During the late 1940s and early 1950s disappointing passenger revenues, mounting inflation, and expensive technological changes produced a wave of mergers and attempted mergers in the American commercial aviation industry. No airline was more deeply involved in merger negotiations during these years than Delta, whose route system, comprised of an east-west axis stretching from Dallas–Fort Worth through Atlanta to Charleston, South Carolina, and a north-south axis leading from Chicago through Atlanta to Miami, needed to be expanded if the company was to make economic use of new equipment it had acquired to keep abreast of its major competitor, Eastern Airlines.

Delta first conducted merger talks with another primarily southeastern carrier, National, but these negotiations failed to produce an agreement satisfactory to the two firms. In the summer of 1950, Delta did reach a merger agreement with Northeast Airlines, but its consummation was contingent upon the acquisition by Delta of a route which would connect the systems of the two companies at New York City. Delta attempted to win approval from the Civil Aeronautics Board (CAB) of a route from Columbia, South Carolina, to New York, but the CAB was hesitant at this time to award any new route mileage and instead it was intimated that Delta might attempt to solve the problem by purchasing an existing route from another carrier. At the time, Capital Airlines and Northwest Airlines were engaged in merger discussions, and it was intimated that the CAB might make approval of such a merger contingent upon the sale of Capital's southern routes, one of which terminated in New York, to Delta. Complex negotiations ensued between the various parties involved, but the idea came to naught when the projected Capital–Northwest merger was voted down by Northwest's stockholders, and Northeast eventually withdrew from its merger agreement with Delta.

Meanwhile, however, Delta had begun merger discussions with Chicago and Southern (C & S), a Memphis-based carrier whose route system connected such cities as Chicago, St. Louis, Memphis, New Orleans, Detroit, Houston, Kansas City, and a number of Caribbean destinations. Negotiations were facilitated by a long-standing
friendship between the chief executives of the two lines, C. E. Woolman of Delta and Carleton Putnam of C & S; in July, 1952, a definitive merger pact was signed specifying a purchase price of approximately $10 million, to be financed by convertible debentures issued by Delta as the surviving carrier.

Because the route systems of the two companies integrated well and the merger promised important operating economies which were in the public interest, CAB hearings were conducted with dispatch and the consolidation received government approval by the end of 1952. Meanwhile, Delta and C & S worked out a series of administrative assignments combining their respective staffs and completed other arrangements to promote a smooth transition to unified operations. Despite organized opposition from C & S pilots who wanted their company to continue as an independent entity, the stockholders of both firms approved the merger by wide margins and it was officially consummated on 1 May 1953. As a result, Delta became the sixth-ranking domestic carrier in the industry with a considerably expanded route system capable of making economic use of its growing fleet. In addition, the merger brought into the Delta organization a number of key C & S officials who would make major contributions to the development of the enterprise in future years. It was the most important airline merger of the period immediately following World War II, and worked out to the long-range benefit of both firms taking part.