R_2 = R_3$ = Et, Ar = 4-MeO-2-NO_2Ph



9; $R_1 = R_2 = R_3 = R_4$ = Et, Ar = 2,4-$(NO_2)_2$Ph
10; $R_1 = R_2 = R_3 = R_4$ = Me, Ar = 2,4-$(NO_2)_2$Ph
11; $R_1 = R_2 = R_3 = R_4$ = Me, Ar = 2-MeO-4-NO_2Ph
12; $R_1 = R_2 = R_3 = R_4$ = Et, Ar = 2-MeO-4-NO_2Ph
13; $R_1 = R_2 = R_3 = R_4$ = Pr^i, Ar = 2,4-$(NO_2)_2$Ph
14; $R_1 = R_2 = R_3$ = Me, R_4 = Na, Ar = 2-MeO-4-NO_2Ph
15; $R_1 = R_2 = R_3 = R_4$ = dcha/H Ar = 2,4-$(NO_2)_2$Ph

Samples: **1** – **5**, ref. 7; **6** – **15**, refs. 5,6. [a] Dicyclohexylammonium. [b] Prepd. *in situ*; ionisation status of imino hydroxy proton under investigation. [c] Data for isomer mixture. [d] Z data for isomer mixture.

Scheme 1

or greater than 160–170 Hz could be used to assign tentatively a single isomer in the absence of data for the complementary one. With the exception of the pH-dependent behaviour of **1** noted above, the ^{31}P δ values of the (*E*)-isomers so assigned were at lower field than those of the corresponding (*Z*)-isomers for each isomer pair; however the absolute values overlapped for the (*E*) (δ −1.05–7.72) and (*Z*) oxime populations (δ −3.95–6.16) [Fig. 1(*b*)].‡ Thus, this method was restricted to relative assignments for isomer pairs.

In COPAA oximes or hydrazones, the geometry of the C=N–X moiety is distinguished between isomers. In the corresponding COMDP derivatives, the geometry of the C=N–X moiety is distinguished within one molecule wherein one P atom is *syn* to the X group, and the other P atom is *anti* (Scheme 1). Accordingly, we compared the ^{13}C NMR $^{1}J_{PC}$ data for a series of alkyl ester COMDP arylhydrazones **9–14**,[6] including one triester with an asymmetric phosphonate negative charge **14** [Fig. 1(*b*)]. The values (209–220 Hz; 134–142 Hz; average ΔJ 76 ± 2 Hz) segregate within the (*E*/*Z*) ranges found for the COPAA derivatives, suggesting that the larger *J* value of each pair be assigned to the *anti* P atom, and the smaller to the *syn* P atom. A structural correlation supporting this assignment is provided by the P–Cα–N bond angles of the oximes and hydrazones in our sample group for which X-ray data are available.[6,7] The COPAA derivatives (*E*)-**1**, (*E*)-**6** and (*E*)-**7** and the *anti*-P atom of the COMDP derivative **9** all have P-Cα-N < 120° (114–117°), whereas (*Z*)-**1** and the *syn*-P atom of **9** have P–Cα–N > 120° (125–128°), leading to 'canting'[6,7] of the oxime or hydrazone moiety. This pattern of isomer-dependent distortion from ideal sp^2 hybridization correlates with the magnitude of $^{1}J_{PC}$ in a consistent way, such that a larger P–Cα–N angle corresponds to a smaller $^{1}J_{PC}$ value, and *vice versa*.§

As seen in comparing the (*E*/*Z*) coupling constant data for the mono-dealkylated COMDP hydrazone **14** *vs.* **11** and **12**, and for the completely dealkylated COMDP hydrazone **15** *vs.* **9**, **10** and **13**, increasing negative charge is generally associated with a smaller *J* value. The oxime and hydrazone COPAA triacids show a similar pattern: the C-methyl ester phosphonic acids **1** at pH 1.5 have $^{1}J_{PC}$ values about 20 Hz larger than the corresponding anions at pH 7–8, or the carboxylate-phosphonate anions **2**; **1**, **2** and the P-methyl ester **3** have $^{1}J_{PC}$ values substantially smaller than those of the neutral triesters **4** and **5**. Although the comparison is not exact because the aryl groups are not the same, the $^{1}J_{PC}$ of the COPAA hydrazone triacid salt (*E*)-**7** is about 40 Hz smaller than those of the triesters **6** and **8**. The absolute ^{31}P chemical shifts of the COMDP hydrazone esters **9**, **10** and **13** (*syn* 2.3–6.3 ppm, *anti* 5.8–10.3 ppm) or **11** and **12** (*syn* 7.4–9.9 ppm, *anti* 9.8–12.2 ppm) [Fig. 1(*a*)] vary with hydrazone aryl substitution and ester alkyl group as would normally be expected.[14] By analogy with the COPAA hydrazones, the more downfield of each value pair is assigned to the *anti* P atom. The ^{31}P and ^{13}C data can be spectroscopically linked by measurement of ^{13}C satellites for each of the two ^{31}P NMR peaks in a given compound. This was done for **13**, confirming our assignment.¶

This research was supported by NIH Grant AI-25697.

Received, 24th September 1993; Com. 3/05786K

Footnotes

† ^{1}H NMR is more limited in this application, being inherently less general (since the same type of proton-containing group will obviously not be common to all phosphonate α-oximes and α-hydrazones). Furthermore, for a given set of derivatives having such a group in common, ^{1}H NMR may not always be useful for isomer assignment.[8]

‡ We have previously shown that in α-fluorinated MDP acids, the ^{19}F-^{31}P coupling constants are virtually the same at pH 6–12, whereas the ^{31}P NMR chemical shifts are pH-sensitive: C. E. McKenna and V. Harutunian, Symposium on Recent Aspects of Phosphorus Chemistry, 1984 Pacific Conference, Sacramento, California, October 11–12, 1984: ^{19}F NMR Spectra of α-Fluoromethylene Diphosphonates and β,γ-Fluoromethylene ATP Analogs as pH Probes.

§ Theoretical understanding of ^{31}P-^{13}C NMR spin-spin coupling magnitudes is currently approximate;[11] in addition to the hybridizations (% s character) and effective nuclear charges of both coupled nuclei, other factors such as isomer-dependent imino N and phosphonate O lone pair effects on the Fermi contact contribution to the coupling[12] are likely to contribute significantly. It is worth noting that the less complexly determined $^{1}J_{CH}$ values for the α-C of simple aldehyde oximes and hydrazones RCH=NX correlate with the configuration both experimentally and theoretically such that *syn* isomers have larger values.[13] Adjusting for the difference in nomenclature (their *syn* is our *anti*/*E*, etc.), this finding is consistent with our $^{1}J_{CP}$ results.

¶ The ^{31}P NMR spectrum (202.46 MHz) was obtained by Mr A. Kershaw with Mr G. Duncan.

References

1 C. E. McKenna and J. N. Levy, *J. Chem. Soc., Chem. Commun.*, 1989, 246.
2 O. T. Quimby, J. B. Prentice and D. A. Nicholson, *J. Org. Chem.*, 1967, **32**, 4111.
3 R. V. Talanian, N. C. Brown, C. E. McKenna, T.-G. Ye, J. N. Levy and G. E. Wright, *Biochemistry*, 1989, **28**, 8270.
4 C. E. McKenna, J. N. Levy, L. A. Khawli, V. Harutunian, T.-G. Ye, M. C. Starnes, A. Bapat and Y.-C. Cheng, in *Nucleotide analogues as anti-viral agents*, ed. J. C. Martin, ACS, Washington DC, 1989, vol. 401, pp. 1.
5 C. E. McKenna, A. Khare, J.-Y. Ju, Z.-M. Li, G. Duncan, Y.-C. Cheng and R. Kilkuskie, *Phosphorus, Sulfur and Silicon*, 1993, **76**, 139.
6 J.-Y. Ju, A. Khare, M. Heagy, E. Yi, R. Bau and C. E. McKenna, in preparation.
7 B. A. Kashemirov, J.-Y. Ju, R. Bau and C. E. McKenna, in preparation.
8 E. Breuer, R. Karaman, A. Goldblum, D. Gibson, H. Leader, B. V. L. Potter and J. H. Cummins, *J. Chem. Soc. Perkin Trans. 1*, 1988, 3047.
9 J. Katzhendler, R. Karaman, D. Gibson, E. Breuer and H. Leader, *J. Chem. Soc., Perkin Trans.*, 1989, **2**, 589.
10 E. Breuer, A. Schlossman, M. Safadi, D. Gibson, M. Chorev and H. Leader, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3263.
11 L. D. Quin, in *Phosphorus-31 NMR spectroscopy in stereochemical analysis*, ed. J. G. Verkade and L. D. Quin, pp. 391; vol. 8, in *Methods in Stereochemical Analysis*, VCH, Deerfield Beach, FL, 1987.
12 V. M. S. Gil and W. v. Philipsborn, *Magn. Reson. Chem.*, 1989, **27**, 409.
13 R. R. Fraser and M. Bresse, *Can. J. Chem.*, 1982, **61**, 576; and references therein.
14 D. G. Gorenstein, in *Phosphorus-31 principles and applications*, ed. D. G. Gorenstein, Academic Press, NY, 1984, ch. 1.