mL), and the mixture was stirred at room temperature for 4 days. After silica gel chromatography (EtOAc/hexane), 1.23 g (43% yield; 97% ee) of the ester (-)-5 and 1.02 g (46% yield, 98% ee) of the alcohol (+)-4 were obtained.[15] The excellent optical purity of both enantiomers is due to the high selectivity of the catalyst. Indeed, separate measurements of the initial rates of transesterification of (-)-4 and (+)-4 gave a ratio of 90:1.

Introduction of the 4-(trifluoromethyl)phenyl group was accomplished by alkylation of the alcohol (+)-4 with 4-fluorobenzotrifluoride using sodium hydride in DMF to give ether (+)-6 in 95% yield. The dealkylation of the N-benzyl group of (+)-6 was achieved via a two-step sequence. Reaction with 2,2,2-trichloroethyl chloroformate in refluxing toluene gave carbamate (+)-7 in 95% yield after filtration through silica gel. Then removal of the carbamate group of (+)-7 with zinc dust in 90% acetic acid[16] gave (+)-1, after treatment with ethereal HCl, in 61% yield. A single crystallization from 2-propanol gave (+)-1 (43% overall yield from (+)-4) with excellent optical purity (>99% ee). The enantiomer (-)-1 was similarly prepared in 62% yield (>99% ee) from (-)-4, the product of saponification of ester (-)-5 with NaOH in ethanol (96% yield).

The reaction conditions, developed first for the unlabeled synthesis, were employed for the synthesis of [14C]MDL 28618A. Thus, 96 mg (3.20 mmol) of unlabeled paraformaldehyde and 46.8 mg (1.56 mmol, 95.1 mCi, 61 mCi/mmol as CH_2O) of [14C]paraformaldehyde were condensed with 628 mg (4.75 mmol) of indane 2 and 959 mg (4.75 mmol) of benzylmethylamine hydrobromide to give 928 mg of [14C]-3 (2.68 mmol, 39.1 mCi, 14.6 mCi/mmol). Reduction with L-Selectride gave 630 mg of [14C]-(±)-4 (2.36 mmol, 34.5 mCi) after chromatography.

The enzymatic resolution of [14C]-(±)-4, as conducted for the unlabeled material above, gave a 43% yield (272 mg, 1.02 mmol, 14.9 mCi) of the [14C]-(+)-4 after column chromatography. The optical purity of this material was shown to be >99% ee.[15] Also recovered was 253 mg (1.22 mmol) of the [14C]-(-)-5.

Conversion of [14C]-(+)-4 to [14C]-(+)-1 was accomplished according to the scheme. In the synthesis of the radioactive material, a low yield (44%) was obtained in the final deprotection step ((+)-7 → (+)-1), resulting in an overall radiochemical yield of 5%. A total of 4.8 mCi (117 mg) of [14C]-(+)-1 was obtained with a specific activity of 14.6 mCi/mmol and radiochemical purity of 99.8%.[17]

Supplementary Material Available: Elemental analyses, $[\alpha]^{20}_D$, and spectral data (MS, NMR) for compounds 1–7 and chiral HPLC chromatograms for compounds 1 and 4 (6 pages). Ordering information is given on any current masthead page.

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(13) All compounds have been fully characterized by ¹HMR, MS, and elemental analyses and also melting points and $[\alpha]^{20}_D$ have been determined. Determination of the absolute configurations of these compounds is under investigation. Only one possible option is shown here for clarity. Selected data are cited: (-)-1: mp 205–206 °C; $[\alpha]^{20}_D$ −180° (c 0.91, MeOH). (+)-1: mp 204.5–206 °C; $[\alpha]^{20}_D$ +181° (c 1.01, MeOH); $C_{18}H_{18}F_3NO \cdot HCl$ [m/z 322 (M⁺ + 1)]. Calcd: C, 60.42; H, 5.35; N, 3.92. Found: C, 60.17; H, 5.35; N, 3.83. ¹H NMR (300 MHz, CD_3OD): δ 2.77 (s, 3 H), 3.1–3.3 (m, 5 H), 3.43 (dd, J = 12.8 Hz, 1 Hz), 7.17 (t, J = 7 Hz, 1 H), 7.25–7.37 (m, 5 H), 7.6 (d, J = 8.5 Hz, 2 H).

(14) The resolution of (±)-4 can be achieved by hydrolysis of its O-acetyl derivative in water, catalyzed by porcine liver esterase. However, the moderate selectivity of this enzyme combined with the instability of (±)-4 esters in water makes the hydrolytic pathway less attractive.

(15) Lipase P was supplied by Amano Pharmaceutical Co. Enantiomeric excess was determined by HPLC using Chiralcel OD column (Daicel) with a mobile phase of hexane-2-propanol-diethylamine (80:20:0.1). t_R in min (+)-1, 9.33; (-)-1, 14.06; (+)-4, 10.75; (-)-4, 11.42. The ee for (-)-5 has been measured on the alcohol (-)-4 from saponification of (-)-5.

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(17) Radiochemical purity was analyzed by HPLC. Fifty 15-s fractions were collected and counted by liquid scintillation.

Use of Reaction Cubes for Generation and Display of Multiple Mechanistic Pathways

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Summary: Reaction cubes in which one face represents the charge types of reactants and the opposite face represents the corresponding charge types of products can be used for displaying coherently the multiple mechanistic paths of familiar reactions and for generating systematically mechanistic hypotheses for new reactions.

Three-dimensional energy diagrams and their two-dimensional projections have found extensive use in the analysis of complex reactions, especially eliminations and carbonyl addition reactions.[1] These More O'Ferrall diagrams have also found extensive qualitative use in instruction at the graduate level.[2] They help explain the

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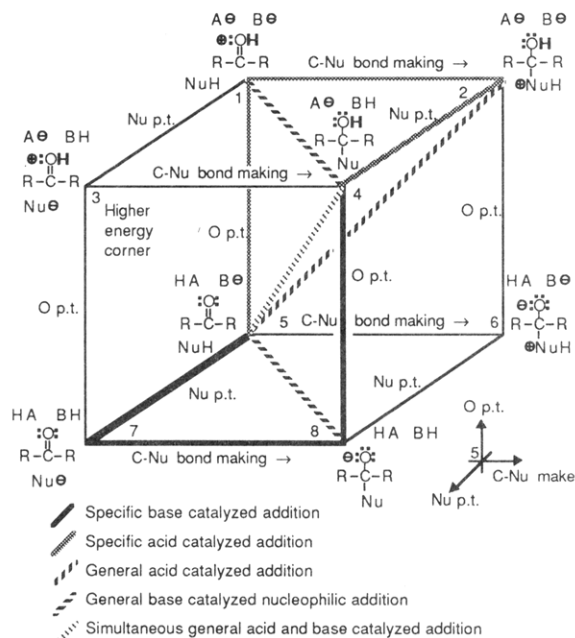
Figure 1. The reaction cube for the addition of a nucleophile to a carbonyl in protic media. The neutral start point (5) is connected to the neutral finish point (4) by the body diagonal. O p.t. is proton transfer to oxygen, and Nu p.t. is proton transfer from the nucleophile. Most diagonals are omitted for clarity. The axes for point 5 are shown at the lower right and correspond to the edge labels.

variable transition-state theory of eliminations[3] and the response of the transition-state structure to changing mechanistic variables.[4]

The progress cube of Grunwald was an extension and quantification of the More O'Ferrall two-dimensional projection so that three, rather than two, reaction progress variables could be easily analyzed for mechanisms involving three concerted reaction events.[5] This report demonstrates that similar cubes have great qualitative potential for generating and relating alternate mechanistic possibilities.

The cube for the addition of a nucleophile to a carbonyl in protic media is shown in Figure 1. The four reactant charge types are related by proton transfer and comprise the left-hand face of the cube (face 1, 3, 5, 7). The corresponding product charge types comprise the right-hand face (face 2, 4, 6, 8). The remaining four faces of the cube are the familiar More O'Ferrall diagrams relating two charge types of reactants to two charge types of products. As a whole, the cube describes the interrelation of all four charge types of both reactants and products. Each charge type can then be related to any of the others by either an edge, face diagonal, or body diagonal. This particular cube is applicable to hemiketal/hemiacetal hydrolysis which occurs with many mechanistic variants.[6] There is a great need for interrelating the various mechanisms so that all alternatives are easily visible, and, especially important, so that none are left unexplored. Twenty-eight possible interactions that require checking are the twelve edges, twelve face diagonals, and four body diagonals of the cube. Specific acid or base processes lie along the edges of the
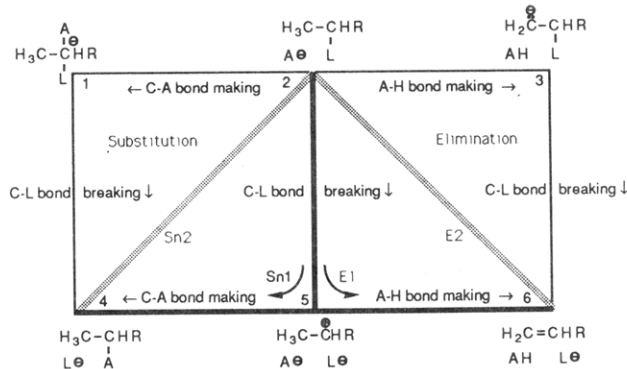

Figure 2. The joint substitution and elimination More O'Ferrall surfaces. The reactants are at point 2: the leaving group is denoted by L, the base/nucleophile by anion A. Note the expected changes in the preferred process as the carbocation is made more stable, or A made a poorer nucleophile, or A made a stronger base, etc.

cube. General acid and general base catalyzed processes constitute face diagonals. The body diagonal is the simultaneous general acid and general base (push–pull) catalysis.[7]

It is useful to join two More O'Ferrall diagrams that share a common edge, such as the loss of a leaving group, as shown in Figure 2. The qualitative tilting of this substitution/elimination surface by raising of the corners or edges in response to changing reaction variables can be used to understand the competition between the two processes. Similarly, reaction cubes can be joined to display alternative mechanistic paths for multistep reactions. The addition–elimination reaction is common to many carboxylic acid derivatives.[8] As shown in Figure 3, an addition cube shares a common face with an elimination cube. The shared face (face 2, 5, 8, 11) represents four charge types of the tetrahedral intermediate. It is obvious that some corners will be energetically less probable and that some diagonals will not correspond to a chemically reasonable process. Only addition followed by elimination routes are shown in this example; elimination followed by addition would require that a new set of cubes be constructed.

Imine formation, Figure 4, is an example in which, although there are many tetrahedral intermediate charge types, most mechanisms pass through the neutral carbinolamine intermediate.[9] In this case, an addition and an elimination cube share a corner (vertex 8), the carbinolamine intermediate.

Amide hydrolysis, Figure 5, is a complex mechanistic system in which more than four charge types of the tetrahedral intermediate are important.[10] An addition and elimination cube now share a common edge (edge 4, 11); a second elimination cube is present to cover routes from

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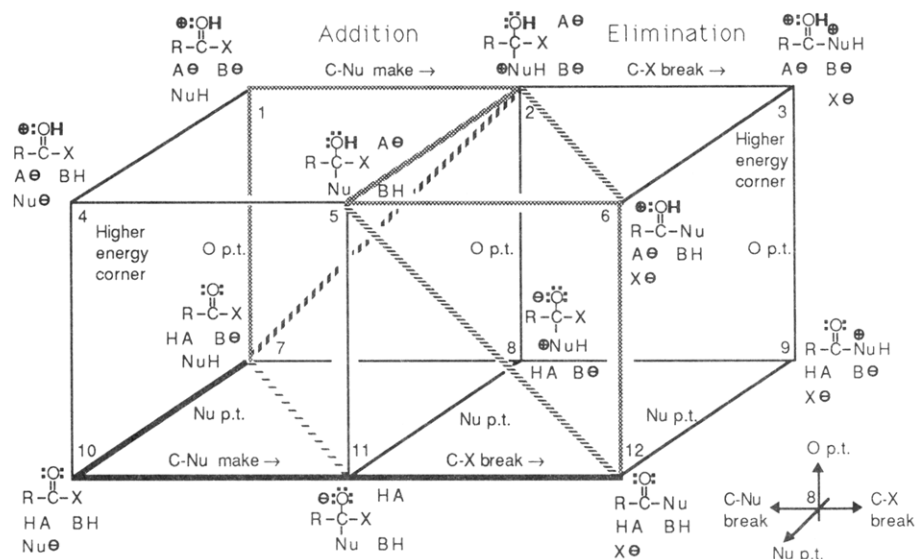
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Figure 3. Addition and elimination cubes sharing a common face: the addition–elimination reactions of an acyl halide with a nucleophile. The neutral reactants (7) are converted into neutral products (12) via the tetrahedral intermediate (face 2, 5, 8, 11). Most diagonals are omitted for clarity (two E2 face diagonals are shown on the elimination cube). The axes for point 8 are shown at the lower right.
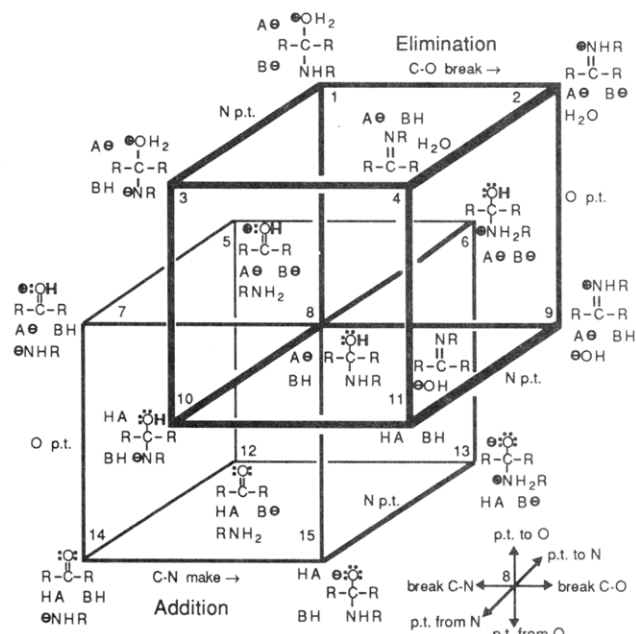
Figure 4. Two reaction cubes sharing a common point: imine formation (or hydrolysis). Neutral reactants (12) are connected by two body diagonals to the neutral product (4). The neutral carbinolamine is the shared vertex (8). All diagonals are omitted for clarity. The axes for point 8 are shown at the lower right.

dianionic tetrahedral intermediates. The face diagonal routes on an elimination cube can correspond to E2 processes or to general acid catalyzed eliminations. The commonly written acidic and basic routes are indicated on the figure.[10,11] Although these reaction cubes are easy to create, they clearly show the complexity of this system (31

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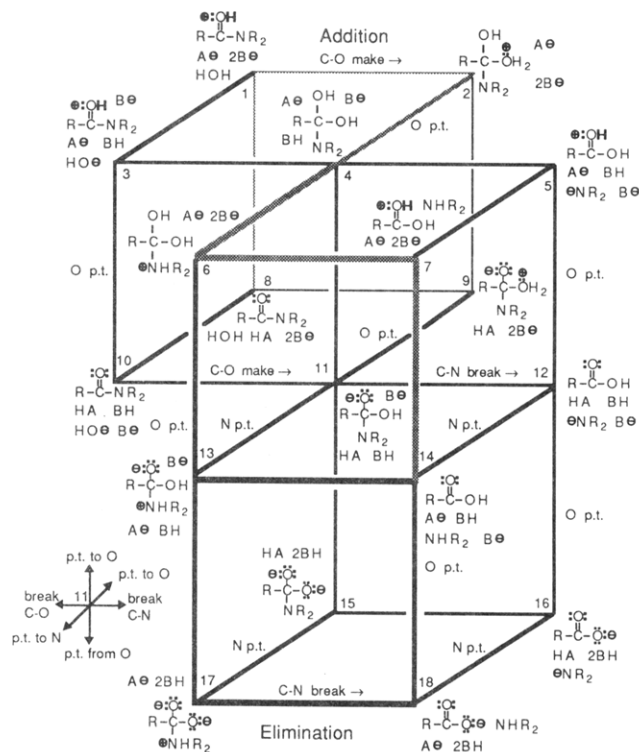
Figure 5. Reaction cubes sharing a common edge: the hydrolysis of amides (neutral reactants appear at point 8). Eight tetrahedral intermediate charge types are shown (2, 4, 6, 9, 11, 13, 15, 17). Six of nine product charge types are shown (5, 7, 12, 14, 16, 18). The three ammonium product charge types and all diagonals are omitted for clarity. The axes for point 11 are shown at the lower left. A common acidic media route (shaded) proceeds from 8 to 1, 2, 4, 6, 7, 14, then p.t. to N (charge type not shown). Basic media routes for various amides are 10 to 11 followed by: (15, 16, 18)[10a,d,e,11a,b,c] or (13, 14)[11a] or (12, 18)[11b,c] or (15, 18)[10b,11c] or (4, 14)[11d] or (18)[10c] or (14).[10d]

edges, 34 face diagonals, and 12 body diagonals). As the preceding examples demonstrate, reaction cubes are an important tool for the generation and selection of alternative mechanistic possibilities.