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A Novel Pulse Sequence Element for Biselective and Independent Rotations with Arbitrary Flip Angles and Phases for I and I{S} Spin Systems

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Recent years have witnessed many pulse sequences wherein two classes of protons are manipulated differently without the use of frequency-selective RF pulses. In biomolecular NMR, the two classes are typically those directly bound to ^{13}C or ^{15}N and those not directly bound to ^{13}C or ^{15}N with the heteronucleus at either natural abundance or isotopically enriched. Historically, the most popular pulse sequence elements for this purpose have been BIRD (*1*), which was designed as a selective-inversion element, and TANGO (*2*), which was proposed as a selective-excitation or combined excitation–inversion element. A later generalization, BANGO (*3*), allows independent and arbitrary rotation angles to be selected for both classes. However, none of these three elements allows arbitrary and independent settings of the phases of the rotations. That is now possible with our new pulse sequence element which enables simultaneous and independent rotation of I and I{S} spin systems with arbitrary flip angles and phases. This new capability opens up an entirely new avenue for simultaneously applying independent phase cycles to different classes of protons. Within the framework of a vector model, this Communication describes how the new pulse sequence element can be derived and demonstrates its essential features by a simple application.

The goal is to derive a pulse sequence element P that achieves simultaneous and independent rotations with arbitrary flip angles and phases for isolated I and I{S} spin systems, i.e.,

$$\begin{cases} \mathrm{I}: (\beta^{\mathrm{I}})_{\varphi^{\mathrm{I}}} \\ \mathrm{I}\{\mathrm{S}\}: (\beta^{\mathrm{IS}})_{\varphi^{\mathrm{IS}}}, \end{cases} \qquad [1]$$

as illustrated in Fig. 1a. In other words, P must effect the transformations (*4*)

$$I_z^{\mathrm{I}} \xrightarrow{P} I_x^{\mathrm{I}} \sin(\beta^{\mathrm{I}})\sin(\varphi^{\mathrm{I}}) - I_y^{\mathrm{I}} \sin(\beta^{\mathrm{I}})\cos(\varphi^{\mathrm{I}}) + I_z^{\mathrm{I}}\cos(\beta^{\mathrm{I}}) \qquad [2a]$$

$$I_z^{\mathrm{IS}} \xrightarrow{P} I_x^{\mathrm{IS}} \sin(\beta^{\mathrm{IS}})\sin(\varphi^{\mathrm{IS}}) - I_y^{\mathrm{IS}} \sin(\beta^{\mathrm{IS}})\cos(\varphi^{\mathrm{IS}}) + I_z^{\mathrm{IS}}\cos(\beta^{\mathrm{IS}}), \qquad [2b]$$

where $(\beta^{\mathrm{I}}, \beta^{\mathrm{IS}})$ are the desired flip angles and $(\varphi^{\mathrm{I}}, \varphi^{\mathrm{IS}})$ the desired phases for I-spin magnetization of I and I{S} spin systems, respectively.

As P generalizes earlier elements of this type, the first of which was the BIRD (*1*) pulse sequence element, we propose it should be known by the acronym BIG-BIRD for *b*iselective *i*ndependent *g*yrations BIRD.

It turns out to be both illustrative and straightforward to derive P^{-1}, i.e., a pulse sequence element which performs the opposite transformation of taking the magnetization vectors from their desired final positions back to the *z* axis, and then to invert that pulse sequence. Three basic steps applied sequentially and individually illustrated in Figs. 1b–1d will achieve the goal: first, apply a rotation of angle $-\varphi^{\mathrm{I}}$ about the *z* axis on both magnetization vectors (Fig. 1b) in order to bring $\mathbf{I}^{\mathrm{I}}$ magnetization into the *yz* plane; second, apply a rotation of angle $-\theta$ on $\mathbf{I}^{\mathrm{IS}}$ magnetization about an axis collinear with $\mathbf{I}^{\mathrm{I}}$ magnetization which is tilted by an angle β^{I} away from the *z* axis (Fig. 1c) in order to bring $\mathbf{I}^{\mathrm{IS}}$ magnetization into the *yz* plane; third, apply the recently described BANGO pulse sequence element (*3*), which can simultaneously and independently rotate $\mathbf{I}^{\mathrm{I}}$ and $\mathbf{I}^{\mathrm{IS}}$ magnetizations with arbitrary flip angles about the same axis (the *x* axis in our case) in order to bring these two magnetization vectors back to their initial state along the *z* axis (Fig. 1d).

A central parameter in the new pulse sequence is the angle χ between the $\mathbf{I}^{\mathrm{I}}$ and $\mathbf{I}^{\mathrm{IS}}$ magnetization vectors in the final state. This angle is determined by the parameters in Eq. [1] according to the formula for the scalar product of the $\mathbf{I}^{\mathrm{I}}$ and $\mathbf{I}^{\mathrm{IS}}$ vectors in Eq. [2],

$$\cos(\chi) = \sin(\beta^{\mathrm{I}})\sin(\beta^{\mathrm{IS}})\cos(\varphi^{\mathrm{I}} - \varphi^{\mathrm{IS}}) + \cos(\beta^{\mathrm{I}})\cos(\beta^{\mathrm{IS}}), \qquad [3]$$

which defines χ in the interval $0 \leqslant \chi \leqslant \pi$.

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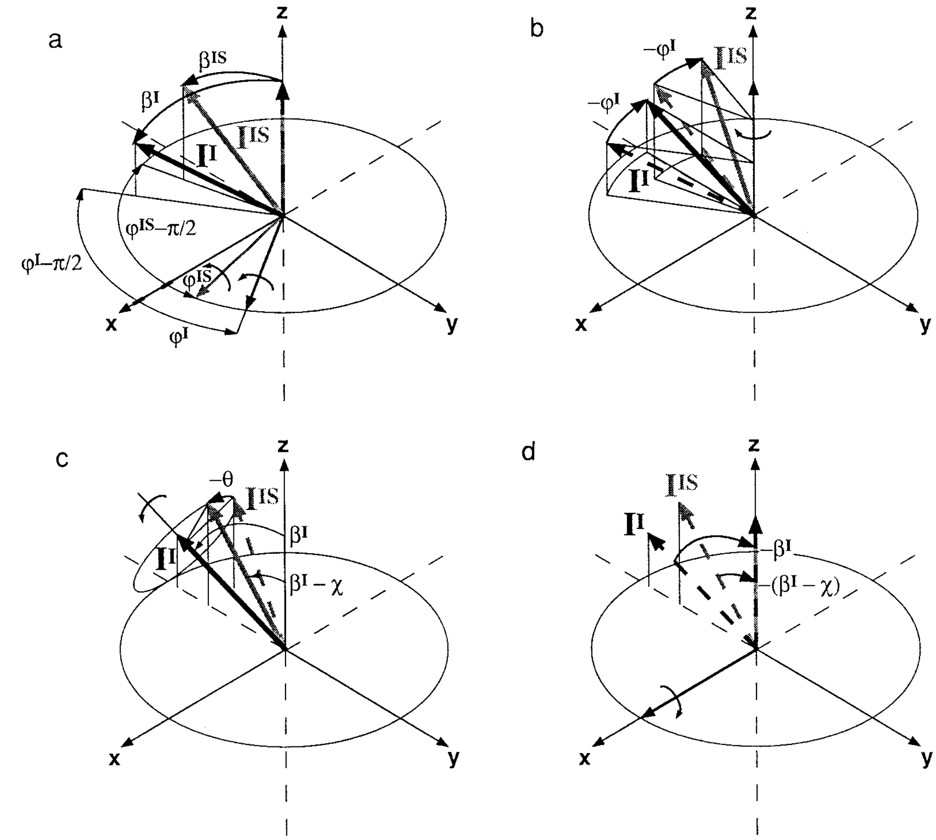

FIG. 1. Vector model representation of the basic steps involved in the design of the BIG-BIRD pulse sequence element. (a) The desired rotations of BIG-BIRD for $\mathbf{I}^{\mathrm{I}}$ and $\mathbf{I}^{\mathrm{IS}}$ magnetizations as if they were rotated by flip angles β^{I} and β^{IS} away from the z axis about fictitious RF fields in the rotating frame with phases φ^{I} and φ^{IS}, respectively. (b–d) The three basic steps involved in the reverse derivation of BIG-BIRD.

The second step, after the $-\varphi^{\mathrm{I}}$ rotation about the z axis, rotates $\mathbf{I}^{\mathrm{IS}}$ magnetization by an angle $-\theta$ about an axis collinear with $\mathbf{I}^{\mathrm{I}}$ magnetization which is tilted by an angle β^{I} away from the z axis (Fig. 1c). The angle θ can be determined from the set of equations

$$\begin{bmatrix} \sin(\beta^{\mathrm{IS}})\sin(\varphi^{\mathrm{IS}}-\varphi^{\mathrm{I}}) \\ -\sin(\beta^{\mathrm{IS}})\cos(\varphi^{\mathrm{IS}}-\varphi^{\mathrm{I}}) \\ \cos(\beta^{\mathrm{IS}}) \end{bmatrix} = \begin{bmatrix} c_\theta & -c_{\beta\mathrm{I}}s_\theta & -s_{\beta\mathrm{I}}s_\theta \\ c_{\beta\mathrm{I}}s_\theta & s^2_{\beta\mathrm{I}}(1-c_\theta)+c_\theta & -s_{\beta\mathrm{I}}c_{\beta\mathrm{I}}(1-c_\theta) \\ s_{\beta\mathrm{I}}s_\theta & -s_{\beta\mathrm{I}}c_{\beta\mathrm{I}}(1-c_\theta) & c^2_{\beta\mathrm{I}}(1-c_\theta)+c_\theta \end{bmatrix} \times \begin{bmatrix} 0 \\ -\sin(\beta^{\mathrm{I}}-\chi) \\ \cos(\beta^{\mathrm{I}}-\chi) \end{bmatrix}, \qquad [4]$$

where abbreviations of the type $s_\theta = \sin(\theta)$, $c_\theta = \cos(\theta)$ have been used. Solving Eq. [4] yields

$$\sin(\theta) = \frac{\sin(\beta^{\mathrm{IS}})\sin(\varphi^{\mathrm{I}}-\varphi^{\mathrm{IS}})}{\sin(\chi)}; \ \chi \neq n\pi \qquad [5a]$$

$$\cos(\theta) = \frac{\cos(\beta^{\mathrm{IS}})-\cos(\beta^{\mathrm{I}})\cos(\chi)}{\sin(\beta^{\mathrm{I}})\sin(\chi)}; \ \beta^{\mathrm{I}}, \chi \neq n\pi \qquad [5b]$$

$$\cos(\theta) = \frac{\sin(\beta^{\mathrm{I}})\cos(\chi)-\sin(\beta^{\mathrm{IS}})\cos(\varphi^{\mathrm{I}}-\varphi^{\mathrm{IS}})}{\cos(\beta^{\mathrm{I}})\sin(\chi)};$$

$$\beta^{\mathrm{I}} \neq (2n+1)\frac{\pi}{2}, \ \chi \neq n\pi. \qquad [5b']$$

In Eq. [5], θ is defined in the interval $0 \leqslant \theta \leqslant 2\pi$. Obviously, $\theta = 0$ if $\chi = 0$ or π, since $\mathbf{I}^{\mathrm{IS}}$ magnetization is aligned either parallel or antiparallel with $\mathbf{I}^{\mathrm{I}}$ magnetization. The two possible solutions for $\cos(\theta)$ ensure that θ is defined also when $\beta^{\mathrm{I}} = 0$ or $\pi/2$.

After the second step, the $\mathbf{I}^{\mathrm{I}}$ and $\mathbf{I}^{\mathrm{IS}}$ vectors are in the yz plane and separated by the angle χ (Fig. 1d). The $\mathbf{I}^{\mathrm{I}}$ and $\mathbf{I}^{\mathrm{IS}}$ vectors must be rotated by $-\beta^{\mathrm{I}}$ and $-(\beta^{\mathrm{I}}-\chi)$, respectively, in order to end up along the positive z axis. These rotations are effected by the BANGO pulse sequence element in the form

$$\left(\pi - \frac{\chi}{2} + \beta^{\mathrm{I}}\right)^{\mathrm{I}}_{-x} — \Delta — (\pi)^{\mathrm{I,S}}_{x} — \Delta — \left(\frac{\chi}{2}\right)^{\mathrm{I}}_{-x}, \qquad [6]$$

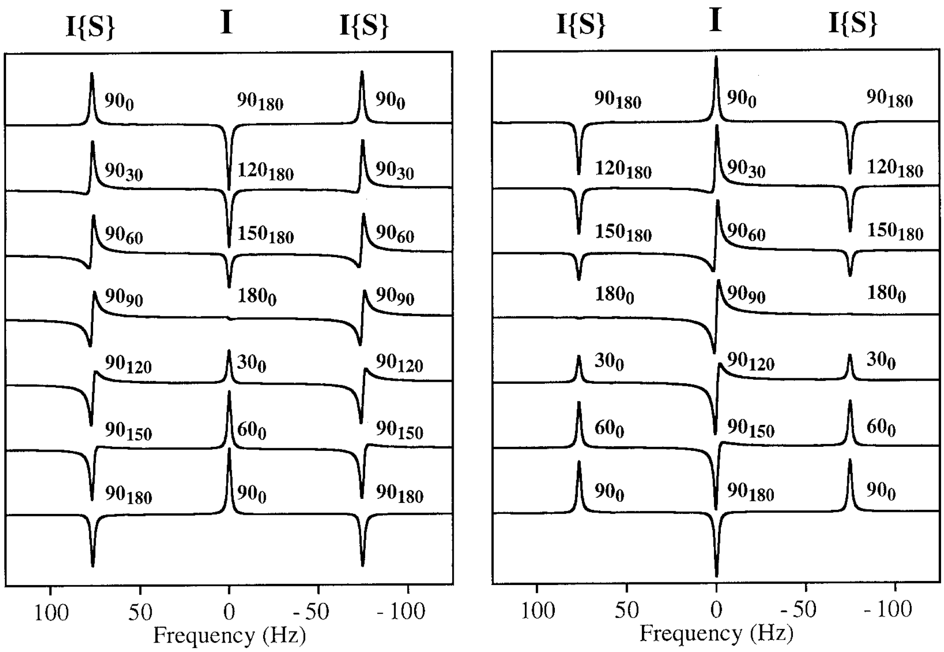

FIG. 2. Series of one-dimensional proton spectra recorded with different combinations of flip angles and phases for I and I{S} spin systems. Each spectrum is labeled with its corresponding combination of $(\beta^{\mathrm{I}})_{\varphi^{\mathrm{I}}}$ and $(\beta^{\mathrm{IS}})_{\varphi^{\mathrm{IS}}}$. Table 1 lists the calculated flip angles and phases $\chi/2$, μ, $-(\theta + \eta + \varphi^{\mathrm{I}})$, $(\psi + \eta + \varphi^{\mathrm{I}})$ used in the pulse sequence element of Eq. [16] to achieve the desired rotations.

where the notation $(\beta)^{\mathrm{I}}_{\varphi}$ refers to an RF pulse with flip angle β and phase φ applied on the I channel and $(\pi)^{\mathrm{I,S}}_{x}$ refers to a 180° pulse with phase x applied simultaneously on the I and S RF channels. The time period Δ is $\frac{1}{2}J_{\mathrm{IS}}$, where J_{IS} is the large one-bond heteronuclear coupling constant.

The next step is to concatenate the three rotations above, which results in the sequence

$$P^{-1}{:}R_z(-\varphi^{\mathrm{I}})—R_{\mathbf{I}}(-\theta)—\left(\pi - \frac{\chi}{2} + \beta^{\mathrm{I}}\right)^{\mathrm{I}}_{-x} —\Delta—(\pi)^{\mathrm{I,S}}_{x}—\Delta—\left(\frac{\chi}{2}\right)^{\mathrm{I}}_{-x}, \qquad [7]$$

where the notation $R_{\mathbf{a}}(\zeta)$ stands for a rotation of angle ζ about the axis defined by the vector $\mathbf{a}$. The desired pulse sequence element P may now be determined by inverting P^{-1} in Eq. [7]. This is achieved by inverting the order of the three basic steps and changing the sign of the rotation angles, which yields

$$P{:}\left(\frac{\chi}{2}\right)^{\mathrm{I}}_{x}—\Delta—(\pi)^{\mathrm{I,S}}_{x}—\Delta—\left(\pi - \frac{\chi}{2} + \beta^{\mathrm{I}}\right)^{\mathrm{I}}_{x} —R_{\mathbf{I}}(\theta)—R_z(\varphi^{\mathrm{I}}). \qquad [8]$$

This pulse sequence can be simplified considerably. The rotation $R_{\mathbf{I}}(\theta)$ about a tilted axis can be reexpressed in terms of rotations about axes located in the transverse plane (*4*):

$$R_{\mathbf{I}}(\theta) = R_x(\pi/2 - \beta^{\mathrm{I}})R_{-y}(\theta)R_{-x}(\pi/2 - \beta^{\mathrm{I}}). \qquad [9]$$

If we substitute Eq. [9] into Eq. [8], combine RF pulses with the same phase, and use the identities $R_x(\pi/2)R_{-y}(\theta)R_{-x}(\pi/2) \equiv R_z(\theta)$ and $(\zeta)_{\epsilon}R_z(\theta) \equiv R_z(\theta)(\zeta)_{\epsilon+\theta}$, Eq. [8] can be simplified to

$$R_z(\theta)—\left(\frac{\chi}{2}\right)^{\mathrm{I}}_{\theta}—\Delta—(\pi)^{\mathrm{I,S}}_{\theta}—\Delta —\left(\pi - \frac{\chi}{2}\right)^{\mathrm{I}}_{\theta}—(\beta^{\mathrm{I}})_x—R_z(\varphi^{\mathrm{I}}). \qquad [10]$$

In Eq. [10], we will seek a solution in which the third and second to last RF pulses are replaced according to

$$\left(\pi - \frac{\chi}{2}\right)^{\mathrm{I}}_{\theta} - (\beta^{\mathrm{I}})_x = (\mu)_{\psi} - R_z(\eta), \qquad [11]$$

where $(\mu)_{\psi}$ is an RF pulse with flip angle μ and phase ψ and $R_z(\eta)$ is a rotation of angle η about the z axis. A solution for Eq. [11] is possible based on the quaternion formalism (*5, 6*)

TABLE 1
Calculated Flip Angles and Phases in BIG-BIRD for a Series of Desired Flip Angles and Phases (β^{I}, β^{IS}, φ^{I}, φ^{IS}) for I and I{S} Spin Systems

β^{I}	φ^{I}	β^{IS}	φ^{IS}	$\chi/2$	$-(\theta+\eta+\varphi^{I})^{a}$	μ	$(\psi+\eta+\varphi^{I})^{a}$
90°	0°	90°	180°	90.0°	0°	180°	0°
90°	30°	120°	180°	69.3°	157.8°	45°	270°
90°	60°	150°	180°	52.2°	129.2°	45°	270°
90°	90°	180°	0°	45.0°	90.0°	45°	270°
90°	120°	30°	0°	52.2°	309.2°	135°	270°
90°	150°	60°	0°	69.3°	337.8°	135°	270°
90°	180°	90°	0°	90.0°	180.0°	180°	180°
120°	180°	90°	30°	69.3°	337.8°	45°	270°
150°	180°	90°	60°	52.2°	309.2°	45°	270°
180°	0°	90°	90°	45.0°	270.0°	45°	270°
30°	0°	90°	120°	52.2°	129.2°	135°	270°
60°	0°	90°	150°	69.3°	157.8°	135°	270°
90°	0°	90°	180°	90.0°	0°	180°	0°

[a] The resulting phases are defined in the interval $0 \leqslant -(\theta+\eta+\varphi^{I}), (\psi+\eta+\varphi^{I}) \leqslant 2\pi$.

$$\cos(\mu/2) = \sqrt{s_b^2 c_c^2 + c_b^2 s_c^2 - 2c_\theta s_b c_b s_c c_c} \quad [12]$$

$$\sin(\eta/2) = \frac{s_\theta s_b c_c}{\cos(\mu/2)} \quad [13a]$$

$$\cos(\eta/2) = \frac{c_b s_c - c_\theta s_b c_c}{\cos(\mu/2)} \quad [13b]$$

$$\sin(\psi) = \frac{\cos(\eta/2)s_\theta c_b c_c - \sin(\eta/2)[c_\theta c_b c_c + s_b s_c]}{\sin(\mu/2)} \quad [14a]$$

$$\cos(\psi) = \frac{\sin(\eta/2)s_\theta c_b c_c + \cos(\eta/2)[c_\theta c_b c_c + s_b s_c]}{\sin(\mu/2)}, \quad [14b]$$

where the abbreviations $s_\theta = \sin(\theta)$, $c_\theta = \cos(\theta)$, $s_c = \sin(\chi/4)$, $c_c = \cos(\chi/4)$, $s_b = \sin(\beta^{I}/2)$, and $c_b = \cos(\beta^{I}/2)$ have been used. From Eqs. [12]–[14], the angle μ is defined in the interval $0 \leqslant \mu \leqslant \pi$, and the angles ψ, η are defined in the interval $0 \leqslant \psi, \eta \leqslant 2\pi$.

Substituting Eq. [11] into Eq. [10], we obtain the following version of P:

$$P: R_z(\theta) - \left(\frac{\chi}{2}\right)_\theta^{I} - \Delta - (\pi)_\theta^{I,S} - \Delta - (\mu)_\psi^{I} - R_z(\eta + \varphi^{I}). \quad [15]$$

The identity $(\pi)_{\theta+\eta+\varphi^{I}} \equiv R_{-z}[2(\theta+\eta+\varphi^{I})](\pi)_x$ and further phase shifting lead to the final form of P

$$P: R_{-z}(\theta+\eta+\varphi^{I}) - \left(\frac{\chi}{2}\right)^{I}_{-(\theta+\eta+\varphi^{I})} - \Delta - (\pi)_x^{I,S} - \Delta - (\mu)^{I}_{(\psi+\eta+\varphi^{I})}. \quad [16]$$

The accumulated z rotation $R_{-z}(\theta+\eta+\varphi^{I})$ is irrelevant when P is used as an excitation element starting from longitudinal magnetization but causes a phase shift when the element is applied to transverse components of the density operator. The details of this, including a compensation scheme, will be covered in a separate publication.

The BIG-BIRD pulse sequence element was tested on a sample containing 1% iodomethane with about 60% ^{13}C-labeling in $CDCl_3$. A series of one-dimensional spectra was recorded for different combinations of flip angles (β^{I}, β^{IS}) and phases (φ^{I}, φ^{IS}) for I and I{S} spin systems and is illustrated in Fig. 2. These results clearly demonstrate the enhanced capability obtained with BIG-BIRD in being able to arbitrarily and independently vary the phases and flip angles for the two classes of protons. In our specific case, the center line corresponds to a methyl proton not directly bound to a ^{13}C nucleus while the satellite peaks correspond to those directly bound to ^{13}C. Table 1 lists the calculated flip angles and phases $\chi/2$, μ, $-(\theta+\eta+\varphi^{I})$, $(\psi+\eta+\varphi^{I})$, used in the pulse sequence element of Eq. [16] to achieve the desired rotations. Each spectrum represents two scans with phase inversion of the $(\pi)_x^{I,S}$ refocusing pulse on the I channel to compensate for pulse imperfections. All the spectra were processed in an identical manner, phase-corrected with the same zero- and first-order phase corrections, and plotted with the same scaling factor. The experiments were performed on a Varian Unity*plus* 500 MHz spectrometer.

In conclusion, we have added a novel element, BIG-BIRD, to the pulse sequence toolkit. Without the use of selective RF pulses, BIG-BIRD offers full flexibility to set independently the flip angles and phases for protons attached and protons not attached to an NMR-active heteronucleus. However, there is still work to do in evaluating the effects of mismatched delays ($\Delta \neq \frac{1}{2}J_{IS}$), RF inhomogeneity, and resonance offset. Particularly intriguing with applications in mind is the new avenue of simultaneously applying independent phase cycles to different classes of protons.

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